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Current perspectives in stem cell therapies for osteoarthritis of the knee

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Mesenchymal stem cells (MSCs) are emerging as an attractive option for osteoarthritis (OA) of the knee joint, due to their marked disease-modifying ability and chondrogenic potential. MSCs can be isolated from various organ tissues, such as bone marrow, adipose tissue, synovium, umbilical cord blood, and articular cartilage with similar phenotypic characteristics but different proliferation and differentiation potentials. They can be differentiated into a variety of connective tissues such as bone, adipose tissue, cartilage, intervertebral discs, ligaments, and muscles. Although several studies have reported on the clinical efficacy of MSCs in knee OA, the results lack consistency. Furthermore, there is no consensus regarding the proper cell dosage and application method to achieve the optimal effect of stem cells. Therefore, the purpose of this study is to review the characteristics of various type of stem cells in knee OA, especially MSCs. Moreover, we summarize the clinical issues faced during the application of MSCs.

Keywords: Knee joint; Mesenchymal stem cells; Osteoarthritis; Stem cells

Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by loss of cartilage, osteophyte formation, and periarticular bone change, resulting in disability [1,2]. In order to establish the disease-modifying strategies of OA, it is necessary to understand the biomolecular features seen in OA circumstance. Increased proinflammatory cytokines such as interleukin-1 or tumor necrosis factor-α, decreased growth factors such as transforming growth factor-beta (TGF-β), activated matrix metalloproteinase, and ultimate chondrocyte senescence can be observed at the molecular level [3-5] (Fig. 1). Although disease-modifying OA strategies that block inflammatory pathways and enhance cartilage protective function have been developed recently [6,7], their effects on preventing the progression of OA have been still unsatisfactory, and it is particularly difficult to achieve ultimate cartilage regeneration [8].

Meanwhile, since articular cartilage has a limited capacity for spontaneous healing, once damaged, it may eventually progress to OA [9]. Numerous attempts for the regeneration of focal cartilage defect have been made. Depending on the degree of defect size, various surgical options have been used, including multiple drilling, microfracture, abrasion chondroplasty, autologous chondrocyte implantation, and osteochondral autologous transplantation [10-13]. However, there has been no optimal regenerative method for cartilage in knee OA.

Recently, mesenchymal stem cells (MSCs) have been in the spotlight for their disease-modifying and chondrogenic potential along with their ease of harvesting, safety, and differentiation potential into cartilage [14,15]. Moreover, MSCs have been known to have paracrine and immunomodulatory effects through the secretion of cytokines and growth factors [16-19].

Therefore, considering the immunomodulatory and regenerative effect, stem cell therapies might be a promising line of treat-

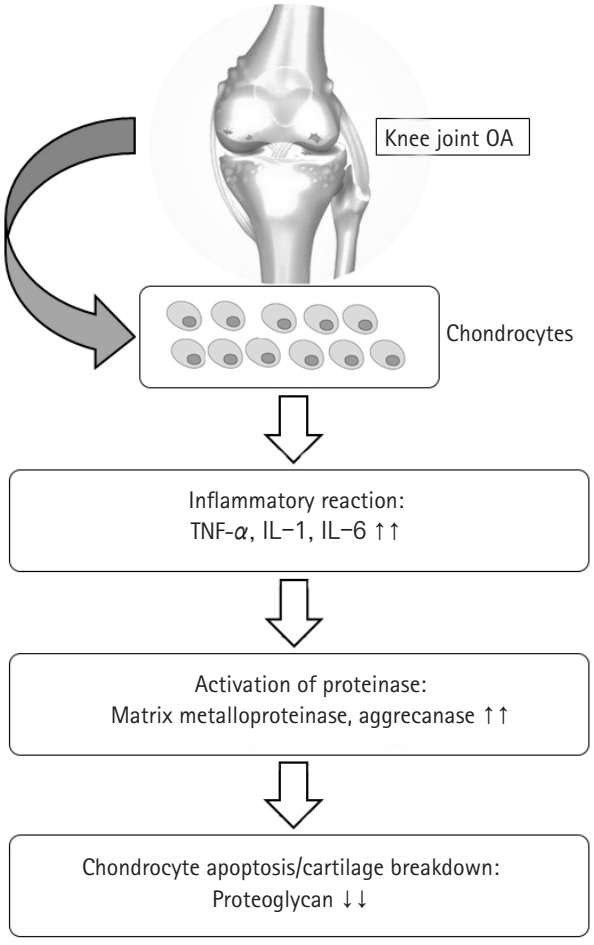

Fig. 1. Molecular mechanisms of osteoarthritis (OA). TNF, tumor necrosis factor; IL, interleukin.

ment for knee OA. The purpose of this study was to review the characteristics of various type of stem cells in knee OA, especially based on MSCs. Moreover, we summarized the clinical issues for application of MSCs (Fig. 2).

General characteristics of stem cells

In general, stem cells can be divided into two major groups: (1) embryonic stem cells (ESCs) from the inner cell mass of blastocyst, with totipotency or pluripotency; (2) adult stem cells (tissue-specific stem cells) from specific organ, with multipotency [20,21]. Although adult stem cells have usually more restricted differentiation capacity compared to ESCs, they exhibit some advantages including safety, easy derivation, and tissue-specific differentiation potential [22]. Among them, MSCs appears to be the promising candidates.

MSCs are multipotent progenitor cells that can be obtained from bone marrow, adipose tissue, synovial membrane, and articular cartilage [23]. Several studies report their multidirectional differentiation potential [24,25]. Particularly, autologous MSCs can be easily harvested and applied in clinical settings, and allogenic cells can be utilized [14,19]. Culture expansion may be required to maximize their clinical effect [14], although that may result in functional deterioration, mutation, and tumorigenesis as passage progresses. Nevertheless, MSCs can be cultivated and amplified while maintaining their potential, and differentiated into a variety of connective tissues such as bone, adipose tissue,

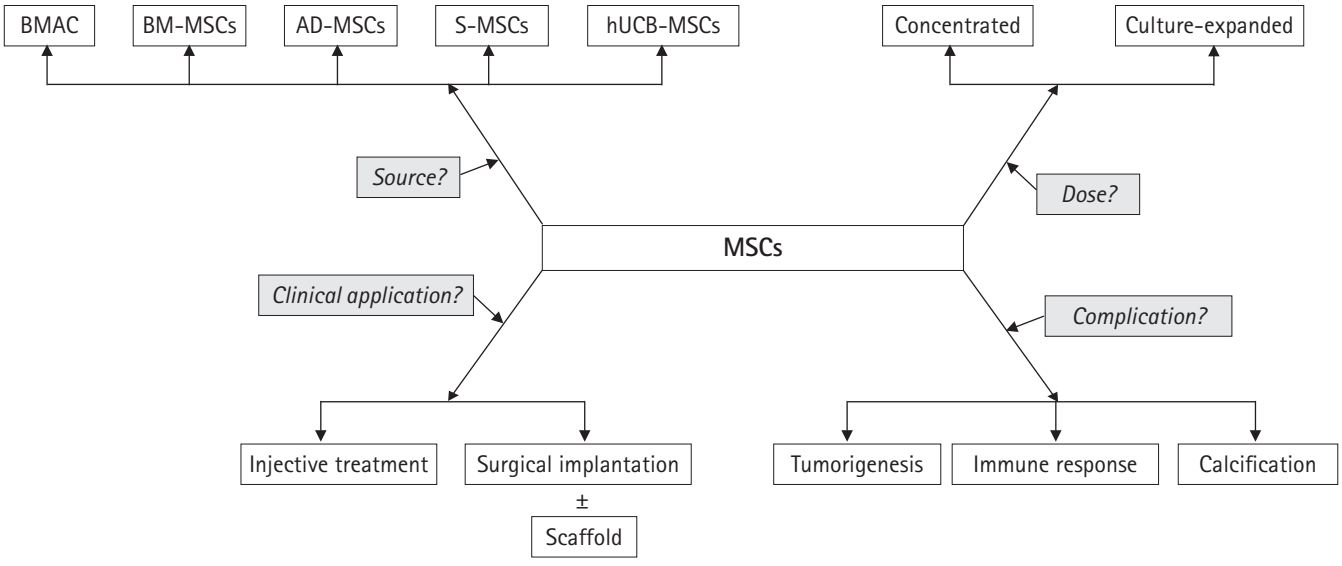

Fig. 2. Considerations for clinical application of MSCs. BMAC, bone marrow aspirate concentrate; MSC, mesenchymal stem cell; BM, bone marrow-derived; AD, adipose tissue-derived; S, synovium-derived; hUCB, human umbilical cord blood-derived.

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cartilage, intervertebral discs, ligaments, and muscles [26,27]. Owing to their inherent ability for self-renewal, proliferation, and differentiation toward mature tissues, MSCs could have promising applications in cell therapy and regenerative medicine [28]. The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed the definition of MSC via the following minimal set of criteria: (1) being plastic-adherent in standard culture conditions; (2) expressing CD105, CD73, and CD90 at their surface; while (3) lacking CD45, CD34, CD14, CD79α, and HLA-DR; and (4) being able to differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro* [27].

Bone marrow-derived mesenchymal stem cells

Bone marrow-derived mesenchymal stem cells (BM-MSCs) have been widely studied for OA treatment because of several advantages, including high expansion ability, and differentiation potential into cartilage [29-31]. Furthermore, due to easy harvesting from autologous bone marrow, they are cost-effective as compared to other types of MSCs. Several studies have reported favorable clinical outcomes in patients with knee OA who underwent intra-articular injection or surgical implantation using autologous BM-MSCs (Table 1) [31-35]. However, donor site pain, limited number of obtainable cells (0.001% of all nucleated cells in bone marrow), and decreased differentiation potential with increase in donor age are a few limitations while using BM-MSCs [31,36]. Bone marrow aspiration from anterior or posterior iliac crest can be performed with local anesthesia under ultrasonographic or fluoroscopic guidance to improve accuracy and efficiency [37].

Meanwhile, bone marrow aspirate concentrate (BMAC), which contains abundant nucleated cells and cytokines has been widely applied to the treatment of knee OA. It contains several factors involved in the healing process such as platelet-derived growth factor, TGF-β, vascular endothelial growth factor, and fibroblast growth factor [17,38]. BMAC can be easily extracted by via FDA approved commercialized kits and this process condenses the buffy coat containing mononuclear cells and increases the number of MSCs relative to baseline [39]. Recently, it is widely used in various orthopedic fields such as nonunion, osteonecrosis and sports injuries.

Centeno et al. [40] reported encouraging clinical outcomes with a low rate of adverse effects in autologous BMAC for intra-articular injection with or without adipose grafts in patients with knee OA. Additionally, significantly better results were observed in patients with Kellgren-Lawrence (K-L) grades I or II than in patients with K-L grades III or IV. Other studies have also reported positive clinical outcomes with simple iintra-articular injections of BMAC [41,42]. Contrastingly, in a recently conducted prospective randomized controlled trial, Shapiro et al. [42] did not report encouraging outcomes of BMAC as compared to the control group. BMAC studies in OA patients have not yet shown consistent results. Further researches comprising well-designed, randomized, controlled trials with larger sample sizes are needed to elucidate the exact mechanism of BMAC.

Table 1. Details of the clinical studies of BM-MSCs in knee OA

Study	Study design (no. of cases)	Mean age (yr)	Mean F/U (mo)	Delivery method	Cell population (cells/mL)	Additional factor	Outcome	Complication
Wakitani et al. (2011) [33]	Case series (45)	50	75	Two-stage surgical implantation	5.0×10^{6}	Collagen sheet from porcine tendon	No serious complications such as tumor or infection	-
Davatchi et al. (2011) [34]	Case series (4)	57.8	12	Intra-articular injection	$8.0–9.0\times10^{6}$	-	Pain, walking time, and the number of stairs to climb were improved	-
Wong et al. (2013) [32]	Prospective RCT (28 MSCs+HA vs. 28 HA)	51	24	Intra-articular injection	$1.46\pm0.29\times10^{7}$	Microfx-+MOWHTO	Better clinical outcomes and MRI in MSCs group	-
Orozco et al. (2013) [31]	Case series (12)	49	12	Intra-articular injection	4.0×10^{7}	-	Improvement in pain relief and WOMAC; improvement of cartilage quality on MRI	-
Davatchi et al. (2016) [35]	Case series (3)	57.8	60	Intra-articular injection	$8.0–9.0\times10^{6}$	-	Previous parameters gradually deteriorated, but better than baseline	-

BM-MSCs, bone marrow-derived mesenchymal stem cells; OA, osteoarthritis; F/U, follow-up; RCT, randomized controlled trial; HA, hyaluronic acid; Microfx, microfracture; MOWHTO, medial open-wedge high tibial osteotomy; MRI, magnetic resonance image; WOMAC, the Western Ontario and McMaster Universities Osteoarthritis Index.

Adipose tissue-derived mesenchymal stem cells

Adipose tissue, along with bone marrow, has been the most frequently used source for isolating MSCs [43]. Adipose tissue is abundant and easily accessible, making it a reliable site for stem cell isolation. It has copious numbers of MSCs (approximately 0.5×10^4–2.0×10^5/1 g fat) compared to BM-MSCs and their differential capacity is relatively less affected by donor age.

The specific premade solution is usually infiltrated into the subcutaneous tissue of the abdominal region through a tumescent technique, and then, a conventional abdominal liposuction is performed using blunt cannulas [44]. Enzymatic digestion of fat tissue is the most used isolation technique to obtain adipose tissue-derived mesenchymal stem cells (AD-MSCs) [45]. The extracted fat tissue is digested with enzyme (collagenase, dispase, or trypsin) to generate the stromal vascular fraction (SVF) that contains AD-MSCs and other endothelial and hematopoietic cells [46,47]. Among them, only the plastic-adherent, cultured and serially passaged multipotent cell populations are termed as AD-MSCs [48]. Meanwhile, non-enzymatic digestion, including mechanical procedures such as centrifugation and filtration is sometimes used. However, the range of yields shows high variation [49].

Several studies have reported encouraging clinical results for intra-articular injection of AD-MSCs in knee OA patients (Table 2) [14,50-53]. Lee et al. [50] reported that intra-articular injection of culture expanded AD-MSCs (1×10^8 cells) showed satisfactory functional improvement and pain relief in patients with knee OA through a prospective randomized controlled trial. Nonetheless, AD-MSCs have some disadvantages such as relatively lower chondrogenic potential and donor site morbidity [54].

SVF also can be obtained via enzymatic digestion and differential centrifugation of adipose tissue. SVF consists of a heterogeneous mesenchymal population of cells that includes not only adipose stromal and hematopoietic stem cells but also endothelial cells, erythrocytes, fibroblasts, lymphocytes, monocyte/macro-phages and pericytes (Table 3) [45,55]. Despite a highly heterogenous composition and low stem cell proportion, some studies have reported favorable clinical outcomes of SVF in knee OA due to their potential and ease of use [56,57].

Synovium-derived mesenchymal stem cells

Synovium-derived mesenchymal stem cells (S-MSCs) have attracted considerable attention due to their high chondrogenic po-

Table 2. Details of the clinical studies of AD-MSCs in knee OA

Study	Study design (no. of cases)	Mean age (yr)	Mean F/U (mo)	Delivery method	Cell population (cells/mL)	Additional factor	Outcome	Complication
Jo et al. (2014) [14]	Case series (dose-dependent) (3 vs. 3 vs. 12)	60	6	Intra-articular injection	Low-dose: 1.0×10^7 Mid-dose: 5.0×10^7 High-dose: 1.0×10^8	Diagnostic arthroscopy	Better clinical outcomes and decreased cartilage defect in high-dose group; Hyaline-like regeneration	No treatment-related AEs Most common AEs: nasopharyngitis Serious AEs: urinary stone
Pak et al. (2013) [51]	Case series (100)	51.2	26	Intra-articular injection	NA (AD-SVF)	PRP+HA+$CaCl_2$	Pain (VAS) was improved	Joint swelling No tumor formation
Kim et al. (2015) [53]	Comparative matched-pair analysis (20 vs. 20)	59.2	28.6	Intra-articular injection vs. surgical implantation	4.0×10^6	Injection: PRP Surgical implantation: fibrin glue Second-look arthroscopy	Better clinical and second-look arthroscopic outcomes in surgical implantation group	NA
Pers et al. (2016) [52]	Prospective (dose-dependent) (6 vs. 6 vs. 6)	64.6	6	Intra-articular injection	Low-dose: 2.0×10^6 Mid-dose: 1.0×10^7 High-dose: 5.0×10^7	-	Improved clinical outcomes in all groups; Limited possible improvement on MRI	-
Lee et al. (2019) [50]	Prospective RCT (12 MSCs vs. 12 saline)	62.7	6	Intra-articular injection	1.0×10^8	-	Significantly improved clinical outcomes in MSCs group; Increased defect in control group	-

AD-MSC, adipose tissue-derived mesenchymal stem cell; OA, osteoarthritis; F/U, follow-up; AE, adverse event; NA, non-available; AD-SVF, adipose-derived stromal vascular fraction; PRP, platelet-rich plasma; HA, hyaluronic acid; VAS, visual analogue scale; MRI, magnetic resonance image; RCT, randomized controlled trial; MSCs, mesenchymal stem cells.

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Table 3. Cell population in stromal vascular fraction

Variable	Percentage (%)
Stromal cell	15–30
Hematopoietic-lineage cell	
Stem and progenitor cell	<0.1
Granulocyte	10–15
Monocyte	5–15
Lymphocyte	10–15
Endothelial cell	10–20
Pericyte	3–5

tential and less hypertrophic differentiation than BM-MSCs [58,59]. Embryologically, S-MSC-derived chondrocytes and articular chondrocytes share similar gene expression profile [60]. They may prove to be the optimal cell source of MSCs as native nature to the joints. Kubosch et al. [58] reported that S-MSCs play an important role in joint homeostasis and possibly in natural cartilage repair. However, most of their evidence was limited to preclinical studies [61]. Only one retrospective study has reported the results of S-MSCs in human OA of the knee joint [62]. They reported clinical improvement and secure defect filling confirmed using second-look arthroscopy and magnetic resonance image, 48 months postoperatively. Further researches are needed to elucidate the interaction of S-MSCs and chondrocytes, and the promising role of S-MSCs in cartilage tissue engineering.

Human umbilical cord blood-derived mesenchymal stem cells

Umbilical cord compartments including Wharton's jelly, perivascular tissue, and umbilical cord blood (UCB) can be utilized to isolate MSCs [43,63]. Umbilical cord-derived MSCs can be obtained through pain-free collection methods with fewer ethical issues. An experimental comparative study [64] confirmed that UCB-MSCs have biological advantages in comparison to bone marrow or adipose tissue, including higher rate of proliferation and clonality, retardation of senescence, and superior anti-inflammatory effect.

Recently, clinical outcomes of human UCB-MSCs (hUCB-MSCs) for cartilage regeneration have been reported [65-67], and their medicinal product mixed with hyaluronic acid (Cartistem; Medipost, Seongnam, Korea) has been widely applied in clinical settings. hUCB-MSCs are also isolated in a non-invasive manner and have the advantage of being hypoimmunogenic. Moreover, they show a hyaline-like histological morphology [67]. Park et al. [65] reported that an hUCB-MSC-based product appeared safe and effective for the regeneration of hyaline-like cartilage in OA of the knee after 7 years of follow-up. In our institution, commercialized hUCB-MSCs were performed on OA of the knee to obtain favorable clinical outcomes and highly qualified regeneration (Fig. 3).

Clinical issues for application of mesenchymal stem cells

There is no consensus on the optimal dose or cell number to achieve the utmost effect of stem cells. The optimal dose of MSC implantation for cartilage regeneration has not yet been established. In a dose-dependent prospective study, Jo et al. [14] reported that significant clinical improvement was shown only in the high dose group (1×10^8 cells). Based on this result, culture expansion may be needed to obtain the optimal effect of MSCs.

Treatment strategies for clinical application may also be one of the issues faced by clinicians. Injective treatment is relatively efficient because it is easy to apply and does not require hospitalization, but precise delivery to target site may be difficult [54]. Conversely, surgical implantation allows direct delivery to the lesion site, but requires hospitalization and is a more invasive approach. Another option is to mix MSCs with biodegradable scaffolds followed by surgical implantation. The three-dimensional scaffold maintains the phenotype of differentiated chondrocytes, promotes improved chondrogenesis through uniform cell distribution, and reduces the risk of chondrocyte leakage [68]. Scaffold materials include hyaluronic acid, collagen derivatives, agarose, fibrin glue, and chitosan [69]. However, chondrocyte dedifferentiation, apoptotic cell leakage, inadequate cell distribution, and low differentiation have been reported in scaffold-based studies [70].

Potential risks of MSCs in clinical use, such as tumorigenesis, immune response, and heterotrophic calcification are also considerable issues [71]. Therefore, it should be recognized that such risk of MSC-mediated abnormal reactions might occur in some cases, and mandating a careful assessment of the patient's condition. Further research is also needed to guarantee the safety of MSCs. Each type of MSCs is summarized in Table 4.

Other advanced techniques

1. Induced pluripotent stem cell

Induced pluripotent stem cells (iPSCs) are also becoming a promising cell source for stem cell-based therapy [72]. They are a kind of stem cells established in the laboratory that can be reprogrammed into somatic cells. Although therapeutic models of neurological and cardiovascular diseases using iPSCs have been reported [73,74], the research using iPSCs in orthopedic fields is still in its nascent stages, particularly for cartilage regeneration. iP-

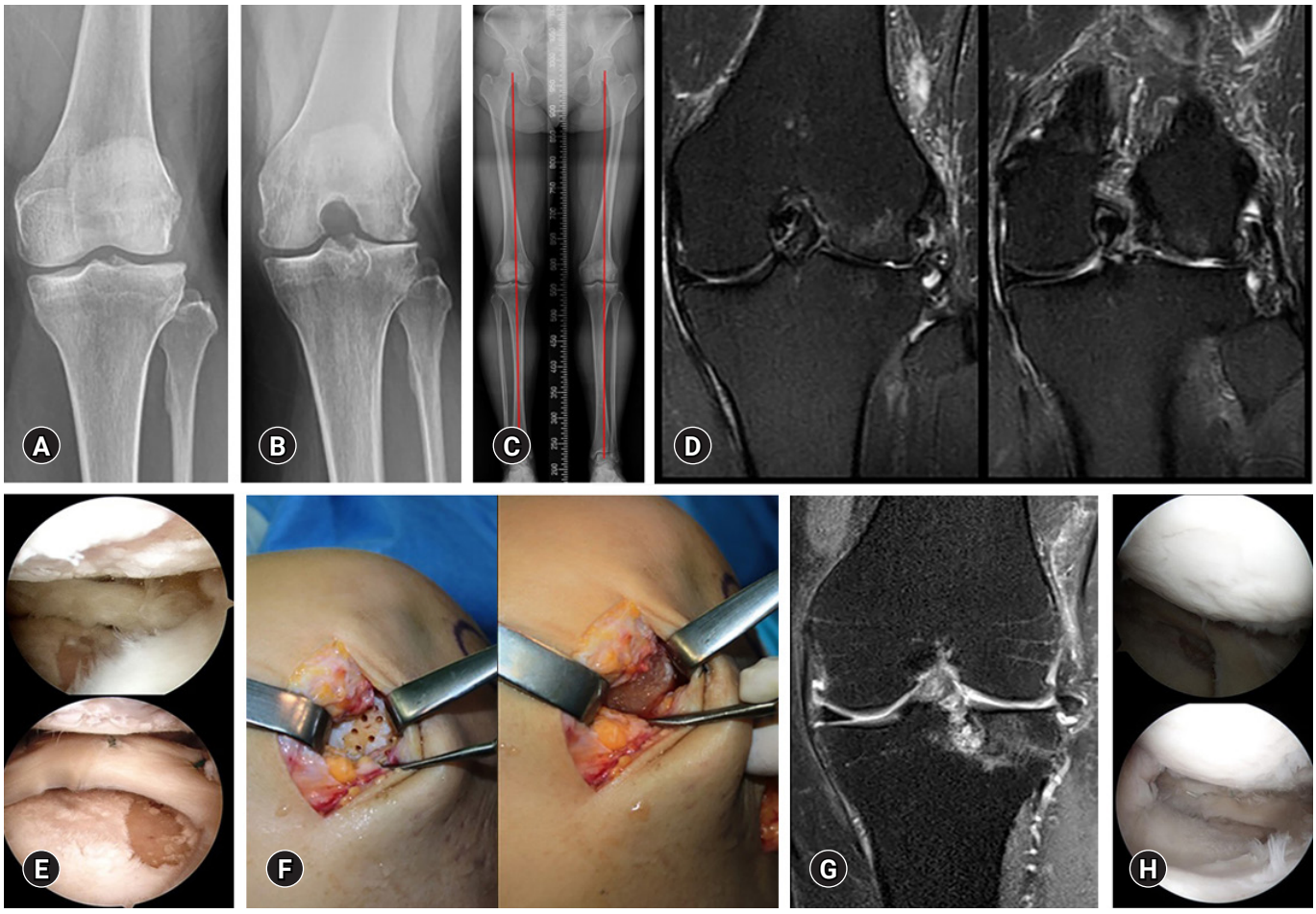

Fig. 3. (A, B) Kellgren-Lawrence grade III osteoarthritis is observed in the left knee anteroposterior and 45° flexion standing radiographs in a 49-year-old woman. (C) The scanography image shows neutral alignment of the both lower extremities. (D, E) Coronal T2-weighted fat suppressed magnetic resonance image (MRI) and arthroscopy show the focal chondral defects of International Cartilage Repair Society (ICRS) grade IV in the lateral femoral condyle and lateral tibial plateau. (F) Surgical implantation is performed using a commercialized mixture of human umbilical cord blood-derived mesenchymal stem cells and hyaluronic acid gel (Cartistem). (G, H) The coronal T2-weighted fat suppressed MRI and second-look arthroscopy confirm regenerated cartilage at 18 months after surgery.

Table 4. Summary of advantages and disadvantages of each MSC

	BM-MSC	AD-MSC	S-MSC	hUCB-MSC
Advantage	High chondrogenic and osteogenic potential Good expansion ability	Easily accessible, reliable for isolation Plentiful number of cells Less affected by donor age	Greater chondrogenic potential (same embryological origin as cartilage)	Direct delivery on defect Hypoimmunogenic Histology: hyaline-like cartilage
Disadvantage	Donor site pain Limited number of cells More affected by donor age	Relatively lower chondrogenic potential Donor site morbidity (hematoma, infection)	Less osteogenic potential Not easy to obtain Evidence still limited to preclinical studies	Surgical implantation High cost Not easy to obtain

MSC, mesenchymal stem cell; BM, bone marrow-derived; AD, adipose-derived; S, synovium-derived; hUCB, human umbilical cord blood-derived.

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SCs exhibit similar proliferation capacity and pluripotency as other tissue-derived stem cells, with no immune rejection and ethical issues [72]. Recently, new methods for producing iPSCs without viral vectors to reduce the risk of tumorigenicity have been developed [75].

Nonetheless, to date, limited data exists regarding the in vitro chondrogenic differentiation of iPSCs and the yield of iPSCs is relatively low.

2. Genetically modified MSCs (engineered MSCs)

The efficacy of MSCs *in vivo* may still be low due to poor survival, retention, and engraftment of the cells. Most MSCs often die within the first few hours after *in vivo* delivery [76]. Therefore, MSCs need to be genetically modified to improve survival, migration, and secretion of growth factors for their application in regenerative medicine [76]. Genetic modification of MSCs is usually achieved through viral vectors [76]. The most commonly used vectors include retrovirus, lentivirus, baculovirus, and adenovirus [22]. Viral transduction has improved homing of MSCs to the defect or inflammation site through the overexpression of homing receptors. MSCs have been transduced with adenovirus expressing C-X-C chemokine receptor 4 (CXCR-4) and runt-related transcription factor-2 (Runx-2), and with retrovirus expressing receptor activator of nuclear factor-kB and CXCR-4 [77,78]. Although the efficacy of genetically modified MSCs has been demonstrated in preclinical studies, it has not been investigated in clinical trials.

Conclusion

MSCs are the hottest topic in recent stem cell research. The application of stem cells in cartilage regeneration has been tried a lot, but so far, the effect of cartilage regeneration is not consistent from one study to another. Moreover, the most appropriate cell source is still controversial. Further research is needed to determine which tissue-derived stem cells, which usage and dose will be ideal for the treatment of osteoarthritis. In this review, we briefly reviewed the most up-to-date knowledge, including the characteristics, types, and clinical issues of MSCs. It is expected that in future, treatment with MSCs will be applied more clinically in the treatment of knee OA.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: GBK, OJS; Data curation: GBK; Formal analysis: GBK; Methodology: GBK; Project administration: OJS; Investigation, Resources: GBK; Supervision: OJS; Validation: GBK; Writing-original draft: GBK; Writing-review & editing: GBK, OJS.

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Drug selection for sedation and general anesthesia in children undergoing ambulatory magnetic resonance imaging

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The demand for drug-induced sedation for magnetic resonance imaging (MRI) scans have substantially increased in response to increases in MRI utilization and growing interest in anxiety in children. Understanding the pharmacologic options for deep sedation and general anesthesia in an MRI environment is essential to achieve immobility for the successful completion of the procedure and ensure rapid and safe discharge of children undergoing ambulatory MRI. For painless diagnostic MRI, a single sedative/anesthetic agent without analgesia is safer than a combination of multiple sedatives. The traditional drugs, such as chloral hydrate, pentobarbital, midazolam, and ketamine, are still used due to the ease of administration despite low sedation success rate, prolonged recovery, and significant adverse events. Currently, dexmedetomidine, with respiratory drive preservation, and propofol, with high effectiveness and rapid recovery, are preferred for children undergoing ambulatory MRI. General anesthesia using propofol or sevoflurane can also provide predictable rapid time to readiness and scan times in infants or children with comorbidities. The selection of appropriate drugs as well as sufficient monitoring equipment are vital for effective and safe sedation and anesthesia for ambulatory pediatric MRI.

Keywords: Ambulatory; Anesthesia; Deep sedation; Magnetic resonance imaging; Pediatrics

Introduction

The prevalence of magnetic resonance imaging (MRI) for diagnosing and monitoring a wide range of disease in children continues to expand with the efficacy benefit of providing high-resolution images of tissue anatomy and quantitative function and the safety advantage of a lack of ionizing radiation [1,2]. Aspects of MRI scans such as loud noises, confined bore of the magnet, and the required immobility to prevent motion artifacts are the causes of anxiety and barriers to successful performance of the procedure in children younger than 6 years and those at any age with development delay, claustrophobia, or involuntary movements or convulsions. Given the increase in MRI utilization and growing interests in the pain and anxiety of children, the demand for drug-induced sedation during MRI scans have substantially increased over the past decade. Generally, pediatric MRI scans require deep sedation or general anesthesia to achieve absolute immobility (sometimes with breath-holding) for up to 1 hour (Table 1) [3-5].

The greater the level of sedation, the greater the risk for complications. In addition, it is common that the child easily progresses to a deeper level of sedation without easily recognizable signs. For these reasons, patients who require more than conscious sedation in an MRI suite must be provided with the same level of safety and monitoring (pulse oximetry, capnography, electrocardiogram,

Table 1. Levels of sedation defined by American Society of Anesthesiologists

Factor	Minimal sedation	Moderate sedation	Deep sedation	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable even with painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

Reprinted from "Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia" developed by the American Society of Anesthesiologists [5].

heart rate, and blood pressure at least 5 minutes interval by an independent observer) as in the operating room [6]. However, pediatric sedation in an MRI environment presents unique challenges that are not existent in the operating room. Powerful static and dynamic magnetic fields with radiofrequency pulses restrict the use of standard ferromagnetic anesthesia machines and monitoring equipment and limits access to the patients throughout the scanning process. Emergently halting MRI for patient safety takes several minutes to be effective and is expensive. In addition, adverse events including incoordination of movements, dizziness, and agitation occurs in 64.4% patients, and a return to baseline takes more than 9 hours after discharge in children undergoing MRI [4]. Thus, sedation providers should have an in-depth knowledge of drugs including a clear understanding of the sedating medication's pharmacokinetics and pharmacodynamics, drug interactions, and potential complications, as well as the presence of appropriate monitoring equipment and personnel with the skills needed to rescue a patient from adverse events for safe and efficient sedation for pediatric MRI.

This article reviews currently used sedative/anesthetic agents for deep sedation or general anesthesia for ambulatory pediatric MRI. The benefits and risks of deep sedation and general anesthesia are also included. In this article, the most commonly used drugs in Korea will be highlighted.

Consideration in sedative/anesthetic regimen determination

Selecting sedation or general anesthesia for MRI should be made on an individual patient basis, considering the benefits and risks. The goals of sedation or anesthesia for ambulatory pediatric MRI are as follows: (1) to guard the patient's safety and welfare; (2) to minimize physical discomfort and pain; (3) to control anxiety, minimize psychological trauma, and maximize the potential for amnesia; (4) to control movement to allow the safe and efficient completion of the procedure; and (5) to provide early, safe discharge from the hospital [6]. The ideal drug regimen to achieve these goals should have the following desirable characteristics: (1) rapid onset of action; (2) predictable duration; (3) easy titratability within the desired range of the sedation continuum; (4) rapid and consistent cessation of effects; (5) multiple delivery options; (6) a wide therapeutic window; (7) minimal cardiorespiratory depression; (8) minimal drug interaction; and (9) be minimally affected by renal or hepatic disease [7]. Generally, decisions regarding the drugs to be used for sedation depends on the patient-related (neurodevelopmental status, underlying health condition, and previous sedation/anesthesia history) and procedure-related factors (degree of cooperation/immobility required, invasiveness, and duration). A single sedative/hypnotic without an analgesic is preferred for obtaining immobility for nonpainful MRI procedures [3]. A combination of two or more sedating medications may have the potential for adverse outcomes [8,9].

Drugs for deep sedation or general anesthesia for pediatric magnetic resonance imaging

1. Sedative/hypnotic agents

1) Chloral hydrate

Choral hydrate is a sedative hypnotic agent with no analgesic properties. It is believed that its sedative mechanism is mediated by the γ-aminobutyric acid type A ($GABA_A$) receptor in the central nervous system. Chloral hydrate is well absorbed from the gastrointestinal tract via an oral or rectal route and rapidly metabolized into an active metabolite, trichloroethanol, which is responsible for its sedative and hypnotic effects. The onset of action is 30–60 minutes and the duration of action is 60–120 minutes. However, individual responses may be highly variable and sedative effects may last up to 24 hours. The half-life is age dependent and varies from 4 to 12 hours and may extend to 37 hours and 28 hours in preterm and term infants, respectively [10]. Thus, chloral hydrate has the potential for resedation after initial recovery from sedation and may produce residual effects up to 24 hours after ad-

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ministration.

Although it has little effect on the cardiovascular and respiratory systems, adverse events including nausea and vomiting, gastritis, diarrhea, prolonged sedation, paradoxical excitement, agitation, and minor respiratory depression should be considered. Children receiving chloral hydrate should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and desaturation especially in infants younger than 6 months [9,11]. It should be avoided in children with moderate to severe renal failure, severe hepatic dysfunction, hypersensitivity to chloral hydrate, gastritis, esophagitis, peptic ulcer, adenoid hypertrophy, and porphyria [12].

The recommended dose of chloral hydrate is 50–100 mg/kg (up to a maximum of 2 g) [13]. The success rate of chloral hydrate sedation for pediatric MRI varies from 78%–100% [14-19] and is affected by the total dose administered, age, fasting status, and neurodevelopmental disability [14,15,18,19]. When 100 mg/kg of chloral hydrate is administered, the sedation success rate was 96% in children under 48 months but decreased to 86% in those older than 48 months [20]. The United Kingdom (UK) National Institute for Clinical Excellence (NICE) also recommends the use of oral chloral hydrate with a wide margin of safety in children under 15 kg. In contrast, chloral hydrate can be used as a first-line sedative agent for MRI in newborns and infants with the lowest risk of cardiorespiratory adverse events compared to phenobarbital and propofol [17,21]. Although there are no clear guidelines for pre-procedural fasting for chloral hydrate, fasted children require a greater dose of chloral hydrate, which is related to a longer onset and duration of action. Thus, children may be encouraged to take at least clear fluids 2 hours before the procedure for successful sedation without breaking institutional fasting protocols for chloral hydrate sedation [22]. Choral hydrate should not be used in children with neurodevelopmental disorders due to the increased incidence of adverse effects and decreased efficacy as compared with neurologically intact children [18]. In contrast, it may be used safely and effectively in properly monitored children who have congenital heart disease, including those with cyanotic heart disease, for painless diagnostic procedures [23].

Currently, both the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have withdrawn the approval of chloral hydrate partly due to the potential risk of carcinogenicity. In conclusion, chloral hydrate seems to provide safe and effective sedation for children under 48 months old undergoing MRI. However, its use is progressively decreasing based on the high failure rate for MRI sedation, prolonged recovery time, and introduction of more effective sedative agents in many countries [24].

2) Pentobarbital

Pentobarbital is a medium duration barbiturate that provides potent sedation with no analgesic property. It can be administered via an oral or intravenous (IV) route. Following IV administration, the onset of action is 2–3 minutes, with peak effects after 10–15 minutes and a duration of action of 45–60 minutes due to rapid redistribution [25]. Following oral administration using an IV formulation of pentobarbital, sedation begins at 20–30 minutes and lasts 60–90 minutes [16,26,27]. The oral dose of 4–8 mg/kg and IV dose of 2–3 mg/kg (to a maximum 5–8 mg/kg) are required to achieve deep sedation. The sedation success rates of pentobarbital for MRI in children are 87.8%–99.5% for IV administration [16,17,26-28] and 67%–99.7% for oral administration [26,29-31] with a trend towards increasing failure rates with increasing age and weight. Retrospective comparison analysis found that oral pentobarbital has comparable sedation success rate (99.5% vs. 99.7%) and time to discharge and a lower rate of desaturation (0.2% vs. 0.9%) compared with IV pentobarbital in 2,164 infants undergoing CT or MRI [26]. Both oral and IV pentobarbital are as effective as oral chloral hydrate for providing sedation for pediatric MRI [16,29]. However, when compared to oral chloral hydrate, oral pentobarbital has the advantage of fewer respiratory events in infants, whereas IV pentobarbital has the disadvantage of a higher incidence of more paradoxical reaction and major motion artifacts and prolonged recovery despite the advantage of earlier onset in children. Children with neurodevelopmental disability have similar dose requirements for pentobarbital but more respiratory adverse events and hypoxemia during MRI scans [27,32,33].

Pentobarbital is associated with adverse reactions such as oxygen desaturation, nausea and vomiting, paradoxical hyperreactivity, respiratory depression, agitation, and prolonged sedation [16,17,26-29,31]. Airway obstruction is more likely to occur in infants. Oral pentobarbital results in a longer duration of action and less respiratory adverse events than IV administration [26]. Pentobarbital, like other barbiturates, is contraindicated in patients with porphyria.

3) Midazolam

Midazolam is a short-acting, water soluble benzodiazepine that has anxiolytic, sedative, amanestiec, and muscle relaxant properties. Its sedation mechanism is GABA-mediated enhancing chloride conductance in the central nervous system. Although midazolam can be given for sedation via mutiple routes, IV administration is preferred, if vascular access is present. The onset of action is typically 3–5 minutes and lasts 30–45 minutes with IV admini-

station at 0.1 mg/kg with successive 0.05 mg/kg every 5 minutes (maximum 4 mg).

Although NICE recommends the consideration of midazolam as one of the first-line sedative drug for painless imaging procedures owing to a wide margin of safety [13], it is currently used as an adjuct sedative with either dexmedetomidine or ketamine rather than single primary agent for pediatric MRI [18,34-37] because of the high sedation failure rates, short duration of action, as well as frequent significant respiratory depression at deeply sedating doses [38,39]. However, coadministration of midazolam and other sedative agents, especially opioids, in children is not acceptable because of siginficant increases in cardiorespiratory depression and difficulty in predicting sedation effects [9]. Paradoxical excitement or delirium have been reported, usually following an IV dose, and may be managed with low-dose flumazenil.

Flumazenil is a benzodiazepine antagonist used to reverse sedation and/or respiratory depression caused by midazolam. Dosing starts at 0.01–0.02 mg/kg and can be repeated until adequate reversal of midazolam is noted (maximum 1 mg) [40]. As flumazenil is highly lipohlic, its onet of action is rapid (1–2 minutes) but duration of action is relatively short (30–45 minutes), so monitoring for resedation is necessary [41].

4) Ketamine

Ketamine is a phencyclidine analog and N-methyl-D-aspartate (NMDA) receptor antagonist that induces sedation, dissociative amnesia, and analgesia. Ketamine is used as a sedative for MRI because its analgesic component is not necessary for MRI. Administration routes are IV (0.05–2 mg/kg), intramuscular (IM; 4–5 mg), oral (5–6 mg/kg), and intranasal (5–10 mg/kg). IV use is preferable if IV access is available. The onset of action is rapid (1–2 minutes), the duration is brief (10–15 minutes) and the recovery is short (30–60 minutes) [42]. Ketamine is attractive for pediatric sedation because of its relatively short duration of action, multiple routes of administration, preservation of airway reflexes, and sympathomimetic properties including increase heart rates and blood pressure. Although sedation can be achieved with minimal respiratory depression, ketamine has various and lengthy adverse effect profiles including hallucination, emergence delirium, agitation, nausea and vomiting, hypersalivation, and laryngospasm, which may be distressing to both the child and parent. Often there are random movements of the extremities rendering this drug less than ideal for procedures where the patient must lie perfectly still during MRI scans. Thus, ketamine is used with a combination of other sedative agents to counterbalance the side effects and enhance the beneficial effects for each drug rather than as a sole sedative agent for MRI. Ketamine can counterbalance the cardiorespiratory depression effect of propofol and prolonged recovery of dexmedetomidine by reducing the dose requirements of each drug for MRI sedation in children [43-45].

5) Dexmedetomidine

Dexmedetomidine is a selective central α_2 receptor agonist that has sedative, analgesic, anti-shivering sympatholytic, and anxiolytic properties. Its sedative mechanism results from a decrease in norepinephrine release from presynaptic neurons with the initiation of postsynaptic activation, attenuating central nervous system excitation. The most unique characteristic of dexmedetomidine is the preservation of respiratory drive with a low incidence of apnea, respiratory depression, or airway obstruction, which is highly advantageous in children who are prone to respiratory depression, such as those with neurodevelopmental disabilities or obstructive sleep apnea, while receiving sedation/analgesia [46-48].

Patients exhibit biphasic cardiovascular responses after IV administration of dexmedetomidine [49,50]: initial transient hypertension along with a baroreceptor-mediated decrease in heart rate by α_{2B}-adrenoreceptor vasoconstriction followed by hypotension and bradycardia (10%–30% from baseline) by α_{2A}-adrenoreceptor-mediated inhibition of central sympathetic outflow. The hypertensive effect and associated bradycardia can be reduced by infusion of loading dose over a 10 minutes period. Prehydration of 10 mL/kg of normal saline solution is effective in decreasing the incidence of dexmedetomidine-related hypotension [51]. However, prophylaxis with glycopyrrolate for bradycardia is not routinely recommended because of transient severe hypertension [52]. Children are usually able to maintain systemic blood pressure with minimal impact on cardiac output and ultimately end organ perfusion.

Dexmedetomidine may be administered by oral, buccal, nasal, rectal, subcutaneous, IM, and IV routes. Dosing and bioavailability vary depending on the route of administration. When administered through IV, the average onset of sedation is 8.6 minutes with a recovery time of 41.4 minutes [53]. The rapid phase redistribution half-life is approximately 7 minutes, and the terminal elimination half-life is approximately 2 hours [54]. The success rate of sedation for pediatric MRI ranges from 83.3% with a 1 μg/kg bolus followed by 0.5 μg/kg/hr infusion to 98% with a 3 μg/kg bolus followed by 2 μg/kg/hr infusion [47,53]. Buccal (a mean of 2.20 ± 0.38 μg/kg) and intranasal (3 μg/kg) administration of dexmedetomidine may be useful in children with difficult IV cannulation, but their success rates of sedation for MRI are lower than IV administration and more sedative supplementation is required than IV administration [34,35,55,56]. Generally, a lack of respiratory depression combined with a relatively short half-life

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makes dexmedetomidine a useful single sedative agent for an ambulatory pediatric MRI setting. However, in spite of a similar success rate, it has slower onset and longer recovery compared to propofol in children undergoing MRI [54,57,58].

With the evolution of more complex MRI studies, dexmedetomidine is preferred to propofol for magnetoencephalography scans, which are employed for presurgical planning with intractable epilepsy due to the preservation of epileptiform activity [59]. The MRI sleep study is a relatively new imaging technique for the evaluation of obstructive sleep apnea. Minimal respiratory depression of dexmedetomidine decreased the use of artificial and manual airway supports such as the chin lift and shoulder roll, which can artificially alter the MRI results [60].

2. Anesthetic agents

1) Propofol

Propofol (2,6-diisopropylphenyl) is a potent IV anesthetic agent that has hypnotic but no analgesic properties via the potentiation of $GABA_A$ receptors and inhibition of NMDA receptors. Unlike with other sedative agents, propofol use is limited to the IV route. Propofol has a fast onset of action (10–50 seconds) and short distribution half-life (approximately 9 minutes in the pediatric population) [60]. Deep sedation is typically induced with a bolus dose of 1–3 mg/kg and 0.5–1 mg/kg supplementation every 1–2 minutes [61]. Higher dosing is often required for younger pediatric patients because of their higher volume of distribution, shorter elimination half-life, and higher plasma clearance [62]. A single dose or intermittent bolus doses of propofol may be suitable for brief procedures (< 30 minutes) [63], but continuous infusion of 2–5 mg/kg/hr rather than intermittent administration is recommended for longer procedures [64] in children undergoing MRI. The use of MR-compatible infusion pumps allows for consistent maintenance of accurate dosing and reduces the amount of propofol need to achieve adequate and safe sedation in children undergoing MRI [65]. Although propofol is easily titratable, its narrow therapeutic margin combined with ultra-short-acting pharmacokinetic profiles is associated with the rapid progression of sedation levels leading to general anesthesia.

Because of its rapid onset, short recovery time, antiemetic properties, and low incidence of emergence delirium, propofol has gained popularity as a primary sole sedative agent for MRI in children. Compared to most other sedative regimens, propofol provides the shortest onset and recovery and a high sedation success rate for pediatric MRI [66-70]. However, propofol commonly causes hypotension and dose-dependent respiratory depression including hypoventilation, apnea, and airway obstruction, which may be exaggerated with concomitant opioid use [27,71-73]. Sedation providers must monitor the respiratory rate and $etCO_2$ in children receiving propofol sedation. As mentioned above, coadministration of ketamine may be an option to counterbalance propofol-induced cardiorespiratory depression [45]. Pain during peripheral IV injection can be distressing to the parent and child but may be limited with low-dose lidocaine, fentanyl, or ketamine pretreatment [74]. Because propofol contains egg lecithin, patients with a history of egg allergy are at increased risk of an allergic reaction to propofol [75]. Because of its rapid acting and reliable titration of drug concentration, propofol is also used for general anesthesia with spontaneous ventilation, endotracheal intubation, or laryngeal mask airway (LMA) for MRI in children [76-78].

2) Sevoflurane

Generally deep sedation with spontaneous ventilation is preferred for MRI because of limited medical resources (mechanical ventilation and longer surveillance period). However, general anesthesia for MRI is indicated in select children with congenital heart defects or airway abnormalities, long-duration scans for staging investigations of malignancies, or those who have had previous sedation failure. Some MRI scans (cardiac, thoracic, or abdominal) require breath-holding to obtain adequate images. In such cases requiring the need for a secure airway, it is necessary to control airway with LMA or endotracheal intubation and deliver general anesthesia.

Sevoflurane is the inhalational agent of choice in children due to its lack of airway irritability and ability to provide stable hemodynamic function, together with its rapid onset and offset. Sevoflurane has been successfully used in newborns and infants with a maximum vaporizer setting of 4 vol% for MRI [79,80]. Sevoflurane anesthesia provides higher success rates (92% vs. 80%) and faster onset and recovery, but a higher incidence of emergence delirium than propofol anesthesia in children undergoing MRI [70,76]. Major airway-related adverse events such as respiratory apnea and severe airway obstruction occurred in 0.4% of children, while preterm infants are at higher risk compared to term infants after sevoflurane anesthesia for MRI [81]. Positive pressure ventilation with endotracheal intubation or LMA may result in more extensive atelectasis in children after MRI compared to spontaneous ventilation in children receiving sevoflurane-based anesthesia [78,82].

Sevoflurane-based anesthesia is also reported to be highly feasible and safe in children with neuropsychiatric disorders undergoing MRI. Mongodi et al. [83] found that induction and maintenance of sevoflurane anesthesia inhaled by a reservoir bag mask at 8.0 and 2.5 vol%, respectively, provides a median time of 15 min-

utes for full recovery and lower rates of mechanical ventilation compared to other pharmacological approaches in retrospective analysis of data of 10 years at a single center. They identified children with an American Society of Anesthesiologists (ASA) score > 1, male sex, prolonged procedures, and neuromuscular diseases as higher risk for general and respiratory complications in this population.

Special consideration for pediatric drug use and development

Many of the drugs used for sedation and analgesia in children are not approved by the Ministry of Food and Drug Safety (MFDS), formerly the Korean Food and Drug Administration (KFDA), for use in children under certain ages (e.g., fentanyl < 2 years; remifentanil < 1 year; propofol < 3 years for anesthesia and < 18 years for sedation; and dexmedetomidine < 18 years of age). The lack of MFDS approval does not imply that a drug can/should not be used; rather, it means that pharmaceutical manufacturers never carried out the appropriate research to gain MFDS approval. Off-label use of drugs for sedation of children has grown exponentially prior to the development of well-controlled clinical trials in the pediatric population. A number of legislative changes are intended to improve drug labeling for safe and efficacious sedation in children [84,85].

Conclusion

As the need for deep sedation and general anesthesia for children in an MRI suite continues to expand, anesthesiologists continue to be frequently requested to provide anesthesia services for these venues. The choice of agent and technique used for sedation or general anesthesia reflects the experience of the sedation provider, potential constraints imposed by the patient and procedure, availability of appropriate monitoring equipment, and institutional policies in place.

The use of traditional sedative agents such as pentobarbital and chloral hydrate has decreased due to long onset and recovery. Midazolam and ketamine are preferred as the adjunct rather than single use to counterbalance adverse events of other sedative agent. Currently, the use of propofol with high effectiveness and rapid recovery and dexmedetomidine with respiratory drive preservation have increased as the single agent for deep sedation and general anesthesia in children undergoing ambulatory MRI.

To provide the most effective, efficient, and safe sedation and anesthesia for children, the anesthesia service team should be familiar with MRI-specific safety issues and the requirements of optimal quality images for precise diagnosis before induction. Further improvements of quality and cost effectiveness with new promising drugs are also necessary.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Current aspects and prospects of glass ionomer cements for clinical dentistry

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Glass ionomer cement (GIC) is a tailor-made material that is used as a filling material in dentistry. GIC is cured by an acid-base reaction consisting of a glass filler and ionic polymers. When the glass filler and ionic polymers are mixed, ionic bonds of the material itself are formed. In addition, the extra polymer anion reacts with calcium in enamel or dentin to increase adhesion to the tooth tissue. GICs are widely used as adhesives for artificial crowns or orthodontic brackets, and are also used as tooth repair material, cavity liner, and filling materials. In this review, the current status of GIC research and development and its prospects for the future have been discussed in detail.

Keywords: Bioactive glass; Compomers; Glass ionomer cements; Hydroxyapatites; Resin-modified glass ionomer

Introduction

Glass ionomer cement (GIC), an acid-base cement, is formed by the reaction of weak polymeric acids with inorganic glass powder [1]. GIC has multiple advantages: First, it adheres specifically to the teeth to prevent corrosion or leakage. Second, there is slow release of fluoride ion over time to maintain dental health. Third, its color is very similar to that of human teeth [2,3]. Despite the advantages of GIC, further improvement is required in terms of its mechanical characteristics. In order to improve the mechanical strength of GIC, the resin-modified glass ionomer (RMGI) was developed; it has an additional monomer compared to GIC and improved mechanical strength through photopolymerization and acid-base reaction [4,5]. RMGI obtained by resin curing has improved physical properties, but the amount of the released fluoride ion, which is important in preventing dental caries, is low [4]. Studies have reported on the manufacture of GIC using macromonomer and viscosity dilution materials to exclude the effects of water and the production of a material known as a compomer [6].

Clinically, GIC is applied close to the pulp. However, it is difficult to use RMGI in deep underlined cavities. In dental clinics, either GIC or RMGI may be used, depending on the purpose. There has been a recent focus on the study of "smart" materials that confer biocompatibility and cause remineralization, while maintaining the physical properties of materials [7]. Bioactive glass (BAG), composed of NaO, SiO, PO, and CaO, is known to be used for the loss of osseous tissue; therefore, a study was conducted to increase the biocompatibility of GIC by adding BAG to GIC [3,8]. Studies have also reported an increase in biocompatibility with the addition of synthetic hydroxyapatite (HA) to the inorganic components of GIC, since HA is highly analogous to the major components of tooth enamel or dentin in terms of structure [7].

In this review, we will describe the history of the development of GIC and determine the direction that GIC research should take in the future.

Glass ionomer cement

GIC is a combination of silicate and polycarboxylate that releases fluoride and attaches to dental tissue. It is used in a variety of applications, including the filling material of dental cervical lesions; the restoration of children's teeth; the core construction of tubular fluid; and the adhesion of tooth fillings [9]. GIC was first introduced in 1972 by Wilson and Kent [10]. It consists of a water-soluble polyacrylic acid and fluoroaluminosilicate glass. When the silicate powder and polymeric liquid are mixed, an acid-base reaction takes place (Fig. 1). As metallic polymer salts begin to form, gelation begins, and continues until the cement hardens. Early GIC was considered an alternative to amalgam as tooth filling material. However, the mechanical properties of early GIC were not as advantageous as those of amalgam and required further improvement. Thus, the metal-reinforced GIC was first introduced in 1977. Williams et al. [11] described the addition of silver-amalgam alloy powder to GIC to increase the strength of the cement and provide radiopacity at the same time. However, both early GICs and metal-reinforced GICs had low viscosity, making them uncomfortable for clinical use. To overcome these issues, high viscosity GICs called viscous or condensable GICs were developed [12,13]. These materials were used in atraumatic restorative treatment in the early 1990s [14]. The developed materials are composed of fine glass particles and high molecular weight anhydrous polyacrylic acids and possess a high powder/liquid mixing ratio, resulting in fast setting time and conferring high viscosity [13,14]. The setting reaction mechanism of high viscosity GICs is the same as that of conventional GICs based on the acid-base reaction.

GICs release biologically active ions, fluoride, sodium, phosphate, and silicate that are biologically beneficial around the medium, therefore, these ions are naturally bioactive substances [15]. As more of these ions are released under acidic conditions when compared to neutral conditions, GIC can lower the pH of the surrounding medium under acidic conditions [15].

Resin-modified glass ionomer cement

RMGI is composed of resin added to the GIC. Due to resin addition, the binding strength, tensile strength, and compressive strength of the GICs are maintained and their solubility in aqueous environment is lowered, thereby improving the shortcomings of GIC [5,9]. Resin in RMGI is obtained by first putting the monomer into the liquid component of the GIC and then photo polymerization. Ultraviolet irradiation results in monomer polymerization, followed by an acid-base reaction, which improves mechanical strength (Fig. 2). Owing to this improved mechanical strength,

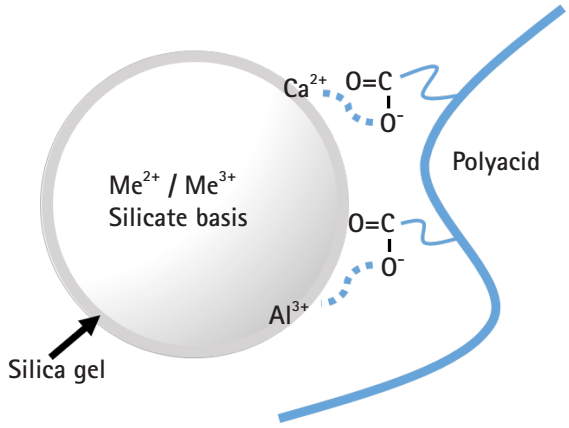

Fig. 1. Model of ionic bond formation with inorganic filler and polyacid. When calcium fluoroaluminosilicate filler and polyacid are mixed, the carboxyl ion of polyacid is ion-bonded with aluminum and calcium ion in the silicate filler.

RMGI is widely used as a dental filling material.

Earlier, Mathis and Ferracane [16] attempted to manufacture dental filling materials by mixing GIC and a composite prepared by mixing resin with commercial GIC. The resulting material did not exhibit clinically acceptable properties but it did demonstrate the possibility of combining acid-base and resin polymerization settings within a single material. RMGI, which is obtained by light curing, was developed in 1992 [5]. The basic acid-base reaction in these materials is mainly supplemented by the second resin created by light curing [5,17]. They are GICs containing a small number of monomers that can be polymerized in aqueous medium. Another method has also been reported that alters the side chain of polyalkenoic acid, but the GIC is still prepared through mechanisms based on acid-base reactions [7]. The term 'resin-modified glass ionomer' means that resins are formed, however, they retain the characteristics of glass ionomers [4]. With regard to the materials in the wider context of material science, RMGIs are all 'composite materials' as they consist of a matrix phase and a dispersed phase. The variation in the composition of commercial materials could then be considered to be continuous on a scale from purely resin-matrix produced by photo irradiation to purely salt-matrix produced by acid-base reaction [4]. One example of resin additives in RMGI is the addition of methacrylate to polyacrylic acid. In the preparation of these materials, the basic acid-base reaction is replenished by light curing. Another example of RMGI is polyacid-modified composite resins composed of macro-monomers, which are commonly used in composite resins, containing bisphenol A-glycidyl dimethacrylate (bisGMA) or urethane dimethacrylate with a small amount of acidic monomer [18,19]. They use the same ion-releasing glass as do the filler particles used in conven-

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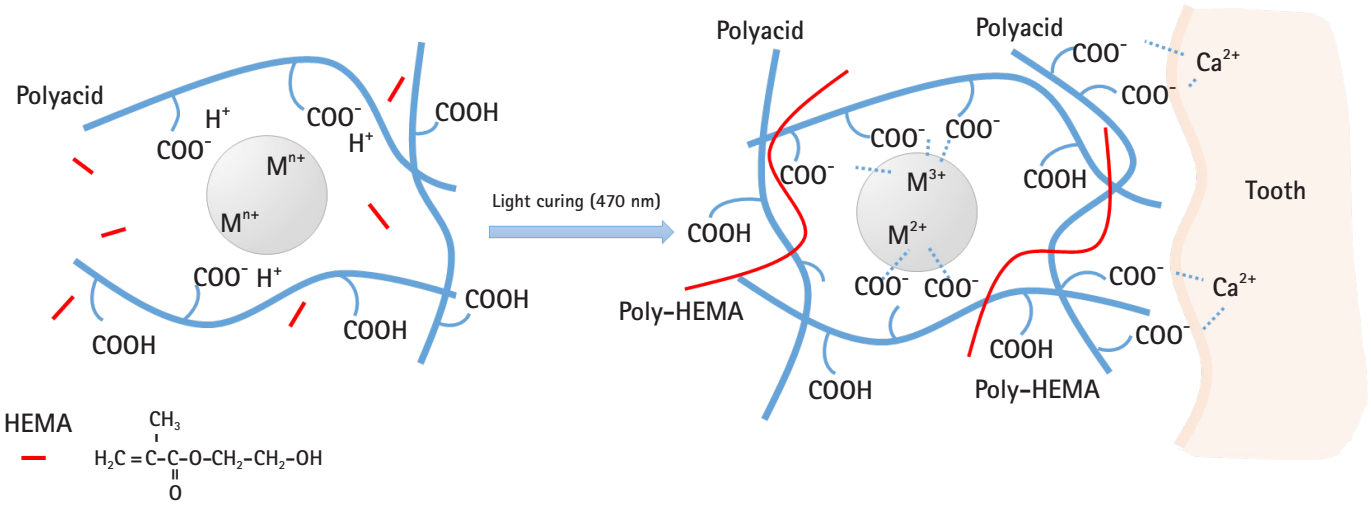

Fig. 2. Model of interaction between resin-modified glass ionomer (RMGI) and dental tissue. When the filler, polyacid, and 2-hydroxyethyl methacrylate (HEMA) are mixed and irradiated, HEMA polymerizes and becomes poly-HEMA, acting as a bridge, followed by acid-base reactions of polyacid and filler. Meanwhile, carboxyl residues in polyacid are strongly ionized with calcium present in tooth tissue, allowing RMGI to adhere to teeth.

tional GIC, however, they are small in size. The initial setting reaction is initiated by light curing, followed by an acid-base reaction after water absorption [20].

The release of fluoride from tooth filling materials is very important in terms of preventing tooth corrosion. Many researchers have reported that RMGIs can release fluoride at a rate similar to that of conventional GIC [3,20,21]. However, this release rate can be influenced not only by the formation of complex fluoride derivatives by reaction with polyacrylic acid, but also by the type and amount of the resin used for light polymerization [22-24]. Depending on the storage environment, fluoride is released from RMGI for the first 24 hours [20,25-27], then the amount of releasing fluoride decreases after 7 days, and stabilizes at 10 days to 3 weeks [20,24,28,29]. Fluoride release is affected by variables such as matrix component, filler, and fluoride content [20,30-33]. In addition, it is also affected by experimental factors such as storage environment, number and frequency of preserving solution changes, composition and pH of saliva, plaque and pellicle formation, powder-to-liquid ratio, mixing, curing time, and exposed surface [20]. Fluoride release from RMGI in artificial saliva containing esterase was proved to be higher than in artificial saliva with no enzyme [20]. Bleaching and brushing did not affect fluoride release. Removal of the outer layer of the restoration by air polishing or finishing increased fluoride release. When the surface of the restorative material was covered with an adhesive or a surface coating agent, contamination due to moisture and dehydration was prevented in the initial stage, and fluoride release was reduced by 1.4 to 4 times [20]. Mousavinasab and Meyers [34] studied the amount of fluoride released from four kinds of GIC (Fuji II LC, Fuji IX Extra, Fuji VII, and Fuji IX; GC Corporation, Tokyo, Japan), one compomer (Dyract Extra; Densply Detrey GmbH, Konstanz, Germany), and one giomer (Beautifil; Shofo Dental Corp., San Marcos, CA, USA). There was a significant difference in fluoride release depending on the type of material and time; GIC released more fluoride than the compomer and giomer. Khoroushi and Keshani [3] and Mousavinasab and Meyers [34] emphasized the role played by the amount of GIC matrix used, in releasing fluoride ion of materials.

Compared with GIC, RMGI shows improved mechanical strength but decreased biocompatibility. This is because the 2-hydroxyethyl methacrylate (HEMA) monomer escapes from RMGI mainly during the first 24 hours [2,35]. The amount of HEMA released depends on the photometric intensity of the GIC [2,35]. HEMA penetrates the dentine [2,36] and is toxic to pulp cells [2,37]. As mentioned above, the mechanical properties have been improved at the same time the working time has been reduced, but its ability to prevent cavities is relatively low owing to the low release of fluoride and its biocompatibility remains unsatisfactory because of HEMA.

Polyacid-modified composite resins (compomer)

The mechanical properties of the GIC limit its applications because it is composed of carboxylic acid groups that make the resin easily interact with water. Polyacid-modified composite resins, commonly known as compomers, are used for aesthetic materials

for oral rehabilitation, especially dental caries treatment [6,38]. This material was introduced to clinical dentists in the early 1990s [6,39] and was proposed as a new dental material that combines the existing synthetic resin aesthetics with the fluoride release and adhesion capabilities of GIC [6].

The main feature of compomers is that they do not contain water and most of the components are identical to those of composite resins. Typically, these are bulky macro-monomers, such as bis-GMA or its derivatives and/or urethane dimethacrylate, which are mixed with viscosity-reducing diluents, such as triethylene glycol dimethacrylate [6]. These polymer systems are filled with non-reactive inorganic powders, such as quartz or a silicate glass, such as $SrAlFSiO_4$ [6,40]. Powders are coated with a silane, which strengthens the bond between the filler and matrix of the set material [6,41]. The compomers also contain additional monomers that are different from those of conventional composites; therefore, they contain acidic functional groups as a very minor component. The most widely used monomer of this type is TCB, which is a di-ester of 2-HEMA with butane tetracarboxylic acid [6,40]. In addition, compomers also contain reactive glass powders similar to those used in GIC [6,38].

Compomers are designed to absorb water [6,41,42], and soaking in water can lead to a 2% to 3.5% increase in their mass [41]. It has been shown that this water absorption process involves neutralization of the carboxylic acid group. Neutralization is controlled by the rate of water diffusion and is therefore a rather slow process [42]. The mechanism through which compomers absorb water to promote neutralization is found to have a negative effect on their physical properties [43,44]. This mechanism is different from that of conventional composite resins, which are known to absorb moderate amounts of water without significant alterations to their mechanical properties [44]. Adusei et al. [45] conducted the most comprehensive study of the adverse effect of water on compomers. For all tested materials, there was no difference in the measured parameters after 24-hour storage in wet or dry conditions. However, for most materials, all strength measurements tended to decrease over a 4-week period. Not all physical parameters showed reductions with long-term storage in water. In addition, it was found that microtensile strength and surface hardness appeared to remain unaffected [46,47].

The presence of minor amounts of both acid functional monomers and basic ionomer-type glass confers new properties to the material, namely, the ability to absorb moisture to trigger an acid-base reaction that can lead to the release of fluoride and creation of an acidic environment [6]. However, some studies have shown that water uptake reduces mechanical strength by up to 40% over several weeks; therefore, these clinically desirable features income at a price [44]. Conversely, clinical studies have shown that these materials perform well in a variety of applications. The decrease in mechanical strength due to water uptake does not appear to be of clinical importance, and these materials are suitable for use *in vivo* [48,49].

A recent study on improvements in glass ionomer cement function

Several efforts have been made to enhance the properties of GIC while maintaining the bioactivity gained by releasing the ion. However, it was necessary to develop a "smart" material that can overcome the adverse effects of the resin monomer and further induce remineralization on the defective dentin. Efforts have also recently been underway to improve physical properties and biocompatibility by using both BAG and HA as fillers.

1. Glass ionomer cement containing bioactive glass

In some recent studies [18,50-53], BAG has been used with GIC to improve bioactivity and induce tooth regeneration. The use of bioactive materials has attracted attention in dentistry, particularly for the purpose of dentin remineralization. The main inorganic component of the GIC comprises Si, Al, and Ca and is ionized with polyacid, so it does not exhibit decomposition performance [10]. Meanwhile, BAG contains specific weight percentages of Si, Na, Ca, and P and was introduced by Hench in 1969 as 45S5 Bioglass with the following chemical composition and weight percentages: 45 wt% SiO_2, 24.5 wt% CaO, 24.5 wt% Na_2O, and 6.0 wt% P_2O_5. BAGs are amorphous silicate-based materials which are compatible with the human body and can stimulate new bone growth while dissolving over time [54].

In clinical situations, BAG was first used as a biomaterial to replace the loss of osseous tissues. BAG is able to bind strongly to bone via the formation of HA and firm bonding between the collagen and HA, and the body therefore tolerates the material well [3,54]. This material was initially used in the reconstruction of bone loss due to periodontal diseases in bony defects [3,54]. BAG has recently been used in the treatment of dentinal hypersensitivity; fine BAG particles are incorporated into toothpaste or applied to tooth surfaces. BAG attaches to the dentin surface and quickly forms a hydroxycarbonapatite layer, which seals the tubules and relieves pain [3].

Some researchers have studied the physical and chemical properties to evaluate the effect of BAG materials on tooth structure. There are several studies on the effect of BAG addition on the physical properties of RMGI [3,53,55,56]. Although the compressive strength of the composition is reportedly slightly reduced, it is

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much higher than that of the GIC containing BAG. Yli-Urpo et al. [50] added BAG to GIC and evaluated its physical and biological properties. They reported that the experimental composition is bioactive under physiological conditions and is capable of mineralizing human dentin *in vitro* [3,50].

Adding BAG particles to GIC decreases compressive strength and the modulus of elasticity [50,55,57]. This suggests that the BAG particles might be only loosely attached to the GIC matrix. Thus, BAG particles probably acted as fillers that had not been adhered into the GIC matrix, leading to decreased compressive strength and modulus of elasticity [50]. Therefore, the development of bioactive GICs, that does not involve a deterioration in mechanical properties, seems to be needed. Main research has been specifically focused on the application of nanoparticles to dental materials, including GICs, to improve the mechanical properties of the matrix and strengthen communication with cells derived from dental tissue to facilitate regeneration [57-61]. Several nanomaterials such as hydroxyl- (or fluoro-) apatite, titanium oxide, zirconia, and resin and combinations thereof have been incorporated into the existing GIC. One of the nanoparticles indicated for use in GIC is a BAG nanoparticle [7,62,63]. The BAG nanoparticle, combined with the matrix of GIC, increases surface area and biological activity and greatly improves mechanical/biological properties as an additive per particle weight over that of conventional micro-sized BAG particles [64,65].

2. Glass ionomer cement containing hydroxyapatite

HA has been beneficial in the field of dentistry due to its unique radiopacity and other properties [66-68]. The application of current nano-sized biomaterials is known to be potentially more useful in dentistry. They have wide applications because of greater strength, polishability, and aesthetic value than commercial modifiers [69,70]. Recent advances in the synthesis of HA [71] in various sizes and forms have enabled HA to be used as a biocompatible filler for natural tooth materials. In addition, HA showed excellent biological activity and played an important role in orthopedics because of its bone-inducing and bioactive properties [66,72].

Nanotechnology involves the use or modification of 1 to 100-nm materials [7,73-75]. Major applications of nanotechnology in dentistry include surface modification of implants [76], enhanced polymer composites with nano-sized particles [74], and caries prevention [77]. Recent research shows that the addition of nanoparticles or nanoclusters increases the mechanical strength of tooth fillers such as resin composites [78-80]. Similar attempts have been made to improve the mechanical properties of the GIC using nanotechnology [67,81]. Introduction of nano-sized apatite not only maintains the mechanical properties of the GIC at all times, but also increases the release of fluoride ions [33,67]. Studies have also reported that GIC containing nano-sized apatite has better biocompatibility than conventional GIC [82,83]. Haider et al. [83] reported that there are differences in biological properties depending on the shape of the nanoparticles incorporated into the nanofiber scaffold. In their experiment, nanorod HA showed a better biocompatibility than spherical HA. In the HA effect study on GIC, nanorod HA-fixed silicate showed better cellular compatibility than the non-fixed silicate (Fig. 3).

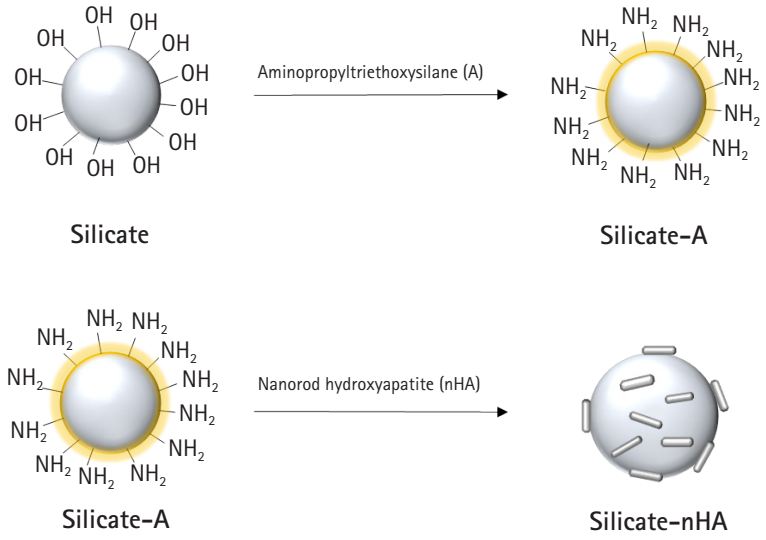

Fig. 3. A schematic diagram that binds the nanorod hydroxyapatite (nHA) to the silicate surface. Aminopropyltriethoxysilane (A) is a coupling agent used to conjugate amino groups to the glass surface. The amino acids introduced on the surface of the silicate can react with nHA fixed carboxylic acid to produce silicate-nHA.

Apatite crystals increase the crystallinity of cured matrix, further stabilizing the hardening cement and improving the bond strength with the tooth structure [74,84,85]. Increasing fluoride release can reduce secondary caries around the restoration site [73,86]. However, the possibility of interfacial failure of glass and bioceramic can be a problem that can affect the physical properties of the cured cement [87]. The crystals of nano-HA preferentially remineralize enamel [7,88,89]. Recent reports suggest that the nano-HA-modified resin composite has improved mechanical properties over the unmodified resin composite [7,90,91]. Similarly, adding nano-HA or nano-fluoroapatite to the powder content of GIC had a positive effect on compressive, tensile, and flexural strength of the cured cement [67]. Fourier-transform infrared spectroscopy showed that adding apatite to GIC powder has been found to increase the crystallinity of cured GICs, which in turn improves chemical stability and water insolubility [67,92]. This results in a better survival rate than that observed with commercialized GICs [67].

The improved mechanical properties of GIC modified by HA are due to ionic bonds of polyacrylic acid and HA crystals [92]. As a strong ionic bond is formed between the calcium ion of the tooth structure and the crystal of the apatite of the cement, the GIC containing nano-HA is expected to strongly bond to the surface of teeth (Fig. 2) [33]. In addition, reducing the particle size of HA from a micrometer scale to a nanometer scale significantly increases the surface area, and improves infiltration into dentin and enamel pores where crystals have been demineralized; this can improve bonding at the tooth-ionomer interface [93].

HA infiltered GIC, called glass carbomer, includes substances that are established by the acid-base reaction between the aqueous polymer acid and the ion leaching base glass, but they also include substances not commonly included in glass ionomer formulations [94]. As such, the bioactive component acts as a secondary filler. According to solid state nuclear magnetic resonance spectroscopy, this filler is actually HA [95] and is included to promote the formation of enamel-like substances in contact with the tooth, as previously studied with GIC used as fissure sealants.

Since glass carbomers contain a higher proportion of glass than that in conventional GIC, as well as HA fillers, the set glass carbomers are brittle. Silicone oil is added to overcome this problem [96]. It strengthens the material and remains bound by hydrogen bonding. The setting of glass carbomer involves two parallel reactions, one involving the glass plus polyacid and the other involving HA plus polyacid. Both are acid-base reactions, resulting in an ionic crosslinking polyacid matrix containing embedded filler. However, the filler is not only ion-depleted glass, but in this case also contains a partially reactive HA. Thus, the matrix is similar to that obtained using conventional GIC, except that it contains polydimethylsiloxane oil [97].

There are only preliminary studies on the clinical use of glass carbomer thus far; however, no long-term studies have been conducted for this material. Consequently, the durability of this material in the oral cavity of patients is not yet known.

Conclusion

Since the last decade, interest in the use of "smart" bioactive materials has been growing in dentistry, especially with the aim of remineralization of dentin. More predictable treatment results can be obtained with RMGI's superior handling characteristics, combined quality during final overlay restoration, and possibility of immediate restoration placement. Therefore, future studies should focus on these materials, especially on their cytotoxicity, quality of induced dentin bridges, and protocols for higher bonding strength during final restoration.

Currently, nanotechnology is used to develop nanoscale glass filler to enhance biocompatibility. Furthermore, various studies are being conducted to develop a material that brings high biocompatibility and mineral inducing potential by adding biocompatible nano-sized HA to RMGI. Irrespective of the clinical suitability of the material, clinicians will probably not select materials that are difficult to handle. Thus, a more biocompatible material based on RMGI need to be developed for extensive clinical use in future.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization, Formal analysis, Resources, Supervision, and Validation: SK; Data curation: EYP; Writing-original draft: EYP, SK; Writing-review & editing: EYP, SK.

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Clinical and histopathologic analysis of gynecological cancer: a single institute experience over 7 years

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Background: Approximately 100,000 women are diagnosed with cancer each year in Korea. According to a survey by the Korean central cancer registry in 2016, uterine cervical cancer, uterine corpus cancer, and ovarian cancer were the 5th, 7th, and 8th most prevalent cancers respectively among Korean women. The present study aims to review the clinico-pathologic characteristics of patients who were treated for major gynecological malignancies at Yeungnam University Medical Center.

Methods: Patients with invasive gynecological cancers from January 2012 to February 2019 were retrospectively identified. We analyzed the clinical features, demographic profiles, pathologic data, treatment modality used, adjuvant treatment used, complications, recurrence, and survival outcomes.

Results: A total of 287 patients (cervical cancer 115; corporal cancer 86; and ovarian, tubal, or primary peritoneal cancer 90) were included. Most cervical (82.7%) and corporal cancers (89.5%) were diagnosed in the early stages (stage I or II), while more than half (58.9%) the cases of ovarian, tubal or peritoneal cancers were diagnosed in the advanced stages (stage III or IV). Surgical complications were observed in 12.2% of cervical cancers, 16.3% of uterine corpus cancers, and 11.1% of ovarian, tubal, and peritoneal cancers, respectively. The 5-year overall survival rate was 94.1%, 91.0%, and 77.1% for cervical, corporal, and ovarian, tubal, or peritoneal cancers, respectively.

Conclusion: Surgical treatment was satisfactory in terms of the incidence of complications, and survival outcomes were generally good. Clinicians should be aware of the clinical and histopathological characteristics of patients with gynecological cancers to be able to provide optimal strategies and counseling.

Keywords: Endometrial neoplasms; Female genital neoplasms; Ovarian neoplasms; Uterine cervical neoplasms

Introduction

Cancer is a leading cause of morbidity and mortality, with approximately 14 million new cases diagnosed and 8 million cancer-related deaths worldwide in 2012 [1]. The three major gynecologic cancers are cervical, endometrial, and ovariancancer. Cervical cancer is the 4th most common malignancy in women worldwide and the disease resulted in over 300,000 deaths in 2018 [2]. High-risk subtypes of the human papilloma virus (HPV) are the cause for most cervical cancers, and HPV screening and vaccination programs are effective for disease prevention. Endometrial cancer is the most common gynecologic malignancy in developed countries, with a rising incidence. In 2012, around 320,000 new cases of endometrial cancer were diagnosed worldwide [3]. Ovarian

cancer is the common cause of gynecological cancer associated with death. One of the reasons for high mortality is late presentation in most cases. This cancer usually presents in postmenopausal women without typical symptoms. In 2018, about 295,000 new cases of ovarian cancer were diagnosed worldwide [4]. Based on the characteristics of gynecological cancers discussed above, the purpose of this study is to review the clinico-pathologic characteristics of patients with gynecological cancers treated at our hospital.

Materials and methods

We retrospectively identified patients with invasive gynecological cancers who were treated at Yeungnam University Medical Center from January 1, 2012 to February 28, 2019. This study was approved by the Institutional Review Board of the Yeungnam University Medical Center (IRB No: 2019-11-004). The disease codes used were according to the International Classification of Diseases, 10th edition, which included cervical cancer (C53), uterine corpus cancer (C54, C55), ovarian cancer (C56), tubal cancer (C57), and primary peritoneal cancer (C48). Cervical carcinoma in situ, borderline ovarian malignancy, vaginal cancer, and choriocarcinoma were excluded from the study. Patients who were transferred to other hospitals immediately after diagnosis were also excluded. Finally, 287 cases of gynecological cancer were included in this study. We analyzed the clinical features, demographic profiles, pathologic data, treatment modality used, adjuvant treatment used, complications, recurrence, progression-free survival (PFS), and overall survival (OS) of all patients. All cases were pathologically confirmed as gynecological cancer; however, a few cases of ovarian cancer were clinically diagnosed when cytological and imaging studies strongly suggested ovarian cancer. At our hospital, the baseline investigations for cervical cancer usually include serum squamous cell cancer-antigen (SCC-Ag) level, chest X-ray, cystoscopy, sigmoidoscopy, pelvic magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). For endometrial cancer, the baseline investigations include serum cancer antigen-125 (CA-125) level, chest X-ray, sigmoidoscopy, pelvic MRI, and PET-CT. For ovarian cancer, the initial work-up includes the risk of ovarian malignancy algorithm (ROMA) test, chest X-ray, gastroscopy, colonoscopy, pelvic CT, and PET-CT. The stages of cervical and corporal cancer were classified according to the International Federation of Gynecology and Obstetrics (FIGO) classification 2009, and ovarian cancer was classified according to the FIGO stage 2014.

PFS was determined from the date of diagnosis to the date of first recurrence or the date of last follow-up. OS was determined from the date of diagnosis to the date of death or the date of last follow-up. Statistical analyses were performed using the IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Survival analyses were conducted using the Kaplan-Meier method, and surviving patients were censored at the date of last follow-up.

Results

1. Cervical cancer

Demographic characteristics and clinical features of patients with cervical cancer (n = 115) are described in Table 1. The mean age at diagnosis was 53.8 years. The most common presenting symptom was vaginal bleeding, seen in 55 patients (47.8%). Forty-seven patients (40.9%) were diagnosed with cervical cancer during routine health screening. More than half of the patients (67.0%) were diagnosed at stage I, while 15.7% were diagnosed at stage II. Serum SCC-Ag test was performed in 81 patients, and 43 of them (53.1%) had abnormal results (> 1.5 ng/mL). The mean SCC-Ag level was 5.5 ng/mL at diagnosis. The most frequent histological type was squamous cell carcinoma (74.8%). Adenocarcinomas and adenosquamous carcinomas were found in 18.3% and 1.7% of the cases respectively. Fifty-two patients (45.2%) underwent only surgery while 26 patients (22.6%) received concurrent chemoradiation therapy as front-line therapy. Most patients (96.2%) treated with chemoradiotherapy received cisplatin alone. The most common surgical modality was open surgery (35 cases, 30.4%), followed by laparoscopic surgery (31 cases, 27.0%). Surgical complications occurred in 14 patients including bladder dysfunction in five patients, pelvic abscess in two patients, wound dehiscence in two patients, and deep vein thrombosis, sciatic neuropathy, vaginal vault bleeding, ureter injury and postoperative sepsis in one patient each. During the 32 months of median follow-up period, there were 17 cases with recurrence and seven deaths. Five-year PFS was 81.0%, and 5-year OS was 94.1%. Median PFS and OS were not reached. PFS and OS for each cancer site are shown in Fig. 1.

2. Uterine corpus cancer

Demographic characteristics and clinical features (n = 86) are described in Table 2. The mean age at diagnosis was 56.9 years. The most common presenting symptom was vaginal bleeding, in 66 patients (76.7%). Nine patients (10.5%) were diagnosed during routine health screening. Most cases (83.7%) were in stage I at diagnosis and 9.3% of the cases were in stage III. Mean serum CA-125 level was 59.5 U/mL at diagnosis. The most frequent histological type was endometrioid carcinoma (69.8%), followed by serous carcinomas (7.0%) and carcinosarcoma (7.0%). Leiomyo-

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Table 1. Clinical and histopathologic characteristics of the uterine cervical cancers (n=115)

Clinicopathologic characteristic	Value
Age (yr)	53.8 (31–86)
Symptom	
Vaginal bleeding	55 (47.8)
Incidentally detected on routine health screening	47 (40.9)
Abdominal pain	6 (5.2)
Vaginal discharge	5 (4.3)
Others[a]	2 (1.7)
Gravidity (no. of times)	4.0 (0–30)
Parity (no. of times)	2.3 (0–9)
Body mass index (kg/m^2)	23.2 (15–34)
History of non-gynecologic malignancy	11 (9.6)
Serum SCC-Ag at diagnosis (ng/mL)	5.5 (0.2–70)
Tumor size[b] (cm)	3.1 (0.1–21)
Synchronous primary cervical and endometrial cancers	1 (0.9)
Histology type	
Squamous cell carcinoma	86 (74.8)
Adenocarcinoma	21 (18.3)
Adenosquamous carcinoma	2 (1.7)
Others[c]	6 (5.2)
FIGO stage	
I	77 (67.0)
II	18 (15.7)
III	7 (6.1)
IV	13 (11.3)
Initial treatment	
Surgery alone	52 (45.2)
Concurrent chemoradiation	26 (22.6)
Surgery+radiotherapy	11 (9.6)
Radiotherapy alone	8 (7.0)
Surgery+concurrent chemoradiation	7 (6.1)
Surgery+adjuvant chemotherapy	4 (3.5)
Neoadjuvant chemotherapy+surgery ± any adjuvant therapy	5 (4.3)
Others	2 (1.7)
Surgical mode	
Abdominal	35 (30.4)
Laparoscopic	31 (27.0)
Robotic	4 (3.5)
Vaginal (wide conization)	12 (10.4)
Hysterectomy procedures	
Extrafascial hysterectomy	24 (20.9)
Modified radical hysterectomy	9 (7.8)
Radical hysterectomy	37 (32.2)
Pelvic lymphadenectomy	50 (43.5)
Paraaortic lymphadenectomy	21 (18.3)
Surgical complications	14 (12.2)
Recurrence or progression	17 (14.8)
Death	7 (6.1)

Values are presented as number (%) or mean (range).
SCC-Ag, serum squamous cell cancer-antigen; FIGO, International Federation of Gynecology and Obstetrics.
[a]Abdominal distension in one; headache in one case. [b]Maximal diameter of the tumor either on the initial imaging study or on the pathologic finding. [c]Mucinous carcinoma in two; diffuse large B-cell lymphoma in one; neuroendocrine carcinoma in one; adenosarcoma in one; mixed carcinoma in one case.

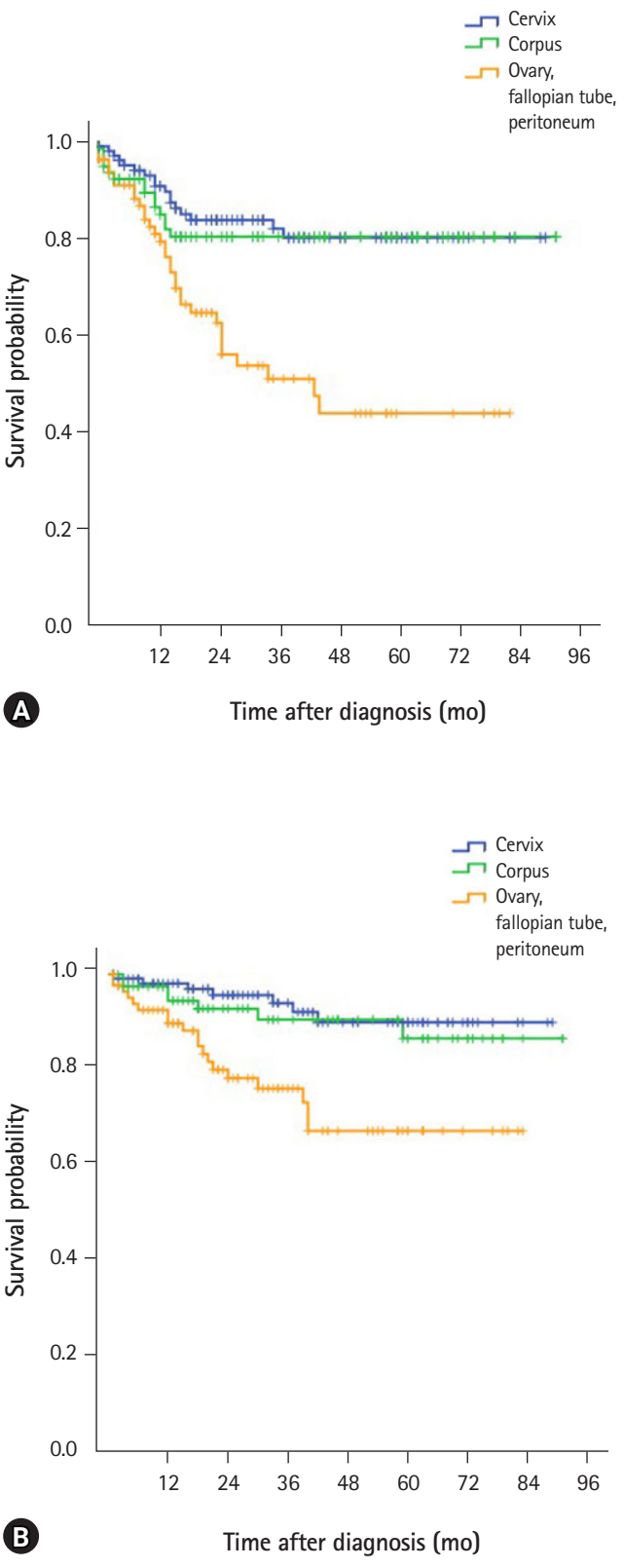

Fig. 1. Progression-free survival (A) and overall survival (B) of the patients by the cancer sites.

Table 2. Clinical and histopathologic characteristics of the uterine corpus cancers (n=86)

Clinicopathologic characteristic	Value
Age (yr)	56.9 (29–85)
Symptom	
Vaginal bleeding	66 (76.7)
Incidentally detected on routine health screening	9 (10.5)
Abdominal pain	4 (4.7)
Abdominal distension	4 (4.7)
Palpable pelvic mass	3 (3.5)
Vaginal discharge	2 (2.3)
Gravidity (no. of times)	3.7 (0–21)
Parity (no. of times)	2.1 (0–7)
Body mass index (kg/m^2)	25.3 (17.1–38.9)
History of non-gynecologic malignancy	13 (15.1)
Serum CA-125 level at diagnosis (U/mL)	59.5 (1.1–1,220)
Tumor size[a] (cm)	4.1 (0.2–20)
Synchronous primary endometrial and ovarian cancers	3 (3.5)
Histologic type	
Endometrioid carcinoma	60 (69.8)
Serous carcinoma	6 (7.0)
Carcinosarcoma	6 (7.0)
Leiomyosarcoma	4 (4.7)
Endometrial stromal sarcoma	2 (2.3)
Others[b]	8 (9.3)
Histologic grade in case of endometrioid carcinoma	
1	30 (34.9)
2	24 (27.9)
3	6 (7)
FIGO stage	
I	72 (83.7)
II	5 (5.8)
III	8 (9.3)
IV	1 (1.2)
Initial treatment	
Surgery alone	45 (52.3)
Surgery+adjuvant chemotherapy	21 (24.4)
Surgery+radiotherapy	16 (18.6)
Surgery+chemoradiation	2 (2.3)
Surgery+hormone therapy	2 (2.3)
Surgical mode	
Abdominal	45 (52.3)
Laparoscopic	36 (41.9)
Robotic	4 (4.7)
Vaginal (dilatation and curettage)	1 (1.2)
Pelvic lymphadenectomy	53 (61.6)
Paraaortic lymphadenectomy	36 (41.9)
Surgical complications	14 (16.3)
Recurrence or progression	16 (18.6)
Death	7 (8.1)

Values are presented as numbers (%) or means (range).
CA-125, cancer antigen-125; FIGO, International Federation of Gynecology and Obstetrics.
[a]Maximal diameter of the tumor either on the initial imaging study or on the pathologic finding. [b]Mixed carcinoma in four; mucinous carcinoma in two; undifferentiated carcinoma in one; Mullerian adenosarcoma in one.

sarcoma and endometrial stromal sarcoma were diagnosed in 4.7% and 2.3% of the cases respectively. Forty-five patients (52.3%) underwent only surgery. A case in stage IA underwent dilatation and curettage followed by adjuvant hormonal therapy using levonorgestrel-releasing intrauterine device for preservation of fertility. Following surgery, 21 patients (24.4%) received adjuvant chemotherapy, 16 patients (18.6%) received radiotherapy and two patients (2.3%) received adjuvant chemoradiation. Almost half of the patients (47.6%) were treated with adjuvant chemotherapy using paclitaxel and carboplatin, and the rest with cisplatin-based combined regimen. The most common surgical modality was open surgery (45 cases, 52.3%), followed by laparoscopic surgery (36 cases, 41.9%). The following surgical complications were observed: wound dehiscence in six patients, infection at the drainage site in two patients, and ureteral injury, bladder injury, vaginal wall laceration, small bowel injury, voiding difficulty and intracranial hemorrhage in one patient each. During the 28 months of median follow-up, there were 16 cases with recurrence and seven deaths. The 5-year PFS was 79.3%, and 5-year OS was 91.0%. Median PFS and OS were not reached.

3. Ovarian, tubal and primary peritoneal cancer

Pathologic characteristics and clinical features of patients with ovarian, tubal and peritoneal cancer (n=90) are described in Table 3. The mean age was 56.3 years. The predominant presenting symptoms were abdominal pain (34.4%), abdominal distension (22.2%), vaginal bleeding (12.2%), and palpable pelvic mass (10.0%). Cases of incidental diagnosis were 14.4%. Serum CA-125 test was conducted in 83 out of 90 patients, and 60 of them (72.3%) had abnormal results (>35 U/mL). The mean CA-125 level was 727.6 U/mL at diagnosis. In our hospital, Breast Cancer Susceptibility Gene (BRCA) mutation test was initiated at the department of gynecology in February 2016 on a whole blood sample using polymerase chain reaction and direct sequencing. In all, 18 patients with ovarian, tubal, or peritoneal cancer underwent the test, and 4 (22.2%) were positive: BRCA1 and BRCA2 were positive in two patients each. The site of primary cancer was ovaries in 87.8%, fallopian tubes in 3.3%, and peritoneum in 5.6%. More than half the patients (58.9%) were in the advanced stage (stage III or IV) at diagnosis. The most common epithelial histological type was serous adenocarcinoma (53.3%) while mucinous carcinoma and clear cell carcinoma were found in 10.0% each. Twenty patients (22.2%) underwent only surgery, while 54 patients (60.0%) received postoperative adjuvant chemotherapy. Ten patients (11.1%) underwent surgery after neoadjuvant chemotherapy. Paclitaxel plus carboplatin was used in 90.0% of the neoadjuvant chemotherapy regimens and cyclophosphamide plus cispla-

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Table 3. Clinical and histopathologic characteristics of the ovarian, tubal, and primary peritoneal cancers (n=90)

Clinicopathologic characteristic	Value
Age (yr)	56.3 (13–80)
Symptom	
Abdominal pain	31 (34.4)
Abdominal distension	20 (22.2)
Incidentally detected on routine health screening	13 (14.4)
Vaginal bleeding	11 (12.2)
Palpable pelvic mass	9 (10.0)
Others	7 (7.8)
Gravidity (no. of times)	2.8 (0–8)
Parity (no. of times)	1.7 (0–6)
Body mass index (kg/m^2)	22.8 (15.9–30)
History of non-gynecologic malignancy	13 (14.4)
Serum CA-125 level at diagnosis (U/mL)	727.6 (0.1–7,187.9)
Tumor size[a] (cm)	9.6 (0.5–25)
Primary cancer site	
Ovary	79 (87.8)
Synchronous primary endometrial and ovarian cancers	3 (3.3)
Fallopian tube	3 (3.3)
Peritoneum	5 (5.6)
Histologic type	
Serous	48 (53.3)
Mucinous	9 (10.0)
Clear cell	9 (10.0)
Endometrioid	8 (8.9)
Others[b]	10 (11.1)
Unknown[c]	6 (6.7)
Histologic grade in case of serous carcinoma	
Low-grade	2 (2.2)
High-grade	45 (50)
Unknown	1 (1.1)
FIGO stage	
I	33 (36.7)
II	4 (4.4)
III	34 (37.8)
IV	19 (21.1)
Initial treatment	
Surgery alone	20 (22.2)
Surgery+adjuvant chemotherapy	54 (60.0)
Neoadjuvant chemotherapy+surgery+adjuvant chemotherapy	9 (10.0)
Neoadjuvant chemotherapy+surgery	1 (1.1)
Palliative chemotherapy	5 (5.6)
Supportive care alone	1 (1.1)
Surgical mode	
Abdominal	67 (74.4)
Laparoscopic	16 (17.8)
Robotic	1 (1.1)
Fertility-sparing surgery	
Unilateral salpingo-oophorectomy	4 (4.4)
Ovarian cystectomy	1 (1.1)
Postoperative residual tumor	
Grossly none	52 (57.8)
Size < 2 cm	9 (10.0)
Size ≥ 2 cm	23 (25.6)
Pelvic lymphadenectomy	49 (54.4)
Paraaortic lymphadenectomy	43 (47.8)
Surgical complications	10 (11.1)
Recurrence or progression	34 (37.8)
Death	19 (21.1)

Values are presented as numbers (%) or means (range).
CA-125, cancer antigen-125; FIGO, International Federation of Gynecology and Obstetrics.
[a]Maximal diameter of the tumor either on the initial imaging study or on the pathologic finding. [b]Adenocarcinoma in two; immature teratoma in two; adult granulosa cell tumor in one; transitional cell carcinoma in one; small cell carcinoma in one; undifferentiated carcinoma in one; dysgerminoma in one; poorly differentiated carcinoma in one case. [c]Clinically diagnosed by both ascites cytology and imaging studies.

tin was used in the remaining 10.0%. Bevacizumab has been introduced in January 2015 in our hospital and has been used in 11 patients. The most common surgical modality was open surgery (67 cases, 74.4%), followed by laparoscopic surgery (16 cases, 17.8%). Five patients (5.5%) underwent fertility preserving surgery. The following surgical complications were observed: wound dehiscence in five patients, and bowel leak, bladder injury, deep vein thrombosis, acute kidney injury and cerebral infarction in one patient each. During the 23 months of median follow-up, there were 34 recurrences and 19 deaths. The 5-year PFS was 62.0%, and 5-year OS was 77.1%. Median PFS was 43 months (95% confidence interval, 20.5–65.5), and median OS was not reached.

Discussion

Cervical cancer is the most common gynecological cancer in developing countries while endometrial cancer is the most common gynecological cancer in developed countries. The incidence of ovarian cancer is also higher in developed countries than in developing countries. In line with this trend, the incidence of cervical cancer is gradually decreasing, while that of uterine corporal and ovarian cancers is increasing in Korea. Our data showed the over-

all clinico-pathologic results in patients who were treated for major gynecological cancers at our hospital. Limitations of the present study include its retrospective design, small sample size, and single-group analysis without comparison of data from other institutions. Nevertheless, this review of our data presents an opportunity to understand the characteristics of local population with gynecological malignancies and to evaluate the outcomes of our management.

The incidence and mortality of cervical cancer have decreased since the introduction of screening programs. Furthermore, in countries where HPV vaccination program has been introduced, a substantial decrease in the incidence of cervical cancer is expected. According to the 2015 annual report of cancer statistics in Korea, the incidence of cervical cancer was high in the age groups of 40s, 50s and 30s [5]. Similarly, our data showed that the incidence was highest with 29.6% in the 50s, followed by 21.7% in the 40s, and 17.4% in the 30s. The Surveillance, Epidemiology, and End Results (SEER) data in the United States reported the incidence of cervical cancer diagnosed in different stages as follows: 44% for localized disease, 36% for regional disease, and 15% for distant disease [6]. The incidence of different stages of cancer in our data was slightly different: 67.0% localized disease, 21.7% regional disease, and 11.3% distant disease. Such a high proportion of localized disease seems to be due to active national cervical cancer screening. Globally, squamous cell carcinoma and adenocarcinoma are the most common histological subtypes accounting for approximately 70% and 25% of all cervical cancers, respectively [2]. The histological analysis of cervical cancer patients in our hospital showed 74.8% to be squamous cell carcinoma, 18.3% adenocarcinoma, and 1.7% adenosquamous cell carcinoma, which is in line with the global trend. According to the SEER data, the 5-year survival rate was 65.5% in 2015 [6], while the 5-year survival rate in the patients in our study was 94.1%. There might be various factors related to the difference in survival rates such as ethnic, racial, sociocultural, and other demographic characteristics, as well as the national medical policy and program. In addition, a better survival rate could be partially because our study included more cases in the early stage of the disease as follows: 25 cases (21.7%) in stage IA1, 5 cases (4.3%) in IA2, 36 cases (31.3%) in stage IB1, and 11 cases (9.6%) in stage IB2. The surgical treatment appeared to be generally tolerable in terms of the incidence (12.2%) and severity of complications.

In endometrial cancer, the most common histologic type is endometrioid adenocarcinoma (80%), while the other types are mucinous carcinoma (5%), papillary serous carcinoma (3%–4%), and clear cell carcinoma (< 5%) [7]. The standard treatment for early-stage endometrial cancer is surgery including total hysterectomy and bilateral salpingo-oophorectomy. The safety and advantages of laparoscopic surgery have been proven in several randomized clinical trials [8,9]. In our data, the rate of laparoscopic surgery was quite high (41.8%). According to the SEER data, the 5-year survival rate was 81.0% in 2015, while the 5-year survival rate in the patients in our study was 91.0% [10].

BRCA 1/2 mutations are the most frequently identified genetic changes associated with ovarian cancer. It has been recently known that a BRCA 1/2 germline mutation is associated with poor prognostic factors such as early-onset cancer, serous histology, and advanced stages of cancer [11]. The incidence of BRCA 1/2 mutations has been reported to be 16.5% in the ovarian cancer patients in Korea [12]. In our data, BRCA 1/2 mutation was seen in 22.2% of the patients with ovarian cancer, which is probably due to the small sample size in the present study. In addition, clear cell carcinoma was found in a high proportion (10.0%) of ovarian cancer patients. In general, clear cell carcinoma accounts for about 5% of all ovarian cancers [13]. According to the SEER data, the 5-year survival rate was 47.8% in 2015, while the 5-year survival rate in the patients in our study was 77.1% [14]. More cases detected at an early stage might be a reason for the better survival. The distribution of various stages of cancer was as follows: localized malignancy and distant metastasis 15% and 59% respectively in the SEER data and 36.7% and 21.1% respectively in our data.

In summary, most characteristics were similar with those of the worldwide data. The survival outcomes of patients with gynecological cancer in our data were generally good. Clinicians should well be aware of the clinical and histopathological characteristics of the patients with gynecological cancer to be able to provide optimal management options.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: YJK; Data curation: SYL, EK, HSK; Formal analysis: SYL, YJK; Methodology: YJK; Project administration: DHL; Software: YJK; Supervision: YJK, DHL; Writing-original draft: SYL; Writing-review & editing: YJK.

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Improvement of catheter-related outcomes after application of tunneled cuffed hemodialysis catheter insertion without fluoroscopy

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Background: Non-tunneled catheters (NTCs) are used for hemodialysis (HD) in many centers in which fluoroscopy is not easily accessed despite high complication rates and conditions requiring long-term HD. Therefore, here we aimed to evaluate the superiority of catheter-related outcomes after the application of tunneled cuffed catheter (TCC) without fluoroscopy versus unconditioned NTC insertion.

Methods: We divided the participants into two phases: those receiving NTCs between March 2010 and February 2011 (phase I), and those receiving TCCs or NTCs between March 2011 and February 2012 (phase II). Catheter survival, nurse satisfaction, and reasons for catheter removal were analyzed.

Results: Two hundred and sixty patients in phase I and 300 patients in phase II were enrolled in this study. The success rate of TCC insertion was 99.2%. The catheter survival rate in phase I was 65.5% at 1 month, while that in phase II was 74.9% at 1 month (p=0.023). We compared catheter survival between TCCs and NTCs for all periods regardless of phase. The TCC survival rate was higher than the NTC survival rate (p<0.001). Catheter-associated problems led to catheter removal in 97 patients (26.6%) in phase I and 68 patients (18.5%) in phase II (p=0.009). Among 14 HD nurses, all reported being satisfied with manipulation during pre-/post-HD, manupulation during HD, and overall. Eleven HD nurses (78.6%) reported being satisfied with the workload.

Conclusion: Compared with unconditional NTC insertion for HD, TCC insertion without fluoroscopy improved the overall catheter survival and nurse satisfaction rates.

Keywords: Central venous catheter; Fluoroscopy; Hemodialysis; Renal dialysis

Introduction

The incidence and prevalence of end-stage renal disease (ESRD) continue to increase worldwide [1-3]. Hemodialysis (HD) is an established renal replacement therapy for patients with ESRD, and the adequate dialysis requires a vascular access, which is achieved via an arterio-venous fistula or graft for chronic HD. However, Yoon et al. [4] showed that in 83.6% of patients initiating HD a central venous catheter is used as the first way of access in Korea.

HD catheters are divided into two groups according to the presence of cuff, that is, into temporary non-tunneled catheters (NTCs) and tunneled cuffed catheters (TCCs) [5,6]. NTCs are usually inserted into a femoral vein (FV) or an internal jugular vein (IJV), whereas TCCs are usually inserted into an IJV. TCCs

are superior to NTCs in terms of infection rates, patient discomfort, and inadvertent removal [7]. In addition, the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends that an NTC should only be used in hospitalized patients and for less than 1 week [7].

Proper tip placement in TCCs is important to proper function. Fluoroscopy guidance for tip visualization would be considered mandatory for TCC insertion. However, NTCs may be inserted for HD in many centers in which fluoroscopy is not easily accessed despite high rates of complications and conditions requiring long-term HD. Therefore, we aimed to evaluate the superiority of catheter-related outcomes after the application of TCC without fluoroscopy versus unconditioned NTC insertion.

Materials and methods

1. Ethics statement

This study was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No: YUH-12-0401-052). The board waived the need for informed consent.

2. Study participants

We reviewed the medical records of Yeungnam University Medical Center in Korea to identify all adults (> 18 years) who underwent HD catheter insertion between March 2010 and February 2012. In March 2011, our center employed a nephrologist with 2 years of experience with TCC insertion. NTCs were inserted between March 2010 and February 2011, while TCCs or NTCs were inserted between March 2011 and February 2012. HD catheter type was chosen by the nephrologist. Therefore, our study was divided into two phases: phase I (March 2010 to February 2011) and phase II (March 2011 to February 2012). Phases I and II were divided according to the application of TCC without fluoroscopy. In phase I, all HD catheters were inserted by NTC. In phase II, the patients requiring HD within 1 week were inserted with NTC and patients requiring HD > 1 week were inserted with TCC without fluoroscopy. At phase I and II, NTC can be used for longer duration than 1–2 week according to clinical progress. Comparison between NTC and TCC using merged data may be associated with selection bias. Therefore, we have divided the study into two phases. NTCs and TCCs were used in the same manner during the two phases. We also compared the outcomes of NTC versus TCC without fluoroscopy regardless of phase.

3. Catheter insertion methods

TCCs were inserted as previously described [8]. All were inserted routinely in a HD unit suite at our institution by two nurses and a nephrologist with 2 years of experience. Informed consent was obtained from all patients before the procedure. Briefly, the right (or left) neck and anterior chest wall were prepped with Betadine, and electrocardiography monitoring was utilized. Under ultrasonographic guidance (SA-8000; Medison, Seoul, Korea), the targeted IJV was punctured with a 21-gauge needle; after the confirmation of good venous return, a 0.018-inch guide wire was inserted (Mini Access Kit; Merit Medical Systems Inc., South Jordan, UT, USA), and a 4F sheath was placed. A pre-packaged Seldinger-type double lumen catheter set (14.5 Fr; Covidien, Mansfield, MA, USA or 14.5 Fr; Medcomp, Harleysville, PA, USA) was used that consisted of a double lumen catheter, two vessel dilators (11 and 13 Fr), a J-tip guide wire, a 15 Fr peel-away sheath, and a tunneler. A J-tip guide wire was advanced under electrocardiogram monitoring. Two skin incisions were made (access site, exit site). A tunnel was created and the catheter was then placed into the tunnel. Serial tract dilation was then performed to accommodate the peel-away sheath. The catheter was inserted using the peel-away sheath placement technique, and catheter function was checked by saline flushes with a 5-mL B.D syringe. Finally, the catheter tip was confirmed by chest X-ray as located within the heart shadow or heading for the right atrium or ventricle. If the catheter tip did not deviate widely from the heart shadow and HD catheter's function was intact, the catheter was not repositioned. Techniques for NTC were same until it is insertion of a 4F sheath into relevant IJV or FV. A 0.038-inch guide wire was inserted and vessel dilator was inserted over the guidewire. Finally, HD catheter was inserted through the IJV (11 Fr; Medcomp) or FV (11.5 Fr; Medcomp).

4. Outcome measurements

The clinical data collected at the HD catheter insertion included age, disease underlying ESRD, sex, dialysis data, laboratory data, and HD catheter position/type, that is, NTC by the FV, NTC by IJV, or TCC by IJV. The data collected during follow-up included reasons for catheter removal classified as malfunction, infection, bleeding, neck edema, withdrawal from dialysis, death, follow-up loss, use of another access method (conversion from catheter to arterio-venous fistula, graft, or peritoneal dialysis), self-removal, and kidney transplantation. Malfunction, infection, bleeding, and neck edema were classified as catheter-associated problems. Catheter malfunction was defined as a negative pressure less than −250 mmHg at a blood flow rate < 300 mL/min or frequent pressure alarm during the HD session for adequate dialysis [7]. A catheter infection was diagnosed if pus, redness, induration, or tenderness was noted within 2 cm around the catheter exit site or along the

catheter tunnel. A catheter infection also was diagnosed if catheter-related bacteremia was suspected. Bleeding was diagnosed if the exit or puncture site was oozing and treatment beyond a dressing change was needed. Neck edema was diagnosed if neck edema related to the catheter was suspected after the exclusion of other causes. In cases of catheter malfunction or infectious complications, the catheter was removed when the problems were not resolved by catheter manipulation or antibiotics. Technical success was defined as no procedure-associated complications with the catheter from venipuncture to HD initiation. Catheter survival was defined as the time that elapsed between catheter insertion and removal. Causes of catheter removal, excluding catheter-associated problems, were analyzed as censored data. Dialysis and laboratory data were reviewed at the time of HD initiation, and dialysis was specified as HD or continuous renal replacement therapy. Laboratory data included hemoglobin (g/dL), platelet count (K/mm^3), calcium (mg/dL), phosphorus (mg/dL), aspartate aminotransferase (AST; IU/L), alanine aminotransferase (ALT; IU/L), blood urea nitrogen (BUN; mg/dL), creatinine (mg/dL), sodium (mEq/L), and potassium (mEq/L).

For all 14 HD nurses who participated in both phases, satisfaction with TCC was assessed by four questions about manipulation during pre-/post-HD, manipulation during HD, workload, and total satisfaction. All 14 nurses responded very satisfied, satisfied, no change, dissatisfied, or very dissatisfied.

5. Statistical analysis

Continuous values are reported as mean ± standard deviation and were compared using the *t*-test. Categorical variables are reported as count and percentage, and were compared using Pearson chi-square test or Fisher exact test. Kaplan-Meier analyses were used to identify the intergroup differences in survival. The *p*-values used for survival curve comparisons were calculated using the log-rank test. We performed Cox regression analyses of hazard ratio (95% confidence interval) for survival. Values of $p < 0.05$ were considered statistically significant.

Results

Two hundred and sixty patients in phase I and 300 patients in phase II were enrolled in this study (Table 1). Sex and age did not differ significantly between groups. There were no significant intergroup differences in dialysis modality, hemoglobin, platelet count, calcium, phosphorus, AST, ALT, BUN, creatinine, or potassium level. Serum sodium levels were higher in phase II than in phase I. A total of 364 HD catheters were inserted in phase I ver-

Table 1. Baseline characteristics

Variable	Phase I	Phase II	*p*-value[a]
No. of patients	260	300	-
Underlying disease of ESRD (DM)	123 (47.3)	144 (48.0)	0.870
No. of catheterizations	364	367	-
Age (yr)	64.0 ± 15.5	63.8 ± 14.3	0.837
Male sex	143 (55.0)	177 (59.0)	0.340
Hemoglobin (g/dL)	9.6 ± 1.8	9.8 ± 1.9	0.216
Platelet (K/mm^3)	206 ± 131	198 ± 126	0.473
Calcium (mg/dL)	7.7 ± 1.2	7.5 ± 1.0	0.297
Phosphorus (mg/dL)	5.1 ± 2.3	5.3 ± 1.9	0.453
Aspartate aminotransferase (IU/L)	215 ± 817	200 ± 496	0.829
Alanine aminotransferase (IU/L)	102 ± 317	103 ± 252	0.987
Blood urea nitrogen (mg/dL)	69.7 ± 39.0	65.0 ± 39.6	0.186
Creatinine (mg/dL)	6.0 ± 3.8	5.8 ± 3.8	0.589
Sodium (mEq/L)	135.2 ± 6.4	136.9 ± 6.7	0.002
Potassium (mEq/L)	4.4 ± 1.0	4.2 ± 0.9	0.206
Continuous renal replacement therapy	41 (15.8)	46 (15.3)	0.887
Type of hemodialysis catheter			< 0.001
Non-TCC (FV)	176 (48.4)	171 (46.6)	
Non-TCC (IJV)	188 (51.6)	76 (20.7)	
TCC (IJV)	0	120 (32.7)	

Values are presented as mean±standard deviation or number (%).
ESRD, end-stage renal disease; DM, diabetes mellitus; TCC, tunneled cuffed catheter; FV, femoral vein; IJV, internal jugular vein.
[a]Statistical significances were determined using the t-test for continuous variables and Pearson chi-square test for categorical variables.

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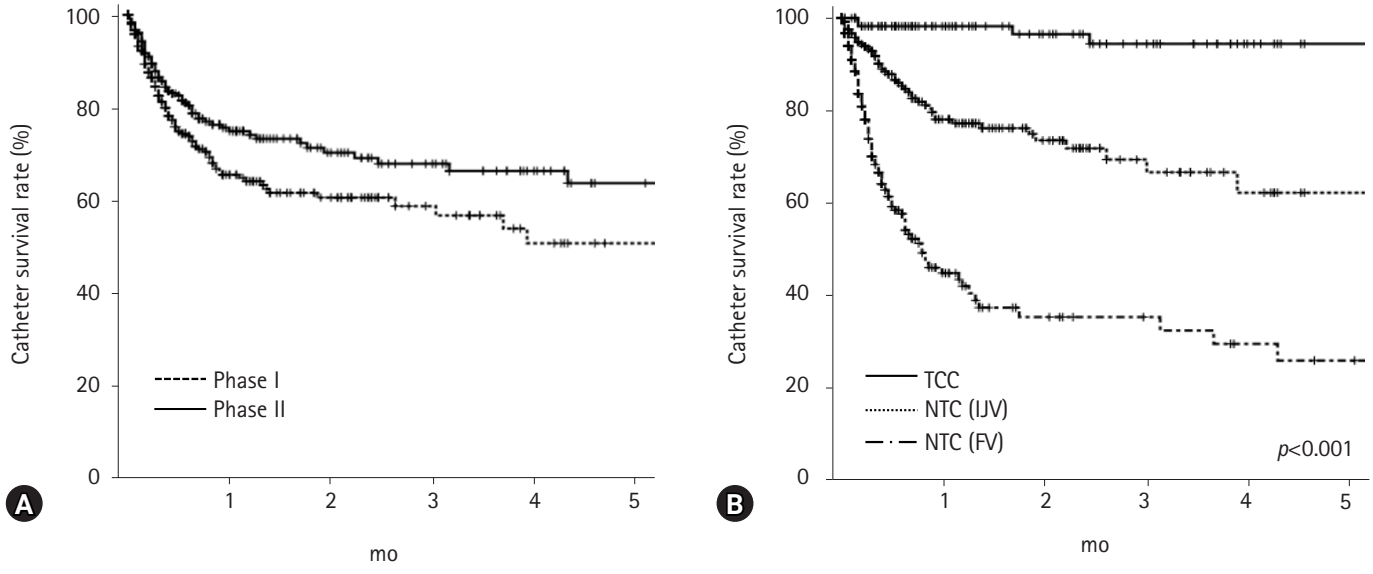
sus 367 in phase II. Of them, 120 TCCs were inserted during phase II (32.7%). The TCC insertion success rate was 99.2%. One complication occurred during TCC insertion due to J-tip guidewire entrapment within the heart. This case was described in a previous paper [9].

The catheter survival rate during phase I was 65.5% at 1 month and 50.7% at 5 months, while that during phase II was 74.9% at 1 month and 63.7% at 5 months (Fig. 1). Thus, the catheter survival rate during phase II was significantly higher than that during phase I ($p=0.023$). Furthermore, TCC survival was significantly greater than NTC survival ($p<0.001$).

Change in access was the most common cause of catheter removal in both phases (24.5% in phase I, 24.8% in phase II). However, the catheter removal rate for a catheter-associated problem was greater in phase I (26.6% in phase I, 18.5% in phase II; $p=0.009$). The intervals from insertion to event in phases I and II were 33.4±74.6 and 34.9±58.4 days, respectively ($p=0.758$). More specifically, in phase I, the removal rate for a catheter-associated problem was 33.0% for NTC by FV and 20.7% for NTC by IJV ($p=0.008$). In phase II, the corresponding rates were 31.0% for NTC by FV, 14.5% for NTC by IJV, and 3.3% for TCC ($p<0.001$). Catheters were removed due to patient death in phases I and II in 62 patients (17.0%) and 80 (21.8%), respectively ($p=0.103$). Catheters were removed due to non-catheter-associated problems and catheter-associated problems in 267 patients (73.4%) and 97 patients (26.6%) in phase I and in 299 (81.5%) and 68 (18.5%) in phase II, respectively ($p=0.009$). Catheter removal rates by catheter-associated problems were lower in phase II than in phase I. Fig. 2 shows the specific causes of catheter removal.

We also analyzed the outcomes according to catheter type regardless of phase (Fig. 3). The catheter survival rate was highest for TCC, while that for NTC (IJV) was higher than that for NTC (FV). There was no significant difference in catheter survival of the same catheter type between phases I and II. The number of catheters removed due to catheter-associated problems were 4 (3.3%), 39 (20.7%), 11 (14.5%), 58 (33.0%), and 53 (31.0%) for TCC, NTC (IJV) in phase I, NTC (IJV) in phase II, NTC (FV) in phase I, and NTC (FV) in phase II, respectively ($p<0.001$). The proportion of removals due to catheter-associated problems for each catheter decreased after the application of TCC without fluoroscopy.



Catheter at risk

Phase I	364	96	57	28	15	9
Phase II	367	107	65	47	30	18

Catheter at risk

TCC	120	70	52	38	24	15
NTC (IJV)	264	95	53	24	13	6
NTC (FV)	347	37	16	12	7	5

Fig. 1. Catheter survival rate. (A) Plot by application of TCC (phase I, 65.5% at 1 month and 50.7% at 5 months; phase II, 74.9% at 1 month and 63.7% at 5 months). (B) Plot according to HD catheter type (NTC [FV], 44.7% at 1 month and 25.6% at 5 months; NTC [IJV], 77.6% at 1 month and 61.7% at 5 months; TCC, 98.2% at 1 month and 94.4% at 5 months). TCC, tunneled cuffed catheter; HD, hemodialysis; NTC, non-tunneled catheter; FV, femoral vein; IJV, internal jugular vein.

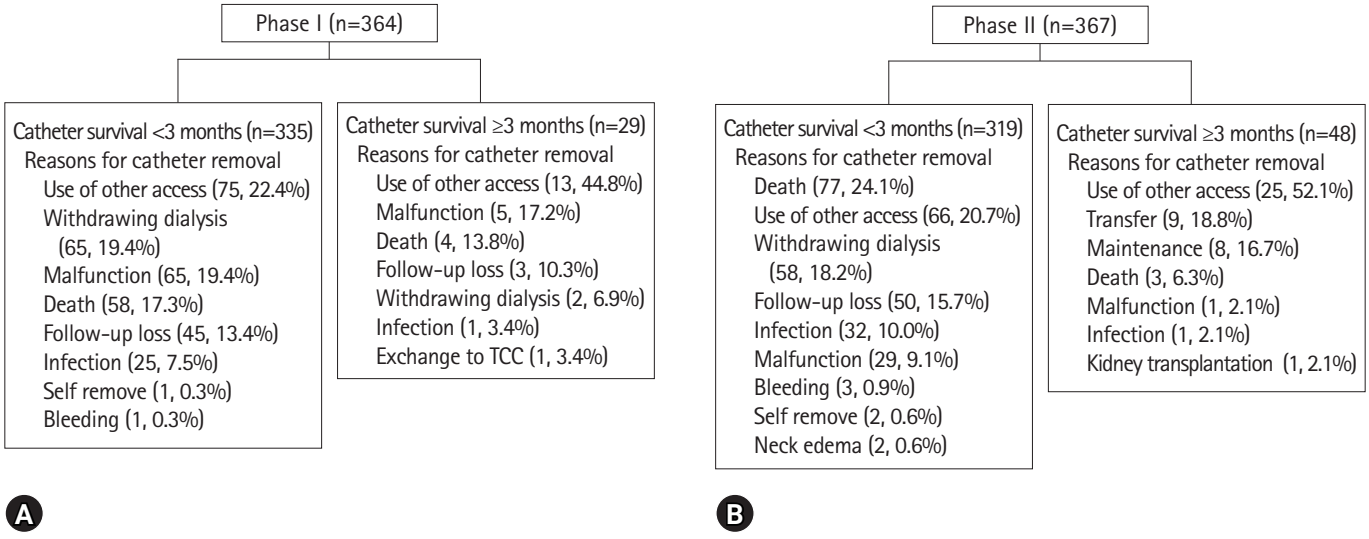


Fig. 2. Study population and reasons of catheter removal by study period and catheter survival at 3 months after catheter insertion in (A) phase I, (B) phase II. TCC, tunneled cuffed catheter.

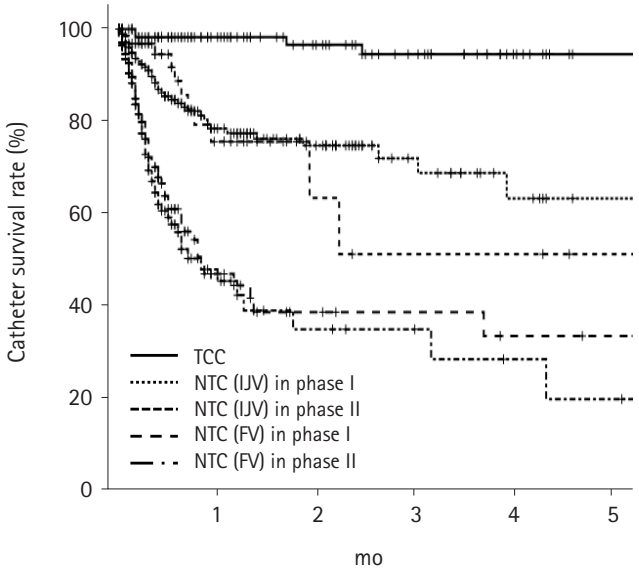


Fig. 3. Catheter survival rates at 5 months for TCC, NTC (IJV) in phase I, NTC (IJV) in phase II, NTC (FV) in phase I, and NTC (FV) in phase II were 94.4%, 62.4%, 50.0%, 31.8%, and 17.8%, respectively. $p<0.001$ for TCC vs. the other catheters, NTC (IJV) in phase I or II vs. NTC (FV) in phase I or II, $p=0.975$ between NTC (IJV) in two phases, and $p=0.494$ between NTC (FV) in phases I and II. TCC, tunneled cuffed catheter; NTC, non-tunneled catheter; IJV, internal jugular vein; FV, femoral vein.

Cox regression analysis, adjusted for diabetes, serum sodium, and old age (>65 years), showed a hazard ratio for catheter survival in phase II of 0.55 (95% confidence interval, 0.37–0.79; $p=0.002$) (Table 2). We performed subgroup analyses of age, sex, and diabetes. For elderly, male, or non-diabetic patients, there was a significantly lower risk of catheter removal due to catheter-associated problems in phase II than in phase I (Table 3). We also performed Cox regression analyses for subgroup (Table 4). The multivariate analysis was adjusted for diabetes mellitus, sex, serum sodium level, and phase for the age subgroup; for age, sex, serum sodium level, and phase for the diabetes mellitus subgroup; and for age, diabetes mellitus, serum sodium level, and phase for the sex subgroup. Elderly, diabetics, or male patients showed significantly greater overall catheter survival in phase II than in phase I. The other results showed similar trends, but statistical significance was not observed.

Among the 14 HD nurses, all reported being satisfied with the manipulation during pre-/post-HD, manipulation during HD, and overall. Eleven HD nurses (78.6%) reported being satisfied with the workload.

Discussion

Our study showed that the rate of catheter removal due to catheter-associated problems was lower in phase II than in phase I. The both univariate and multivariate analyses showed that the overall catheter survival rate was higher in phase II than in phase I. For elderly, male, or non-diabetic patients, there was a significant lower risk of catheter removal due to catheter-associated problems in phase II than in phase I. For younger, female, or diabetic patients, similar trends were shown, but no statistical significance was observed. For elderly, male, or diabetic patients, catheter survival

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Table 2. Cox regression analyses by variables

Variable	Unadjusted		Adjusted	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (ref: ≤ 65 yr)	1.30 (0.96–1.77)	0.096	1.03 (0.71–1.47)	0.895
Comorbidity (ref: non-DM)	1.31 (0.96–1.79)	0.085	1.28 (0.88–1.85)	0.199
Serum sodium (increase 1 unit)	1.00 (0.97–1.03)	0.872	1.00 (0.97–1.03)	0.979
Phase II (ref: phase I)	0.70 (0.51–0.96)	0.024	0.55 (0.37–0.79)	0.002

The multivariate analysis was adjusted for age, DM, serum sodium level, and phase.
HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

Table 3. Removal due to catheter-associated problems according to subgroup of age, sex, or diabetes mellitus

Variable	Phase I (n = 97)	Phase II (n = 68)	*p*-value[a]
Age < 65 yr	41 (17.6)	30 (17.6)	0.120
Age ≥ 65 yr	56 (28.6)	38 (19.3)	0.033
Male sex	56 (27.9)	37 (17.1)	0.008
Female sex	41 (25.2)	31 (20.7)	0.346
Non-diabetes mellitus	57 (28.8)	38 (20.1)	0.047
Diabetes mellitus	40 (24.1)	30 (16.9)	0.095

Values are presented as number (%).
[a]Significant differences between phases were determined using Pearson chi-square test.

Table 4. Cox regression analyses of subgroup of age, sex, or diabetes mellitus

Variable	Unadjusted		Adjusted	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age < 65 yr				
Sex (ref: male)	1.26 (0.77–1.95)	0.392	1.23 (0.72–2.11)	0.443
Comorbidity (ref: non-DM)	1.81 (1.13–2.91)	0.014	1.73 (1.02–2.93)	0.043
Serum sodium (increase 1 unit)	1.00 (0.96–1.04)	0.911	1.00 (0.96–1.05)	0.927
Phase II (ref: phase I)	0.71 (0.44–1.13)	0.144	0.65 (0.37–1.12)	0.122
Age ≥ 65 yr				
Sex (ref: male)	0.84 (0.55–1.27)	0.402	1.00 (0.59–1.68)	0.998
Comorbidity (ref: non-DM)	1.01 (0.67–1.53)	0.947	0.96 (0.57–1.62)	0.885
Serum sodium (increase 1 unit)	1.00 (0.96–1.03)	0.863	1.00 (0.97–1.04)	0.922
Phase II (ref: phase I)	0.70 (0.46–1.07)	0.097	0.49 (0.29–0.83)	0.008
Male sex				
Age (ref: ≤ 65 yr)	1.53 (1.01–2.31)	0.044	1.02 (0.63–1.66)	0.938
Comorbidity (ref: non-DM)	1.54 (1.01–2.34)	0.044	1.43 (0.86–2.37)	0.167
Serum sodium (increase 1 unit)	0.99 (0.95–1.02)	0.460	0.99 (0.95–1.02)	0.525
Phase II (ref: phase I)	0.58 (0.38–0.88)	0.011	0.47 (0.28–0.78)	0.003
Female sex				
Age (ref: ≤ 65 yr)	1.05 (0.66–1.68)	0.830	0.84 (0.47–1.49)	0.551
Comorbidity (ref: non-DM)	1.06 (0.67–1.69)	0.799	1.12 (0.64–1.94)	0.701
Serum sodium (increase 1 unit)	1.01 (0.97–1.06)	0.567	1.02 (0.97–1.06)	0.476
Phase II (ref: phase I)	0.88 (0.55–1.41)	0.594	0.72 (0.40–1.30)	0.273
Non-DM				
Sex (ref: male)	0.85 (0.56–1.29)	0.452	0.95 (0.59–1.56)	0.850
Age (ref: ≤ 65 yr)	0.98 (0.65–1.47)	0.916	0.76 (0.48–1.23)	0.268
Serum sodium (increase 1 unit)	0.98 (0.95–1.02)	0.346	0.99 (0.95–1.02)	0.508
Phase II (ref: phase I)	0.83 (0.55–1.25)	0.369	0.68 (0.41–1.11)	0.125
DM				
Sex (ref: male)	1.26 (0.79–2.02)	0.332	1.24 (0.71–2.19)	0.450
Age (ref: ≤ 65 yr)	1.79 (1.11–2.89)	0.017	1.44 (0.82–2.52)	0.207
Serum sodium (increase 1 unit)	1.02 (0.98–1.07)	0.406	1.03 (0.98–1.08)	0.241
Phase II (ref: phase I)	0.60 (0.37–0.96)	0.033	0.42 (0.23–0.75)	0.003

The multivariate analysis was adjusted for DM, sex, serum sodium level, and phase for the age subgroup; for age, sex, serum sodium level, and phase for the DM subgroup; and for age, DM, serum sodium level, and phase for the sex subgroup.
HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

rates were higher in phase II than in phase I. For younger, female, or non-diabetic patients, catheter survival was favorable in phase II, but statistical significance was not observed. Nurse satisfaction rates were higher in phase II than in phase I.

Fluoroscopy is not always available at HD centers because it is expensive and requires materials to protect staff from radiation exposure. TCCs have been inserted in many centers by interventional radiologists familiar with fluoroscopy. TCCs are now being inserted by interventional nephrologists who can perform the procedures necessary for access management. We wanted to evaluate the superiority of TCC without fluoroscopy versus unconditioned NTC, even when fluoroscopy was not available. Catheter outcomes of TCC are undoubtedly better than those of NTC. Oliver reviewed HD catheter infections and showed a higher risk in NTC versus TCC [10]. Wang et al. [11] investigated 865 dialysis patients and demonstrated a 3.49 odds ratio for catheter dysfunction in NTC versus TCC on multivariate analysis. Mendu et al. [12] showed that TCC had improved dialysis delivery and lower mechanical complication rates than NTC. In our study, 4 (3.3%) and 161 (26.4%) TCC and NTC catheters were removed due to catheter-associated problems, respectively ($p < 0.001$). However, NTC may be used for HD in many centers in which fluoroscopy is not easily accessed despite high complication rates of NTC and conditions requiring long-term HD.

In our hospital, all patients requiring HD were inserted using NTC regardless of the needs for long-term catheterization during phase I. In phase II, although fluoroscopy was not available, we try to use TCCs for patients requiring relatively long-term HD. The success rate of TCC insertion without fluoroscopy was high and only one immediate catheter insertion-related complication was observed. In addition, TCC insertion without fluoroscopy significantly improved the rates of overall catheter survival and catheter removal due to catheter-associated problems. Fluoroscopy is usually used to identify catheter tip position and prevent arterial catheter insertion or puncture. A previous study compared TCC insertion with or without fluoroscopy and found that TCC insertion without fluoroscopy was associated with reduced immediate success rate [13]. However, our study showed favorable results for TCC insertion with versus without fluoroscopy and that the application of TCC without fluoroscopy improved overall catheter survival, catheter-associated complication, and nurse satisfaction rates versus unconditioned NTC insertion.

The KDOQI guideline recommends that TCC be used in patients requiring dialysis for longer than a week and that TCCs should be inserted in centers in which ultrasonography and fluoroscopy are available [7]. However, most patients requiring emergent HD cannot be withdrawn from HD within 1 week therefore, most HD catheters used for emergent HD are a TCCs. A study using a NTC showed that the mean dialysis session was 11.3 ± 6.8 and catheters were left in place for a mean 19.5 ± 15.3 days [14]. Beathard et al. [15] reported 1,765 cases of TCC placement and 2,262 of TCC exchange. The success rates were 98.24% and 98.36%, respectively, and the complication rates were 1.42% and 1.41%, respectively. Motta Elias et al. [16] reported their single-center experiences with 130 catheter exchanges from NTC to TCC without fluoroscopy. In their study, the catheter survival rate was 68.0% at 120 days and the catheter removal rate for a catheter-associated problem was 37%. However, although this previous study was prospective, it involved a single arm and only catheter exchange from NTC to TCC. Furthermore, catheter survival was lower in the in this previous study than in the present study. In the present study, the study period were divided into two phases and the TCC survival rate at 5 months was 94.4%.

This study is limited by its retrospective and single-center nature. Furthermore, we could not evaluate complications during HD regardless of catheter removal. In addition, all TCCs were inserted by a nephrologist, as practitioner skill can obviously affect complication rates. Therefore, we suggest the need for a larger prospective multi-center study.

In summary, our study showed that TCC insertion without fluoroscopy can be performed with high success rates. Compared with unconditional NTC insertion for HD, the application of TCC insertion without fluoroscopy improved the overall catheter survival and nurse satisfaction rates. Although fluoroscopy was not accessible, TCC insertion without fluoroscopy would help improve catheter-related outcomes.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: SHK, JYD; Data curation, formal analysis, and funding acquisition: SHK; Investigation, methodology, software and supervision: JYD; Writing-original draft: SHK; Writing-review & editing: JYD.

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Polyunsaturated fatty acids, lung function, and health-related quality of life in patients with chronic obstructive pulmonary disease

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Background: Dietary polyunsaturated fatty acids (PUFA) are thought to modify systemic inflammation. The present study aimed to evaluate the relationship between PUFA intake, lung function, and health-related quality of life (HRQoL) in patients with chronic obstructive pulmonary disease (COPD).

Methods: In this study, we used the dataset of 6th Korea National Health and Nutrition Examination Survey, in which, a total of 22,948 individuals including 573 participants with a high probability of developing COPD were enrolled. Participants with missing data for the investigated variables were excluded. Linear regression analyses were used to evaluate the association between PUFA intake (omega-3 [N3], omega-6 [N6], and total) with lung function, and HRQoL. HRQoL was determined according to the European Quality of Life-5 Dimensions (EQ-5D). Subgroup analysis of older patients was performed. Age, sex, body mass index, smoking, alcohol, education, residence, total calorie intake, and predicted FEV_1% were adjusted in all analyses.

Results: Although lung function was not associated with PUFA intake, EQ-5D index was remarkably associated with N3, N6, and total PUFA intake in a dose-dependent manner. This association was more pronounced in elderly COPD patients. Mean levels of N3, N6, and total PUFA intake were significantly higher in patients having better HRQoL with respect to mobility, self-care, and usual activities.

Conclusion: Our results suggest that N3, N6, and total PUFA intake are associated with HRQoL in COPD patients. This association may be attributed to mobility, self-care, and usual activities. Further longitudinal study is required to clarify this relationship.

Keywords: Chronic obstructive pulmonary disease; Korea National Health and Nutrition Examination Survey; Polyunsaturated fatty acid; Quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable inflammatory disease characterized by persistent respiratory symptoms and airflow limitation measured by spirometry [1]. The disease burden of COPD is steadily increasing, not only in western countries but also in Asian countries [2]. Since COPD requires constant management, it imposes substantial social, economic, and medical burdens. For example, a recent multicenter observational study in Korea showed that 1,245.6 million

US dollars were required to provide COPD-related direct and indirect medical services [3].

The pathogenesis of COPD involves airway and systemic inflammatory response [4]. Individuals exposed to noxious particles may develop airway inflammation with loss of terminal and transitional bronchioles, emphysematous destruction, and lung function declines [5]. Systemic inflammation is associated with poor clinical outcome. For instance, Agusti et al. [6] evaluated systemic inflammatory biomarkers in peripheral blood and showed that the increased inflammatory reaction in COPD patients is associated with increased all-cause mortality and exacerbation frequency. Patients with severe disease have an elevated inflammatory burden, as they usually experience more rapid decline in lung function, increase in severity of symptoms, and frequent exacerbations [7]. Therefore, it is important to alleviate inflammatory response not only in the airway, but also in the circulatory system.

Polyunsaturated fatty acids (PUFA) play a role in modifying inflammation [8]. For example, a study involving 80 patients with COPD, who received 9 g of PUFA or placebo for 8 weeks, demonstrated improvement in exercise capacity [9]. Although recent data from a study on US adults with COPD showed that omega-3 (N3) PUFA was associated with respiratory symptoms [10], this association was not investigated among Korean COPD patients.

In this context, the present study aimed to evaluate the association between dietary PUFA, including total, N3, omega-6 (N6) PUFA, and disease severity as well as the HRQoL in patients with COPD using data from a nationwide representative sample survey.

Material and methods

1. Ethics statatement

The survey protocol of the Korea National Health and Nutrition Examination Survey (KNHANES) was approved by the Institutional Review Board of the KCDC (IRB No: 2013-07CON-03-4C in 2013, 2013-12EXP-03-5C in 2014). Since the KNHANES of 2015 was conducted for public welfare, approval of the IRB was not required. Written informed consent was obtained from all participants before the survey, which was conducted according to the Declaration of Helsinki. All procedures were in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies.

2. Study participants

The present study used the dataset of the 6th (2013–2015) KNHANES. The KNHANES is an annually conducted nationwide population-based cross-sectional survey by the Korea Centers for Disease Control and Prevention (KCDC) and the Korean Ministry of Health and Welfare. The KNHANES was designed as a complex sample survey using a multistage sampling method to represent the general non-institutionalized Korean population. The dataset of the KNHANES is freely accessible online, and detailed survey profiles are described in a previous report [11].

The 2013–2015 KNHANES assessed the health and nutritional status of 29,321 South Koreans, and 22,948 responded to the survey (response rate 78.3%). The KNHANES collected health-related and nutritional information by evaluating laboratory samples, physical examinations, face-to-face interviews, and nutritional consumption. Pulmonary function testing (PFT) was performed in participants aged over 40 years; thus, 10,109 participants without PFT results were excluded. Participants with missing values in other variables (i.e., residential area, education level, smoking status, alcohol consumption, body mass index [BMI], and European Quality of Life-5 Dimensions [EQ-5D], and nutrition intake) were excluded (n = 6,408). Participants diagnosed as asthma by their physician or having medication for asthma were excluded (n = 112). Participants with the value of forced expiratory volume in 1 second (FEV_1) divided by forced vital capacity (FVC) above 70% were excluded, due to the low probability of having COPD (n = 5,746). Finally, 573 participants with a high probability of having COPD without missing values in the possible confounding variables were included in the analysis. The study flow chart is presented in Fig. 1.

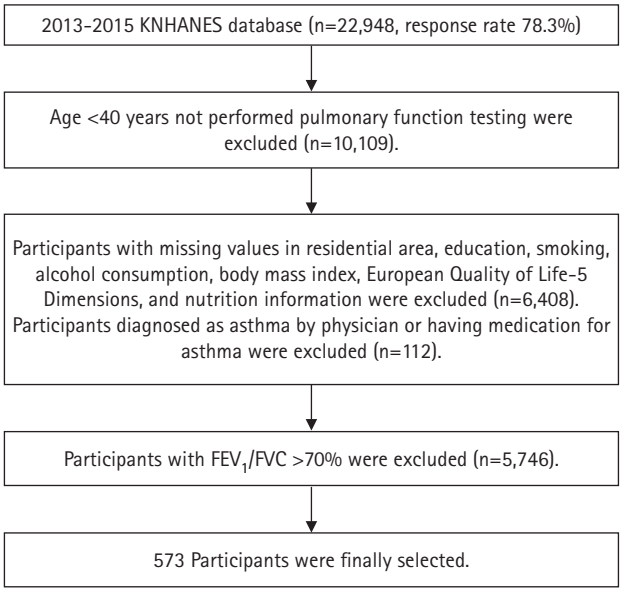

Fig. 1. Flow chart of the study using the dataset of the 6th Korea National Health and Nutrition Examination Survey (KNHANES). FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

3. Data collection and measurements

PFT was performed using dry rolling seal spirometers (Model 2130; SensorMedics, Yorba Linda, CA, USA) by highly-trained medical technicians. The quality control of the PFT was conducted according to the standardization guidelines of the American Thoracic Society and the European Respiratory Society [12]. Participants with $FEV_1/FVC < 70\%$ were considered to have COPD based on the classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report. Indices of lung function in participants with COPD included FEV_1 (L), predicted FEV_1%, FVC (L), predicted FVC%, FEV_1/FVC%, and peak expiratory flow (PEF, L/sec).

Smoking status was categorized into three groups (current, former, and never) based on the Centers for Disease Control and Prevention classification [13]. Current smokers were defined as participants who smoked more than 100 cigarettes in his/her lifetime and smoke currently. Former smokers were defined as participants who smoked more than 100 cigarettes in his/her lifetime; however, had stopped smoking for more than 1 year. Participants who never smoked were defined as participants who never smoked or smoked less than 100 cigarettes in his/her lifetime.

The EQ-5D was used to evaluate the HRQoL in participants with COPD. The validity and usefulness of the EQ-5D for measuring the quality of life in COPD patients have been demonstrated previously [14]. The EQ-5D consists of five dimensions to measure the quality of life: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The participants were asked to select one of the three following responses for each of the five dimensions: G1, no problem; G2, some problems; G3, severe problems. Furthermore, the EQ-5D index was used to evaluate the dose-dependent relationship between PUFA intake and HRQoL. The formula for the EQ-5D index has been described in a previous report by Nam et al. [15], with higher scores indicating higher HRQoL.

Dietary PUFA intake was measured using a 24-hour recall method. The 24-hour recall method is a structured interview for estimating the intake of food or drink that an individual participant consumed during the day. Although the method can have a day-to-day variability, the reliability, validity, and reproducibility have been previously demonstrated [16]. The amounts of dietary N3 PUFA (g/day), N6 PUFA (g/day), and total PUFA (g/day) were measured.

Data regarding socio-economic status and anthropometric indices were measured by trained survey assistants. Residential areas were categorized into two groups: urban and rural. Educational level was categorized into three groups: middle school or less, high school, and college or more. Heavy alcohol consumption was defined as ≥ 7 drinks in men and ≥ 5 drinks in women on an occasion. The participants were categorized into two groups: whether they consumed more than one heavy alcohol drink in a week, or not. BMI was categorized based on the Korean Society for the Study of Obesity guidelines [17]: underweight (< 18.5 kg/m^2), normal (18.5–22.9 kg/m^2), pre-obese (23–24.9 kg/m^2), and obese (≥ 25 kg/m^2).

4. Statistical analysis

Since the KNHANES was conducted using a complex, multistage, stratified, and probability verified sample design, all statistical analyses were performed under complex sample analyses, and sampling weights were applied. The sample, therefore, represents the non-institutionalized South Korean population.

Continuous variables (age and spirometric values) were compared using the ANOVA test and presented as a mean value with a standardized error. Categorical variables (residence, education, smoking status, alcohol consumption, and BMI) were compared using a chi-square test and presented as percentages with standard errors. Post-hoc analysis was performed with Bonferroni correction, and $p < 0.017$ was considered statistically significant between groups.

HRQoL was categorized into five dimensions according to the EQ-5D as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The mean estimated level and standard error of PUFA intake in the G1, G2, and G3 groups were calculated using linear regression analysis. The trend for significance between PUFA intake and HRQoL was evaluated using linear regression analysis considering the G1, G2, and G3 of HRQoL as a continuous variable.

Multivariable linear regression analyses were used to evaluate the dose-dependent relationship between N3, N6, total PUFA intake, and spirometric values (FEV_1% predicted, FVC% predicted, and PEF). The association between PUFA intake and HRQoL (EQ-5D index) was measured using linear regression analysis. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, smoking status, and alcohol consumption. Model 3 was adjusted for age, sex, BMI, smoking status, alcohol consumption, residence, education, total calorie intake, and predicted FEV_1%. Prior to placing these variables into the model, a multi-collinearity test was performed in order to identify any inter-correlations among the investigated variables. As the distribution of N3, N6, and total PUFA intake violated the assumption of normality and skewed left, the value was log-transformed. Subgroup analysis was performed in elderly COPD patients.

All statistical analyses were performed with IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA). For all analyses, a *p*-val-

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ue < 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants are presented (Table 1). The relationships between N3, N6, and total PUFA intake and lung function are presented (Table 2). Lung function, which was measured using predicted FEV_1%, FVC%, and PEF, was not significantly associated with PUFA intake. The association between PUFA intake and HRQoL is presented (Table 3). The estimated amounts of N3, N6, and total PUFA intake were significantly associated with mobility and self-care ability in a dose-dependent manner, and statistical significance remained after covariate adjustment. N3, N6, and total PUFA intake also showed a positive association with the capacity of usual activities, although the degree of significance varied with covariates adjustment. Although N3 PUFA intake was positively associated with pain/discomfort, N6 and total PUFA intake were not. With respect to anxiety/depression, statistical significance was not observed. The associations between N3, N6, and PUFA intake and the EQ-5D index are presented (Table 4). High PUFA intake was significantly associated with a better EQ-5D score after covariate adjustment. Despite statistical significance, the magnitude of association was low. The association in older COPD patients is presented (Table 5). The strength of association was intensified in older patients, and the same statistical significance was observed.

Table 1. Baseline characteristics of study participants (n=573)

Characteristic	Total
Age (yr)	57.7 ± 0.5
Man (%)	63.6 ± 2.2
Residential area (%)	
Urban	78.3 ± 2.4
Rural	21.7 ± 2.4
Education	
Middle school or less	40.8 ± 2.3
High school	37.7 ± 2.2
College or more	21.6 ± 1.9
Smoking status	
Current	31.1 ± 2.3
Former	30.7 ± 2.3
Never	38.1 ± 2.3
Heavy alcohol consumption (/wk)[a]	
< 1	64.8 ± 2.2
≥ 1	35.2 ± 2.2
Body mass index (kg/m^2, %)	
< 18.5	2.2 ± 0.7
18.5–22.9	39.5 ± 2.4
23–24.9	27.0 ± 2.2
≥ 25.0	31.2 ± 2.2
Spirometric value	
FEV_1 (L)	2.3 ± 0.0
FEV_1%, predicted	75.5 ± 0.7
FVC (L)	3.7 ± 0.0
FVC%, predicted	92.1 ± 0.7
FEV_1/FVC%	62.9 ± 0.4
PEF (L)	6.0 ± 0.1

Values are presented as mean±standard error (SE) or weighted percentage±SE.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.
[a]Heavy alcohol consumption was defined as ≥7 drinks in men and ≥5 drinks in women on an occasion.

Discussion

In a population-based sample from South Korea, we investigated the association between PUFA intake, lung function, and HRQoL in patients with COPD defined as FEV_1/FVC% < 70%. We adjusted for socio-economic status, health behaviors, total calorie intake, and predicted FEV_1%, and found that N3, N6, and total PUFA intake were associated with HRQoL in a dose-dependent manner. Specifically, high dodes of N3, N6, and total PUFA intake showed a positive association with mobility, self-care, and usual activities in COPD patients, whereas there was no significant association with pain/discomfort and anxiety/depression. In a subgroup analysis of older patients (age ≥ 60 years), this association was reinforced, supporting the importance of proper nutritional supplements in older populations. Our results provide insight regarding the association of nutrition intake and HRQoL in patients with COPD.

HRQoL has been an important primary outcome in several studies and focus areas in the management of COPD. Triple inhaled treatments with long-acting beta-agonists, long-acting anticholinergics, and inhaled corticosteroids demonstrated improvement of HRQoL in COPD patients [18]. The evaluation of treatment efficacy and detection of an individual patient's potential risk for psychological and behavioral problems should be feasible by assessing their HRQoL [19]. The EQ-5D is a useful descriptive methodology evaluating five dimensions of HRQoL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In a previous study measuring the usefulness of the EQ-5D score in COPD patients, the correlation of hospital admissions, comorbidities, COPD Assessment Test scores, and the Medical Research Council scale for dyspnea was observed [20]. Pickard et al. [21] compared nine structured research criteria with the validity and reliability of EQ-5D usage in COPD patients and reported

Table 2. Association between lung function parameters and PUFA intake (n=573)

Variable	Predicted FEV_1%		Predicted FVC%		PEF (L/sec)	
	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value
Total PUFA						
Model 1	0.228 ± 1.874	0.903	−1.152 ± 1.860	0.536	0.177 ± 0.182	0.332
Model 2	0.394 ± 1.897	0.835	−0.806 ± 1.880	0.668	0.195 ± 0.189	0.303
Model 3	−0.458 ± 1.889	0.809	−1.748 ± 1.844	0.344	0.083 ± 0.188	0.661
N3 PUFA						
Model 1	0.970 ± 1.647	0.556	0.203 ± 1.659	0.903	0.196 ± 0.156	0.207
Model 2	1.022 ± 1.701	0.549	0.440 ± 1.681	0.794	0.209 ± 0.162	0.197
Model 3	0.545 ± 1.745	0.894	−0.303 ± 1.650	0.854	0.173 ± 0.162	0.286
N6 PUFA						
Model 1	−0.145 ± 1.804	0.936	−1.411 ± 1.764	0.424	0.145 ± 0.177	0.413
Model 2	0.022 ± 1.821	0.99	−1.085 ± 1.781	0.543	0.161 ± 0.182	0.376
Model 3	−0.845 ± 1.813	0.642	−1.946 ± 1.752	0.267	0.033 ± 0.181	0.854

Intake amount of total, N3, and N6 PUFA was log-transformed, because of left-skewed distribution. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for body mass index, smoking status, and alcohol consumption; and model 3 was additionally adjusted for residence, education, and total calorie intake.

PUFA, polyunsaturated fatty acid; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SE, standard error; N3, omega-3; N6, omega-6.

Table 3. Estimated amount (g) of daily PUFA intake in COPD patients according to degree of health-related problems (G1, G2, and G3)

Variable	N3 PUFA				N6 PUFA				Total PUFA			
	G1	G2	G3	*p*-value	G1	G2	G3	*p*-value	G1	G2	G3	*p*-value
Mobility (prevalence, %)[a]	82.6 ± 1.8	16.9 ± 1.8	0.6 ± 0.3		82.6 ± 1.8	16.9 ± 1.8	0.6 ± 0.3		82.6 ± 1.8	16.9 ± 1.8	0.6 ± 0.3	
Model 1[b]	1.73 ± 0.1	1.16 ± 0.1	1.15 ± 0.7	< 0.001	8.68 ± 0.4	6.53 ± 0.6	4.01 ± 1.4	< 0.001	10.32 ± 0.4	7.64 ± 0.6	5.19 ± 2.0	< 0.001
Model 2	1.64 ± 0.1	1.08 ± 0.1	1.03 ± 0.7	< 0.001	8.22 ± 0.4	6.23 ± 0.6	3.45 ± 1.4	< 0.001	9.79 ± 0.5	7.27 ± 0.6	4.52 ± 1.9	< 0.001
Model 3	1.64 ± 0.1	1.06 ± 0.1	0.99 ± 0.7	< 0.001	8.50 ± 0.5	6.73 ± 0.6	3.55 ± 1.8	0.003	10.09 ± 0.6	7.77 ± 0.8	4.60 ± 2.3	0.001
Self-care (prevalence, %)	95.0 ± 0.9	5.0 ± 0.9	-		95.0 ± 0.9	5.0 ± 0.9	-		95.0 ± 0.9	5.0 ± 0.9	-	
Model 1	1.65 ± 0.1	1.14 ± 0.2	-	0.006	8.38 ± 0.3	6.28 ± 0.8	-	0.011	9.95 ± 0.4	7.33 ± 0.9	-	0.004
Model 2	1.56 ± 0.1	1.08 ± 0.2	-	0.01	7.92 ± 0.4	6.04 ± 0.8	-	0.027	9.42 ± 0.4	7.04 ± 0.9	-	0.011
Model 3	1.55 ± 0.1	1.05 ± 0.2	-	0.005	8.23 ± 0.5	6.48 ± 0.8	-	0.03	9.73 ± 0.5	7.47 ± 0.9	-	0.011
Usual activity (prevalence, %)	89.4 ± 1.5	10.2 ± 1.5	0.4 ± 0.3		89.4 ± 1.5	10.2 ± 1.5	0.4 ± 0.3		89.4 ± 1.5	10.2 ± 1.5	0.4 ± 0.3	
Model 1	1.68 ± 0.1	1.19 ± 0.1	1.12 ± 0.3	< 0.001	8.45 ± 0.4	6.85 ± 0.8	5.40 ± 1.0	0.03	10.05 ± 0.4	7.95 ± 0.9	6.44 ± 1.2	0.01
Model 2	1.58 ± 0.1	1.10 ± 0.1	1.03 ± 0.3	0.003	7.99 ± 0.4	6.52 ± 0.8	5.32 ± 0.9	0.021	9.52 ± 0.4	7.54 ± 0.9	6.28 ± 1.1	0.01
Model 3	1.58 ± 0.1	1.09 ± 0.1	1.06 ± 0.3	0.001	8.29 ± 0.5	6.98 ± 0.8	5.96 ± 0.7	0.075	9.82 ± 0.5	8.00 ± 0.9	6.95 ± 0.9	0.027
Pain/discomfort (prevalence, %)	74.7 ± 2.0	22.7 ± 1.9	2.6 ± 0.6		74.7 ± 2.0	22.7 ± 1.9	2.6 ± 0.6		74.7 ± 2.0	22.7 ± 1.9	2.6 ± 0.6	
Model 1	1.70 ± 0.1	1.48 ± 0.1	1.00 ± 0.2	0.026	8.37 ± 0.4	8.05 ± 0.8	7.36 ± 1.4	0.579	10.00 ± 0.4	9.42 ± 0.9	8.27 ± 1.5	0.358
Model 2	1.60 ± 0.1	1.39 ± 0.1	0.96 ± 0.2	0.05	7.88 ± 0.5	7.66 ± 0.8	7.26 ± 1.4	0.717	9.44 ± 0.5	8.95 ± 0.8	8.14 ± 1.5	0.476
Model 3	1.59 ± 0.1	1.36 ± 0.1	0.99 ± 0.2	0.046	8.16 ± 0.5	8.02 ± 0.8	8.10 ± 1.4	0.893	9.71 ± 0.6	9.31 ± 0.9	9.01 ± 1.5	0.614
Anxiety/depression (prevalence, %)	85.7 ± 1.8	13.1 ± 1.7	1.3 ± 0.5		85.7 ± 1.8	13.1 ± 1.7	1.3 ± 0.5		85.7 ± 1.8	13.1 ± 1.7	1.3 ± 0.5	
Model 1	1.59 ± 0.1	1.94 ± 0.3	0.37 ± 0.1	0.805	8.23 ± 0.4	8.89 ± 1.0	4.17 ± 0.7	0.863	9.74 ± 0.4	10.83 ± 1.2	4.55 ± 0.8	0.988
Model 2	1.51 ± 0.1	1.87 ± 0.3	0.36 ± 0.1	0.75	7.79 ± 0.4	8.53 ± 1.0	4.38 ± 0.7	0.991	9.23 ± 0.5	10.40 ± 1.2	4.72 ± 0.8	0.882
Model 3	1.49 ± 0.1	1.87 ± 0.3	0.37 ± 0.2	0.705	8.05 ± 0.5	8.96 ± 1.1	5.42 ± 0.9	0.768	9.48 ± 0.6	10.85 ± 1.2	5.79 ± 1.0	0.687

Comparison of estimated PUFA intake and *p*-value for trend was measured using multivariable linear regression analysis considering G1, G2, and G3 as continuous variables. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for body mass index, smoking status, and alcohol consumption; and model 3 was additionally adjusted for residence, education, total calorie intake, and predicted FEV_1%.

PUFA, polyunsaturated fatty acid; COPD, chronic obstructive pulmonary disease; G1, no problem; G2, some problems; G3, severe problems; N3, omega-3; N6, omega-6; FEV_1, forced expiratory volume in 1 second.

Estimated prevalence of subjects and amount of PUFA intake according to degree of health-related problems are presented as [a]percentage±standard error and [b]estimated amount of intake±standard error, respectively.

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Table 4. Association of PUFA intake with HRQoL in COPD patients (n=573)

Variable	Total PUFA		N3 PUFA		N6 PUFA	
	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value
Crude	0.877 ± 0.147	< 0.001	0.813 ± 0.168	< 0.001	0.914 ± 0.150	< 0.001
Model 1	0.586 ± 0.141	< 0.001	0.621 ± 0.171	< 0.001	0.602 ± 0.142	< 0.001
Model 2	0.549 ± 0.141	< 0.001	0.596 ± 0.171	0.001	0.562 ± 0.144	< 0.001
Model 3	0.409 ± 0.132	0.002	0.472 ± 0.153	0.002	0.417 ± 0.139	0.003

Multivariable linear regression analyses were performed after log-transforming the value of total, N3, and N6 PUFA because of its left-skewed distribution. HRQoL was measured using European Quality of Life-5 Dimensions. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for body mass index, smoking status, and alcohol consumption; and model 3 was additionally adjusted for residence, education, total calorie intake, and predicted FEV_1%.

PUFA, polyunsaturated fatty acid; HRQoL, health-related quality of life; COPD, chronic obstructive pulmonary disease; N3, omega-3; N6, omega-6; SE, standard error; FEV_1, forced expiratory volume in 1 second.

Table 5. Association of PUFA intake on HRQoL in elderly COPD patients (n=298)

Variable	Total PUFA		N3 PUFA		N6 PUFA	
	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value	Coefficient ± SE	*p*-value
Crude	0.838 ± 0.186	< 0.001	0.797 ± 0.221	< 0.001	0.865 ± 0.186	< 0.001
Model 1	0.627 ± 0.197	0.002	0.528 ± 0.224	0.019	0.673 ± 0.201	0.001
Model 2	0.592 ± 0.193	0.002	0.481 ± 0.215	0.026	0.642 ± 0.198	0.001
Model 3	0.532 ± 0.186	0.005	0.354 ± 0.175	0.045	0.532 ± 0.186	0.005

Multivariable linear regression analyses were performed after log-transforming the value of total, N3, and N6 PUFA because of its left-skewed distribution.HRQoL was measured using European Quality of Life-5 Dimensions. Model 1 was adjusted for age and sex; model 2 was additionally adjusted for body mass index, smoking status, and alcohol consumption; and model 3 was additionally adjusted for residence, education, total calorie intake, and predicted FEV_1%.

PUFA, polyunsaturated fatty acid; HRQoL, health-related quality of life; COPD, chronic obstructive pulmonary disease; N3, omega-3; N6, omega-6; SE, standard error; FEV_1, forced expiratory volume in 1 second.

that the EQ-5D scores were closely related to COPD stages.

Among the five components of the EQ-5D, mobility is defined as the ability to walk, while usual activities refer to an individual's performance at work, study, household, and family/leisure activities; these two components are associated with daily physical activities. Walking ability in COPD patients is further standardized by the measurement of the distance covered by walking in 6 minutes, and lower mean walking distance is generally considered as a poor prognostic factor for mortality [22]. The GOLD report recommends exercise testing and assessment of physical activity based on walking distance to evaluate the effectiveness of pulmonary rehabilitation, which is a key non-pharmacologic management technique for COPD patients [23]. Given that physical activity is a strong predictor of all-cause mortality in COPD patients [22], our results suggest that PUFA intake may correlate with mobility and usual physical activities. However, specific threshold amounts of PUFA for improving physical activity is unclear and further longitudinal study is required.

Several previous studies have shown that PUFA is associated with HRQoL. In patients with systemic lupus erythematosus (SLE) from the United States, N3 PUFA intake, calculated from a diet history questionnaire, was found to be beneficial in patient-reported outcomes assessed by the Systemic Lupus Activity Questionnaire [24]. One randomized controlled trial of 1 g/day N3 PUFA supplementation demonstrated a reduction of premenstrual symptoms and improvement of HRQoL [25]. Another double-blind randomized controlled trial of 3 g/day N3 PUFA supplementation for 3 months reported a reduction in several inflammatory markers and improvement of HRQoL in chronic hemodialysis patients [26]. Although the association between PUFA and HRQoL in patients with COPD is under-recognized, Lemoine S et al. [10] suggested that individual factors should be considered while determining the association of N3 PUFA intake and symptoms. PUFA may be beneficial in other chronic diseases such as SLE or chronic kidney disease. PUFA may also have beneficial effects in patients with COPD in terms of HRQoL.

There are several possible mechanisms related to this association. First, COPD is a chronic airway and systemic inflammatory disease, and N3 PUFA might attenuate this inflammatory process. Within the inflammatory processes of the human body, N3

PUFA, eicosapentaenoic acid and docosahexaenoic acid mediate anti-inflammatory responses and several specialized pro-resolving mediators (SPMs, resolvins, protectins, and maresins) are synthesized [8]. Resolvin, one of the SPMs, has been associated with counter-regulated pro-inflammatory signaling and inflammatory resolution pathways in patients with COPD [27]. In a cigarette exposed human lung, an experimental study demonstrated that resolvin dampened the inflammatory reaction via the production of anti-inflammatory cytokines and enhanced phagocytosis of macrophages [27]. Second, the susceptibility of PUFA to oxidative stress could contribute to lowering airway inflammation. Interestingly, we observed that N6 PUFA was beneficial in improving HRQoL in COPD patients, although there is conflicting evidence regarding the health-related benefits of N6 PUFA [28,29]. PUFA can be easily oxidized due to its unstable hydrogen-carbon bonds; an *in vivo* study demonstrated that N6 PUFA decreased serum C-reactive protein [29].

Our study has several strengths. This is the first population-based epidemiologic study in South Korea showing a relationship between PUFA intake and HRQoL in patients with COPD. These results highlight the importance of nutrient intake in patients with COPD to alleviate respiratory symptoms and improve HRQoL. In addition, we adjusted for socio-economic characteristics and health-related behavior, as diet is influenced by an individual's status, as well as social, economic, and cultural factors.

Despite these strengths, our study has several limitations. First, as this is a cross-sectional observational study, the causal relationship is unclear. Although we observed that PUFA intake is associated with increased HRQoL in COPD patients, the inverse correlation could exist. Second, because the nutritional survey of KNHANES was based on a 24-hour recall method, recall bias and day-to-day variability should be considered. Third, spirometric values were obtained through pre- bronchodilator tests. Fourth, information regarding respiratory symptoms, hospital admission or exacerbation history, infections within the 4 weeks prior to the study, and recent use of corticosteroid was unavailable. Therefore, classification based on symptoms or exacerbation (e.g., ABCD grouping of the GOLD report) was not feasible. Fifth, which PUFA derivative is specifically associated with HRQoL in unclear. For example, Noguchi et al. [30] reported that eicosapentaenoic acid might improve the quality of life; however, docosahexaenoic acid was not beneficial. Finally, smoking status in terms of pack-years is an important component when assessing long-term inflammation and oxidative stress, but the data was not available in 6th KNHANES data.

N3, N6, and total PUFA showed a positive correlation with HRQoL in patients with COPD. Specifically, mobility, self-care, and usual activities might be attributable to the observed association between HRQoL and PUFA intake. Further randomized prospective studies are required to clarify the health-related benefits of PUFA in patients with COPD.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: HC, TK; Data curation and Formal analysis: TK; Investigation, Methodology, Project administration, and Supervision: TK; Validation: HC, TK; Visualization: TK; Writing-original draft: HC; Writing-review & editing: TK.

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The effectiveness of prophylactic ipsilateral central neck dissection in selected patients who underwent total thyroidectomy for clinically node-negative unilateral papillary thyroid carcinoma

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Background: Prophylactic central neck dissection (CND) in clinically node-negative (cN0) papillary thyroid carcinoma (PTC) remains controversial. The purpose of this study was to evaluate the benefits of prophylactic ipsilateral CND compared with bilateral CND in total thyroidectomy for cN0 unilateral PTC.

Methods: We retrospectively enrolled 174 patients who underwent total thyroidectomies with prophylactic CND for cN0 unilateral PTC between January 2009 and May 2010. The prophylactic CND patients were divided into group 1, the ipsilateral CND group (n=74), and group 2, the bilateral CND group (n=100). The incidence of central lymph node metastasis (CLNM) and postoperative complications, such as hypoparathyroidism, recurrent laryngeal nerve injury, and recurrence were assessed.

Results: CLNM was found in 22 (29.8%) in group 1 and 69 (69%) in group 2. The incidence of postoperative severe hypocalcemia less than 7.0 was also significantly different (six patients [8.1%] in group 1 and 23 [23%] in group 2; p=0.009). Permanent hypoparathyroidism was significantly more frequent in group 2 (4.1% vs. 19%; p=0.005). However, the incidence of transient hypoparathyroidism, recurrence, and recurrent laryngeal nerve injury was not significantly different.

Conclusion: Prophylactic ipsilateral CND has advantage not only to reduce incidence of some complications but also to have similar recurrence rate compared with bilateral CND. We suggest that prophylactic ipsilateral CND may be safe and effective for selected patients undergoing total thyroidectomy for cN0 unilateral PTC.

Keywords: Hypoparathyroidism; Lymph node; Neck dissection; Papillary thyroid carcinoma

Introduction

The treatment of differentiated thyroid carcinoma has shown excellent outcomes, with a 0.6% recurrence rate and over 95% 10-year disease-free survival [1]. Nevertheless, there are complications associated with total thyroidectomies, such as hypoparathyroidism, recurrent laryngeal nerve and external branch of the superior laryngeal nerve injury, and locoregional recurrence. The risk of these complications may increase with the extent of surgery. Recently, there has been a growing interest in functional complications after total thyroidectomy. The typical long-term functional complication after total thyroidectomy is permanent

hypoparathyroidism, with a 10%–60% incidence [2]. Most endocrine surgeons follow a parathyroid preservation principle during thyroidectomy; however, hypoparathyroidism can occur because of devascularization, thermal or mechanical damage, and inadvertent removal of the parathyroid gland. Permanent hypoparathyroidism can lead to symptomatic hypocalcemia, the need for lifetime calcium supplementation, and seriously impact the patient's quality of life. Furthermore, the incidence of permanent hypoparathyroidism after total thyroidectomy is greatly influenced by the experience of the operator and the decision of whether or not to perform central neck dissection (CND).

Central lymph node metastases (CLNM) have been reported in approximately 30%–80% of the patients with papillary thyroid carcinoma (PTC) [3]. It is difficult to detect metastatic central lymph node (LN) by ultrasound preoperatively because, while the specificity is 80%–93%, the sensitivity is only 53%–61% [4]. Tumor size and extrathyroidal extension are known risk factors for ipsilateral CLNM. And ipsilateral CLNM is a significant factor in contralateral LNM [3,5-8]. Prophylactic CND is defined as the removal of level VI LNs, which includes the pretracheal, prelaryngeal, and paratracheal LNs. Prophylactic CND is performed to remove occult nodal metastases with negative preoperative assessments. Several studies have reported that patients who underwent prophylactic CND had a higher rate of complications and no effect on survival, and prophylactic CND may not be routinely recommended [9-12]. Furthermore, according to the 2015 American Thyroid Association (ATA) guidelines, prophylactic CND should be considered for patients with advanced primary tumors (T3 or T4) and clinically involved lateral neck nodes (cN1b), while CND may not be appropriate for small (T1 or T2), clinically node-negative (cN0) PTC [13]. In contrast, some studies have reported that prophylactic CND should be performed because of the high incidence of central neck LNM and the poor sensitivity of ultrasound [14]. In another study, of the patients who underwent prophylactic CND with cN0 PTC, 45.8% had central neck LNM, 0.9% had recurrent laryngeal nerve injuries, 1.16% had a locoregional recurrence, 6.24% had transient hypoparathyroidism, and 0.13% had permanent hypoparathyroidism [15]. Nevertheless, prophylactic CND in cN0 PTC remains controversial.

Total thyroidectomy without CND helps to reduce the risk of hypoparathyroidism and recurrent laryngeal nerve injury, but it can leave metastatic LNs because of the high incidence of ipsilateral central compartment LNM. Finally, it can affect locoregional recurrence. In contrast, total thyroidectomy with bilateral CND has the advantage of identifying and controlling LNM, but it also has the disadvantage of increased risks of hypoparathyroidism and recurrent laryngeal nerve injury. The incidence of contralateral LNM is below 5%. If the risk factors for contralateral LNM are not present, ipsilateral CND may be reasonable. We focused on the extent of prophylactic CND during total thyroidectomies in cN0 PTC patients. The endpoints of this study were (1) the incidence of transient and permanent hypoparathyroidism, (2) transient and permanent recurrent laryngeal nerve injury, and (3) recurrence. The aim of this study was to evaluate the benefits of prophylactic ipsilateral CND compared with bilateral CND in total thyroidectomy for cN0 unilateral PTC.

Materials and methods

1. Ethics statements

This study was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No: 2019-09-066).

2. Patients

We retrospectively enrolled 324 consecutive patients who underwent total thyroidectomies with prophylactic CND for cN0 unilateral PTC by a single experienced surgeon between January 2009 and May 2010. The inclusion criteria were patients (1) with a final postoperative diagnosis of PTC, (2) who underwent a total thyroidectomy with prophylactic CND, (3) had follow-up parathyroid hormone (PTH) and calcium testing, and (4) had no evidence of clinical node positivity. The exclusion criteria were patients (1) without follow-up examinations or laboratory tests, (2) concomitant modified radical neck dissection, (3) parathyroidectomy due to parathyroid adenoma, (4) bilateral PTC, (5) 11 male sex in only group 1, and (6) other types of pathological results. One hundred-fifty patients (bilateral carcinoma, male, modified radical neck dissection, lack of follow-up or laboratory tests and parathyroidectomy) who met the exclusion criteria were excluded among of 324 patients. Finally, 174 patients were divided into two groups according to the extent of CND. Seventy-four patients in group 1 underwent prophylactic ipsilateral CND with total thyroidectomy and 100 patients in group 2 received prophylactic bilateral CNDs with total thyroidectomy. Ipsilateral CND was defined as the removal of ipsilateral paratracheal, pretracheal, and prelaryngeal LNs. Bilateral CND was defined as the removal of paratracheal, pretracheal, and prelaryngeal LNs. All patients received prophylactic ipsilateral CNDs and whether or not a prophylactic bilateral CND was performed depended on the frozen biopsy result of the ipsilateral LN and enlarged contralateral LN intraoperatively.

3. Study design

Patients with intraoperative findings, such as parathyroid color

change and autotransplantation, were excluded because of subjective evidence. Robotic or endoscopic thyroidectomies were also excluded because those techniques offer magnified views that can make it easier for the surgeon to preserve the parathyroid. We classified PTC according to the American Joint Committee on Cancer 7th edition and minimal extrathyroidal extension was categorized as T3. The indications for radioactive iodine ablation were extrathyroidal extensions and LN involvement. We reviewed basic characteristics of the patients (age, tumor location, size, multifocality, concomitant benign tumor, and length of the lobe), histopathological factors (lymphocytic thyroiditis, extrathyroidal extension, margin status, number of retrieved LN, metastasis, and parathyroid on tissue) and laboratory tests (postoperative PTH and calcium). We investigated the incidence of transient and permanent hypoparathyroidism, transient and permanent hoarseness, and recurrence by reviewing the patients' medical records. Recurrence was defined as tumor in the thyroidectomy bed or metastatic central or lateral cervical LN after surgery. Recurrent laryngeal nerve injury was assessed by patient's self-assessment and physician's objective assessment. Permanent recurrent laryngeal nerve injury was defined as persistent hoarseness and vocal cord palsy identified with laryngeal examination more than 6 months after surgery. Through this study, we sought to find evidence for two hypotheses. The first hypothesis is that prophylactic CND during total thyroidectomy in cN0 PTC should not be routinely discounted because of the rate of incidentally found CLNM. And second, prophylactic ipsilateral CND is more advantageous than bilateral CND according to the complication rate.

4. Hypoparathyroidism

Hypoparathyroidism was defined as PTH levels < 10 pg/mL (range, 10–65 pg/mL). Transient hypoparathyroidism was defined when a low PTH level returned to normal within the follow-up period. And permanent hypoparathyroidism was defined as PTH < 10 pg/mL with persistent low PTH levels during follow-up. PTH was tested on postoperative 1 day and then at annual follow-ups. Calcium levels less than 8.5 mg/dL were classified as hypocalcemia. We tested calcium level perioperatively, then regularly at follow-up. Calcium and vitamin D supplements were used to maintain the calcium and vitamin D levels as close to normal as possible, regardless of the patient's symptoms.

5. Statistical analyses

Chi-squared tests or Fisher exact test or linear and linear association was used to compare the categorical variables. Student t-tests were used for continuous valuables, which are expressed as mean ± standard deviation. All statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and p-values < 0.05 indicated statistical significance.

Results

1. Patient characteristics

Table 1 shows a comparison of the characteristics of patients between the two groups. One hundred seventy-four patients were included in this study, of which 74 were assigned to group 1 and 100 to group 2 according to the extent of CND. All 174 patients were female. The mean age of the patients was 47.8 ± 11.2 years and 45.1 ± 10.2 years and the mean tumor size was 0.8 ± 0.5 cm and 0.9 ± 0.6 cm in groups 1 and 2, respectively. There was no significant difference in age, tumor size, location, multifocality, length of dominant lobe, minimal extrathyroidal extension, lymphocytic thyroiditis, positive margin or stage between the groups. However, radioactive iodine ablation was different in 31 patients (41.9%) and 62 patients (62%) in groups 1 and 2, respectively (p = 0.009). The mean follow-up period was 118.2 ± 4.6 and 115.5 ± 4.1 months in groups 1 and 2, respectively (p < 0.001).

Table 1. Patient characteristics

Characteristic	Group 1 (n = 74)[a]	Group 2 (n = 100)[b]	p-value
Female sex	74	100	NA
Age (yr)	47.8 ± 11.2	45.1 ± 10.2	0.097
Age < 45 yr	28 (37.8)	42 (42)	0.580
Tumor size (cm)	0.8 ± 0.5	0.9 ± 0.6	0.736
Tumor location			0.850
Upper	14 (18.9)	24 (24)	
Middle	52 (70.3)	65 (65)	
Lower	5 (6.8)	6 (6)	
Isthmus	3 (4)	5 (5)	
Multifocality	14 (18.9)	16 (16)	0.614
Length of dominant lobe	4.8 ± 0.8	4.6 ± 0.7	0.096
Minimal extrathyroidal extension	43 (58.1)	66 (66)	0.287
Lymphocytic thyroiditis	17 (23)	34 (34)	0.114
Margin positivity	10 (13.5)	13 (13)	0.675
Stage			0.614
I	45 (60.8)	57 (57)	
III	29 (39.2)	43 (43)	
Calcium replacement	59 (79.7)	88 (88)	0.136
RI ablation	31 (41.9)	62 (62)	0.009
Follow-up (mo)	118.2 ± 4.6	115.5 ± 4.1	< 0.001

Values are presented as mean±standard deviation or number (%).
NA, not applicable; RI, radioactive iodine; CND, central neck dissection.
[a]Group 1, ipsilateral CND group. [b]Group 2, bilateral CND group.

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2. Central neck dissection: ipsilateral versus bilateral

The number of ipsilateral paratracheal LNs was 3.8 ± 2.8 and 4.8 ± 3.1 in groups 1 and 2, respectively ($p = 0.034$). The number of pretracheal and prelaryngeal LNs were 0.6 ± 1.2 and 1.8 ± 2.3, respectively ($p < 0.001$). Ipsilateral paratracheal LNM was found in 21 patients (28.4%) and 44 patients (44%) in groups 1 and 2, respectively ($p = 0.035$). Pretracheal LNM was found in one patient (1.4%) and 15 patients (15%) in each group ($p = 0.002$). Contralateral paratracheal LNM was 10 (10%) in group 2. The final pathologic results showed that the parathyroid gland was inadvertently removed in 15 patients (20.3%) and 22 patients (22%) in groups 1 and 2, respectively. Among these, the ipsilateral parathyroid was removed in 12 patients (16.2%) and 12 patients (12%) ($p = 0.425$) in groups 1 and 2, respectively, the contralateral parathyroid in 2 (2.7%) and 8 (8%) ($p = 0.193$) and both in 1 (1.4%) and 2 (2%). There was no significant difference in the removal of parathyroid glands inadvertently between the groups (Table 2).

3. Postoperative parathyroid hormone and calcium levels

The postoperative PTH and calcium level are shown in Table 3. Postoperative PTH levels were measured at 1 day, 1 year, and 2 years then annually at follow-up. By linear and linear association, there was a decreasing trend of the hypoparathyroidism (PTH < 10 pg/mL) over time ($p < 0.001$). The 1-day PTH levels (average) were significantly different (19.3 ± 12.1 in group 1 and 13.2 ± 9.4 in group 2; $p < 0.001$). One-year PTH levels (average) were 22.9 ± 10.2 and 19.6 ± 10.6 ($p = 0.003$) and 2-year PTH levels (average) were 26.1 ± 10.9 and 19.6 ± 10.6 in groups 1 and 2, respectively ($p < 0.001$). The calcium levels in groups 1 and 2, respectively, were 9.1 ± 0.5 and 8.9 ± 0.4 preoperatively and 8.1 ± 0.6 and 7.8 ± 0.6 postoperatively. The perioperative calcium levels were not different (1.0 ± 0.7 in group 1 and 1.1 ± 0.6 in group 2; $p = 0.302$). But there was a significant difference in the incidence of postoperative severe hypocalcemia defined as calcium levels ≤ 7.0 mg/dL (6 patients [8.1%] in group 1 and 23 [23%] in group 2; $p = 0.009$).

4. Hypoparathyroidism, recurrent laryngeal nerve injury, and recurrence

Postoperative transient hypoparathyroidism was observed in 25 patients (33.8%) and 38 patients (38%) ($p = 0.527$), whereas permanent hypoparathyroidism occurred in three patients (4.1%) and 19 patients (19%) in groups 1 and 2, respectively. There was significant difference in the incidence of postoperative permanent hypoparathyroidism ($p = 0.005$). Transiently recurrent laryngeal nerve injury after total thyroidectomy with CND was estimated through medical record review, at 14 patients (18.9%) and 17 patients (17%) in groups 1 and 2, respectively ($p = 0.744$). Permanently recurrent laryngeal nerve injury totally occurred in three patients (1.7%). One patient in group 1 underwent nerve shaving because of recurrent laryngeal nerve invasion. In two patients in group 2, one patient received nerve repair and returned to a normal voice after 6 months. Laboratory tests and ultrasound examination were performed every 6 months until 2 years after surgery

Table 2. Comparison of ipsilateral versus bilateral prophylactic central neck dissection

Variable	Group 1 (n = 74)[a]	Group 2 (n = 100)[b]	*p*-value
Numbers of retrieved LN			
Ipsilateral paratracheal LN	3.8 ± 2.8	4.8 ± 3.1	0.034
Pretracheal and prelaryngeal LN	0.6 ± 1.2	1.8 ± 2.3	< 0.001
Contralateral paratracheal LN	0	4.0 ± 3.0	NA
Metastasis in level VI LN			
Ipsilateral paratracheal LN	21 (28.4)	44 (44)	0.035
Pretracheal and prelaryngeal LN	1 (1.4)	15 (15)	0.002
Contralateral paratracheal LN	0	10 (10)	NA
Parathyroid in tissue			
Ipsilateral	12 (16.2)	12 (12)	0.425
Contralateral	2 (2.7)	8 (8)	0.193
Both	1 (1.4)	2 (2)	NA

Values are presented as mean±standard deviation or number (%).
LN, lymph node; NA, not applicable; CND, central neck dissection.
[a]Group 1, ipsilateral CND group. [b]Group 2, bilateral CND group.

Table 3. Postoperative PTH and calcium level

Factor	Group 1 (n = 74)[a]	Group 2 (n = 100)[b]	*p*-value
Postoperative PTH (< 10 pg/mL)			< 0.001
1 Day	28 (37.8)	57 (57)	
1 Year	6 (8.1)	23 (23)	
2 Years	3 (4.1)	19 (19)	
Postoperative PTH (pg/mL)			
1 Day	19.3 ± 12.1	13.2 ± 9.4	< 0.001
1 Year	22.9 ± 10.2	18.3 ± 9.6	0.003
2 Years	26.1 ± 10.9	19.6 ± 10.6	< 0.001
Preoperative Ca	9.1 ± 0.5	8.9 ± 0.4	0.029
Postoperative Ca	8.1 ± 0.6	7.8 ± 0.6	0.007
Difference of Ca (perioperative level)[c]	1.0 ± 0.7	1.1 ± 0.6	0.302
Postoperative Ca ≤ 7.0 (severe hypocalcemia)	6 (8.1)	23 (23)	0.009

Values are presented as mean±standard deviation or number (%).
PTH, parathyroid hormone; Ca, calcium; CND, central neck dissection.
[a]Group 1, ipsilateral CND group. [b]Group 2, bilateral CND group.
[c]Perioperative level=postoperative−preoperative calcium level.

Table 4. Hypoparathyroidism, recurrent laryngeal nerve injury, and recurrence after total thyroidectomy with ipsilateral or bilateral CND

Variable	Group 1 (n = 74)[a]	Group 2 (n = 100)[b]	*p*-value
Hypoparathyroidism			
Transient	25 (33.8)	38 (38)	0.527
Permanent	3 (4.1)	19 (19)	0.005
Recurrent laryngeal nerve injury			
Transient	14 (18.9)	17 (17)	0.744
Permanent	1 (1.4)	2 (2)	NA
Recurrence	1 (1.4)	1 (1)	NA

Values are presented as number (%).
CND, central neck dissection; NA, not applicable.
[a]Group 1, ipsilateral CND group. [b]Group 2, bilateral CND group.

and then annually during follow-up. Among the 174 patients, only two patients (1.1%) had a recurrence. Contralateral paratracheal LNM was found in one patient in group 1, 8 years after surgery and another in group 2 was identified with lateral neck LNM 3.5 years after surgery (Table 4).

Discussion

Prophylactic CND (ipsilateral or bilateral) can be considered in cN0 PTC with advanced tumors (T3 or T4) or cN1b [13]. Other study reported routine prophylactic CND is a treatment option for cN0 PTC [15]. It remains controversial. Our study uniquely compared ipsilateral with bilateral CND according to the extent of prophylactic CND. Furthermore, no previous studies have reported the details of postoperative hypoparathyroidism among CND groups. The starting point of our study was whether the need for prophylactic CND could be discounted. Our study was subject to two well-known facts. First, there is a relatively higher possibility of complications in CND patients than in non-CND patients. Second, there is a high incidence of CLNM incidentally in cN0 PTC patients. Surgeons might feel comfortable when only thyroidectomy is performed through capsular dissection, which can lead to decreased operative times and easy preservation of the parathyroid. Until now, the main idea was not to perform a prophylactic CND, which is prudent, except in the case of large tumors and clinically suspicious factors. Nevertheless, many endocrine surgeons might feel uneasy because of the high incidence of CLNM. If prophylactic CND is not preformed, the status and number of metastatic LNs cannot be determined. Ipsilateral CLNM might lead to contralateral central LN and lateral neck LNMs. Whether microscopic metastasis of the central LNs should be ignored is still debatable. However, it is clear that prophylactic CND has an important role in controlling metastatic LNs found incidentally. The incidence of recurrent laryngeal nerve injury can decrease according to the surgeon's experience but the preservation of the parathyroid is more complex. To preserve the parathyroid more experience and strong preservation intent are needed. CND is known to be associated with a higher incidence of hypoparathyroidism. We considered how to decrease the incidence of hypoparathyroidism and to get similar oncologic safety. Finally, we focused on prophylactic ipsilateral CND after considering the pros and cons of prophylactic CNDs. The aim of our study was to evaluate the benefits of prophylactic ipsilateral CND with total thyroidectomy in cN0 PTC patients.

Several studies have reported the risk factors of central and lateral neck LNM [7,14,16,17]. Male sex, age (> 45 years), tumor size (> 5 mm), lower lobe, total tumor diameter (> 10 mm), and extracapsular spread were statistically significant factors for CLNM in multivariate analysis [7]. One study showed that young age (< 45 years), male sex, extrathyroidal extension, multifocal tumors, bilaterality, and tumor size (≥ 1 cm) were significant factors for CLNM, except in Hashimoto's thyroiditis [15]. Based on the above studies, the common risk factors for CLNM were young age, male sex, tumor size, and extrathyroidal extension. Furthermore, several studies found that CLNM was a significant risk factor for lateral neck LNM [18-20]. If some risk factors for CLNM are present preoperatively, prophylactic CND must be considered to control CLNM and reduce the possibility of lateral neck LNM. However, the role of prophylactic CND remains controversial, despite the high incidence of CLNM. A previous study found no significant difference in locoregional recurrence with or without CND and routine CND did not reduce lateral neck recurrence in cN0 PTC patients [21]. Higher complication rates and similar recurrence rates were found in patients who underwent total thyroidectomies with CND than total thyroidectomies alone. Specifically, transient hypocalcemia was significantly higher in total thyroidectomies with CND [12]. CND is associated with higher rates of transient hypoparathyroidism (12.6% in total thyroidectomy, 23.3% in total thyroidectomy with ipsilateral CND, and 36.7% in total thyroidectomy with bilateral CND) and a total thyroidectomy alone may be adequate treatment for patients with cN0 PTC [21]. However, recently, one study reported that CND reduced locoregional recurrence (6.9% difference at 10 years) [22]. Total thyroidectomy with CND resulted in a greater reduction in local recurrence than total thyroidectomy alone. Additionally, total thyroidectomy with bilateral CND showed significantly lower recurrence than total thyroidectomy alone [23]. This raises a question regarding how recurrence was assessed. Most studies used ultraso-

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nography to assess preoperative and recurrent CLNM. However, in our experience, most paratracheal LNs were classified as indeterminate by preoperative ultrasonography. Furthermore, we performed regular ultrasonographic examinations during follow-up. At that time, it was difficult to identify LNM by ultrasonography. Hypoechoic lesions or indeterminate LNs at paratracheal lesions were often found postoperatively which were difficult to completely assess, unless fine needle aspiration was performed. Actual CLNM recurrence might not be detected because of ambiguous ultrasonographic results. This hypothesis can explain why the no-CND group had a recurrence rate similar to the CND group but a high incidence of CLNM. Preoperative ultrasonography has a 77% detection rate for LNM. Detection of CLNM using ultrasound, which has 92% specificity, 81% positive predictive value, 51% sensitivity, and 76% negative predictive value, is difficult [24,25]. Another study also reported the poor diagnostic accuracy of ultrasound for CLNM. Prophylactic CND is recommended due to the low diagnostic efficacy of ultrasound and high incidence of CLNM [14]. As discussed above, prophylactic CND can remove up to 50% of the metastatic LN unidentifiable in ambiguous ultrasound results.

Hypoparathyroidism is a common complication after total thyroidectomy, which was transient in 6.9%–46% of the patients and permanent in 0%–10% of the patients. During surgery, the parathyroid gland can be damaged by thermal or mechanical injury, vascular injury, or removed inadvertently [26]. Permanent hypoparathyroidism is usually defined as PTH levels below normal for more than 1 year. However, in our study, it was defined as persistent PTH levels below normal at follow-up because there have been many cases where PTH levels were shown to improve or decrease after 1 year. Large tumors (≥ 4 cm) or gross extrathyroidal extension were significant factors for permanent hypoparathyroidism postoperatively. Of 65 patients who underwent total thyroidectomies with bilateral CND, postoperative transient and permanent hypoparathyroidism were found in 44 (68%) and 12 (18%), respectively [27]. Other study showed the risk factors of hypoparathyroidism following total thyroidectomy with CND. Of 903 patients who underwent total thyroidectomy plus CND, 399 patients (44.2%) had transient hypoparathyroidism and 10 patients (1.1%) had permanent hypoparathyroidism. On multivariate analysis, female, nonuse of carbon nanoparticles, parathyroid autotransplantation, accidental parathyroid resection and bilateral CND were the independent factors of transient hypoparathyroidism. Nonuse of carbon nanoparticles and a tumor in the upper pole of thyroid gland were significant risk factors for permanent hypoparathyroidism [28]. Our study found severe postoperative hypocalcemia (calcium level ≤ 7.0) in six patients (8.1%) and 23 patients (23%) in groups 1 and 2, respectively ($p = 0.009$). Parathyroid was found on the tissue in 15 (20.3%) of the ipsilateral CND patients and 22 (22%) bilateral CND patients. Permanent hypoparathyroidism was found in three patients (4.1%) and 19 patients (19%) in groups 1 and 2, respectively ($p = 0.005$). CND was associated with a higher incidence rate of hypoparathyroidism and complications. As shown in our study, 21 and 44% of the ipsilateral CLNM was found in cN0 PTC patients incidentally. In contrast, the incidence of permanent hypoparathyroidism and severe hypocalcemia (calcium level ≤ 7.0) in the ipsilateral CND group was significantly lower than in the bilateral CND group. The above results show that ipsilateral CND has the advantages of decreasing complication. A limitation of our study was that it was based on treatments performed 10 years ago. At that time, we focused on complete resection of the tumor burden, rather than preservation of the parathyroid. In conclusion, there were many cases of parathyroid present on removed tissue. Furthermore, we were notified of the loss of parathyroid inadvertently after surgery. If the inadvertent removal of parathyroid could be corrected, we could confidently state the advantages of ipsilateral CND. In group 2, there were higher incidence of RI ablation (41.9% vs. 62%; $p = 0.009$) and ipsilateral LNM (28.4% vs. 44%; $p = 0.035$). These could be caused by advanced disease than extent of CND. There were many cases of total thyroidectomy despite tumor size less than 1 cm, because of contralateral nodule or patient's preference. It might be a variable in determining the role of prophylactic ipsilateral CND.

In conclusion, our study showed lower permanent hypoparathyroidism and severe hypocalcemia rates in prophylactic ipsilateral CND compared with bilateral CND patients. Furthermore, there was no significant difference in recurrence rate between groups. We suggest that prophylactic ipsilateral CND may be safe and effective for selected patients undergoing a total thyroidectomy for cN0 unilateral PTC.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: all authors; Data curation: JGK, YAK; Methodology, Project administration: JGK; Writing-original draft: JGK; Writing-review & editing: JEC, SJL.

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Factors to be considered in designing a faculty development program for medical education: local experience from the Western region of Saudi Arabia

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Background: Among the different aims of medical education, the provision of society with skilled, professional, and knowledgeable healthcare workers who maintain and develop their expertise over a lifetime career is important. The achievement of this goal is linked with the professional development of both faculty members and healthcare workers. This study aims to measure the perception of faculty members regarding their views about the goals of faculty development programs, practices and activities, and factors that determine their achievement.
Methods: A cross-sectional survey was conducted in multiple universities in the Western region of Saudi Arabia. The participants were given a pre-designed self-administered questionnaire generated from literature. The survey questionnaire consisted of three sections that were designed to assess the faculty members' perception on the faculty development program.
Results: A total of 210 faculty members participated in the study. The most important perceived goal was to motivate teachers to become better teachers. The most important perceived practice was establishing a positive climate for teaching and learning. The most important perceived factor was skilled and dedicated staff support.
Conclusion: The results of this study demonstrate that faculty members have positive perceptions regarding all aspects of faculty development programs. This study will raise awareness regarding the importance of faculty development programs in sustaining educational vitality. We recommend the implementation and maintenance of comprehensive faculty development programs in Saudi universities.

Keywords: Faculty; Medical education; Program development; Saudi Arabia

Introduction

Medical education in Saudi Arabia has come a long way since its inception, and continued progress will rely on faculty development, which encompasses all formal and informal activities of health professionals who pursue to improve their knowledge,

skills, and behaviors in both individual and group settings. The need for faculty development programs is crucial in medical schools in Saudi Arabia for several reasons. First, throughout the last decade, there has been a tremendous increase in the number of medical students, which will drive demand for quality medical education [1,2]. Second, fast paced innovations in medical education have taken place over the last two decades, and it is critical to keep up with them [3,4]. Third, continuous changes in learning methods have occurred (e.g., adaptation of learning theories in the methodology of teaching, e-learning, simulation, etc.), and faculty need to be aware of them [5]. Fourth, continuous advancement of technology in medical treatment and management have occurred, and students must receive training in them. Fifth, new assessment methods and tools have been developed (e.g., objective structured clinical examination [OSCE], objective structured practical examination [OSPE], mini-clinical evaluation exercise [miniCEX]), and their appropriate application underpins high quality patient care. Additionally, there are other compelling factors that could possibly affect the performance of faculty members. These include the absence of formal training in academic roles, multicultural distribution of faculty members in the department, different orientations and practices in regard to teaching methodologies, multiple professional job roles (e.g., physician, educator, researcher), heavy workloads, different work assignment (e.g., lecturer, committee chairman), and numerous professional and personal appointments [6-10]. Faculty development programs need to address these issues.

In 2010, the world celebrated the centenary of Abraham Flexner's seminal report on the transformation of American medical schools. This report established the structure of the basic medical education in existence today [11]. Medical education is a lifelong affair with its three different phases—undergraduate, postgraduate, and continuing professional development of practicing clinicians. Among the different aims of medical education, the provision of society with skilled, professional, and knowledgeable healthcare workers who maintain and develop their expertise over a lifetime career is important. The achievement of this goal is linked with the professional development of both faculty members and healthcare workers [12]. In this study, we tried to measure the perception of faculty members from multiple universities in the Western region of Saudi Arabia regarding their views about the goals of the faculty development program, practices and activities, and factors that determine their achievement.

Materials and methods

The Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) approved this study (IRB No: IRBC/430/16).

A cross-sectional survey was conducted in six universities in the Western region of Saudi Arabia. Data collection began in August 2016 and was completed in August 2017. Inclusion criteria included faculty members who were employed full-time or joint appointees, working for the last two years, teaching with or without clinical teaching assignments, and had attended or participated in any faculty development program. This sample included different levels of teachers (clinical and pre-clinical) with variable experience. Faculty members who were newly employed, part-timers, and under the non-teaching category were excluded from the study. This study employed the consecutive sampling technique in the selection of respondents based on the eligibility criteria.

The participants were given a pre-designed self-administered questionnaire generated from the literature [7-10,13,14]. The survey questionnaire was personally distributed among the respondents to be able to maximize the number of completed questionnaires and allow respondents to ask questions. In order to improve the response rate of faculty members, the purpose of the study and its impact on improving the faculty development program were explained with each distributed questionnaire.

The survey questionnaire consisted of three sections that were designed to assess the faculty members' perception on the faculty development program. These sections captured (1) the respondents' views about the stated goals of the faculty development program, (2) practices and activities, and (3) factors that determine whether program goals have been achieved. The questionnaire utilized a five-point Likert scale with five scaled options per item (1, not at all important; 2, not very important; 3, moderately important; 4, important; 5, very important). In addition, a demographic profile of the participants was collected to identify their backgrounds and work experience that might influence their perceptions of the faculty development program.

To ensure the content validity of the questionnaire, it was initially submitted to a panel of experts in the faculty development program for review, and modifications were made accordingly. A pilot testing was conducted, and Chronbach α for internal consistency was calculated, which demonstrated high reliability. In addition, factor analysis was performed to determine the questionnaires' scales and subscales consistency.

Data were collected and analyzed using the IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as means, median, and standard deviation, were used to summarize quantitative variables like age. Qualitative variables, such as sex, were summarized using frequencies and percentages.

To ensure the confidentiality of information, all questionnaires

were anonymous. Furthermore, the cover page of each questionnaire explained the confidentiality issues, included instructions on how to complete the questionnaire, and participants' consent to participate in the study was taken into account.

Results

A total of 210 faculty members participated in the study. The majority of the participants (56.7%; 119 participants) were from King Saud bin Abdulaziz University for Health Sciences, followed by Batterjee College (13.8%; 29 participants), Taif University (10.5%; 22 participants), Ibn Sina National College for Medical Studies (8.6%; 18 participants), Umm Al-Qura University (7.1%; 15 participants), and Rabigh University (3.3%; 7 participants). The majority were full-time faculty members representing 81.4% of the total sample. Most of the participants were above 40 years of age (169 participants) representing 80.5%. The sex distribution showed that the majority of the participants were males (158 participants) representing 75.2%, while only 50 (23.8%) were females, and two (1%) did not specify their sex. More than 50% of the participants were PhD holders (67.1%; 141 participants), followed by master's degree (21%; 44 participants), and bachelor's degree holders (9%; 19 participants). The distribution of academic positions of the participants showed that 114 (54.3%) were assistant professors, 39 associate professors (18.6%), 32 professors (15.2%), 18 lecturers (8.6%), and seven teaching assistants (3.3%). Regarding the length of teaching experience, 110 participants (52.4%) had experience of between 3 and 10 years, 33 (15.7%) had less than 2 years of teaching experience, and only 21 (10%) had more than 20 years of teaching experience (Table 1).

As shown in Table 2, the faculty members' views about the stated goals of the faculty development program, the most important perceived goal was to motivate teachers to become better teachers (4.73 ± 2.99), followed by improving students' learning (4.51 ± 0.74) and enhancing the value of teaching effectiveness (4.47 ± 0.63). The items that were evaluated as important but were least highly rated were to serve personal needs (3.83 ± 1.01), to facilitate effective pedagogy (4.07 ± 0.81), and to foster faculty career development (4.09 ± 0.83).

As shown in Table 3, the faculty members' perception of the faculty development program practices and activities, the most important perceived practice was establishing a positive climate for teaching and learning (4.45 ± 0.71), followed by providing resources (4.37 ± 0.71) and teaching improvement workshops (4.31 ± 0.78). The items that were evaluated as important but were the least highly rated were providing faculty mentoring (3.91 ± 0.84), personal assessment program (4.02 ± 0.85), and being visible and accessible (4.05 ± 0.93).

As shown in Table 4, the faculty members' perception of factors that determine whether the goals of the faculty development pro-

Table 1. Demographic profile of the participants

Item	Frequency (%)
Name of university	
KSAU-HS	119 (56.7)
BC	29 (13.8)
TU	22 (10.5)
ISNCMS	18 (8.6)
UQU	15 (7.1)
RU	7 (3.3)
Employment status	
Full time	171 (81.4)
Joint appointees	39 (18.6)
Age range (yr)	
25–30	4 (1.9)
31–35	9 (4.3)
36–40	26 (12.4)
41–45	64 (30.5)
46–50	51 (24.3)
≥ 51	54 (25.7)
Unclassified	2 (1.0)
Sex	
Male	158 (75.2)
Female	50 (23.8)
Unclassified	2 (1.0)
Educational attainment	
Bachelor	19 (9.0)
Master	44 (21.0)
PhD	141 (67.1)
Unclassified	6 (2.9)
Academic position	
Teaching assistant	7 (3.3)
Lecturer	18 (8.6)
Assistant professor	114 (54.3)
Associate professor	39 (18.6)
Professor	32 (15.2)
Length of teaching experience (yr)	
≤ 2	33 (15.7)
3–5	61 (29.1)
6–10	49 (23.3)
11–15	22 (10.5)
16–20	20 (9.5)
21–35	21 (10.0)
Unclassified	4 (1.9)

KSAU-HS, King Saud bin Abdulaziz University for Health Sciences; BC, Batterjee College; TU, Taif University; ISNCMS, Ibn Sina National College for Medical Studies; UQU, Umm Al-Qura University; RU, Rabigh University.

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Table 2. Level of importance of the following goals to the faculty development program

Rank	Goal	Mean ± SD	Verbal interpretation
1	To motivate teachers to become better teacher	4.73 ± 2.99	Very important
2	To improve students learning	4.51 ± 0.74	Very important
3	To enhance value of teaching effectiveness	4.47 ± 0.63	Very important
4	To help faculty member learn excellent teaching	4.42 ± 0.78	Very important
5	To focus on teaching that are set on high standards	4.38 ± 0.71	Very important
6	To provide faculty development programs	4.36 ± 0.66	Very important
7	To build and develop the culture of teaching	4.34 ± 0.72	Very important
8	To provide skills training	4.33 ± 0.73	Very important
9	To introduce different teaching strategies	4.31 ± 0.80	Very important
10	To improve the learning environment	4.30 ± 0.74	Very important
11	To create a climate of excellent teaching	4.28 ± 0.79	Very important
12	To improve faculty evaluations	4.25 ± 0.87	Very important
13	To create norm of excellent teaching	4.21 ± 0.77	Very Important
14	To foster faculty career development	4.09 ± 0.83	Important
15	To facilitate effective pedagogy	4.07 ± 0.81	Important
16	To serve personal needs	3.83 ± 1.01	Important

SD, standard deviation.

Table 3. Level of importance of the following practices to the success of faculty development program

Rank	Practice	Mean ± SD	Verbal interpretation
1	Establishing a positive climate for teaching and learning	4.45 ± 0.71	Very important
2	Providing resources	4.37 ± 0.71	Very important
3	Teaching improvement workshops	4.31 ± 0.78	Very important
4	Collaboration among faculty	4.20 ± 0.75	Important
5	Providing technical support	4.19 ± 0.76	Important
6	Networking among faculty and across academic and administrative departments	4.17 ± 0.76	Important
7	Assessing needs	4.15 ± 0.79	Important
8	Establishing learning communities	4.13 ± 0.77	Important
9	Being visible and accessible	4.05 ± 0.93	Important
10	Personal assessment program	4.02 ± 0.85	Important
11	Providing faculty mentoring	3.91 ± 0.84	Important

SD, standard deviation.

Table 4. Level of importance of the following factors in achieving faculty development program goals

Rank	Factor	Mean ± SD	Verbal interpretation
1	Skilled and dedicated staff support	4.49 ± 0.72	Very important
2	Strong administrative support	4.47 ± 0.80	Very important
3	Engaged and supportive faculty	4.44 ± 0.74	Very important
4	Adequate budget	4.43 ± 0.81	Very important
5	Ensuring the continuity of programs	4.40 ± 0.73	Very important
6	Location and physical facilities	4.31 ± 0.75	Very important
7	Strategic planning and goal setting	4.29 ± 0.84	Very important
8	Timing of offered program	4.28 ± 0.85	Very important
9	Climate of collaboration	4.26 ± 0.76	Very important
10	Student support	4.17 ± 0.91	Important
11	Grant funding	4.15 ± 0.84	Important
12	Cultural tradition of support	4.06 ± 0.90	Important
13	Providing food and refreshments	3.36 ± 1.22	Important

SD, standard deviation.

gram were achieved, the most important perceived factor was skilled and dedicated staff support (4.49 ± 0.72), followed by strong administrative support (4.47 ± 0.80) and engaged and supportive faculty (4.44 ± 0.74). The items that were evaluated as important but rated lowest were providing food and refreshments (3.36 ± 1.22), cultural tradition of support (4.06 ± 0.90), and grant funding (4.15 ± 0.84).

Discussion

Saudi universities are keen to achieve their strategic goals. One of these goals is to emphasize faculty development programs, especially in the light of continuously developing new pedagogical modalities and expectations. In order to achieve these goals, it is mandated that institutions expand and maintain regular, readily available, accessible, and comprehensive faculty development programs targeting faculty competency needs and educational objectives. Medical education in Saudi Arabia is challenged with the shortage of teachers who are adequately prepared to handle tasks in response to the emergent needs [2]. This was shown clearly in this study since the most important factor perceived in achieving faculty development program goals was skilled and dedicated staff support. Faculty should be engaged in all curricular and extracurricular activities, which require supervision and support by college administration.

In general, teachers view their task as imparting knowledge with disjunction between their practice and their beliefs. One of the primary goals of faculty development is to promote students' learning and motivate teachers to become better teachers. A medical teacher is considered a helper and a guide who fits into many different and simultaneous roles, such as being an instructor, a task master, facilitator, trainer, etc. Achievement of such ends may rest with individual teachers openly and actively engaging in teaching with reflection on their performance [15]. Reflection is considered a key concept of transformative learning theory, which is based on constructivist assumptions. Mezirow [16] considered transformative learning as a learning method that is based on our perceptions and experiences. He defined the process of learning as "the social process of constructing and appropriating a new or revised interpretation of the meaning of one's experiences as a guide to action." Our study confirms the importance of creating a climate and norm for excellent teaching.

McKeachie [17] argued that teaching skillfully may be less time consuming than teaching badly. It is well known that the need for effective learning increases as the time available to spend with students decreases. This was shown in our study as an important goal of faculty development program, which was to provide teaching improvement workshops and help faculty members learn excellent teaching methods.

According to Lueddeke [18], a fundamental education premise is that teaching influences student learning, and by improving educational knowledge and teaching practice, students should benefit. Evidence supporting the assumption that faculty development does impact on student learning and outcomes is accumulating. In our study, goals for faculty development programs included improved students' learning, helping faculty members learn appropriate and targeted teaching methods, and enhancing value of teaching effectiveness.

Teaching is a complex process and a demanding task. It is of paramount importance for the present-day teacher to become a part of the far-reaching changes that are taking place in the field of medical education. These changes include advances in learning styles and assessment methods, innovative curriculum models, and shifting from the conventional role of a teacher. These changes will not be achieved without a strong administrative support and adequate resources [19]. Our study clearly showed the importance of strong administrative support and adequate budget.

Faculty development is not just a "one-shot" intervention or "train the trainer" type of workshop. It is a continuous series of efforts that help faculty evolve their knowledge and skills as educators. This was reflected by the results of our study in which an important perceived factor in achieving faculty development program goals was ensuring the continuity of programs and strategic planning and goal setting. Comprehensive and intensive ongoing faculty development programs are necessary to increase teachers' knowledge and skills and reflection on practice. Protected time (i.e., time with salary support that faculty have for their non-educational responsibilities, such as research studies, manuscripts writing, or quality improvement initiatives) will allow participants to meaningfully test different approaches and use more student-focused activities. This will ultimately lead to improvement in student learning. This was also shown by our study as the timing of offered programs was among the most important factors in achieving faculty development program goals [20].

Limitations of this study include the small number of participants from certain universities. Future studies should initiate an urgent call to encourage participation in studies and research on the faculty development area of medical education. In addition, the results of 119 participants of King Saud bin Abdulaziz University for Health Science may influence the overall outcome. Furthermore, the results of the survey may vary depending on the faculty development program being offered to the survey participants. Therefore, an analysis of the current status of the faculty development program is warranted. An advantage of performing

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this research is creating ideas for future research on this important topic. For example, research may be conducted on the correlation between the recognition of faculty development and the difference in the educational environment at a university with a sample size similar to King Saud bin Abdulaziz University for Health Science.

In conclusions, the results of this study demonstrate that faculty members have positive perceptions regarding all aspects of faculty development programs. This study will raise awareness regarding the importance of such programs in sustaining educational vitality. We recommend the implementation and maintenance of comprehensive faculty development programs in Saudi universities. In addition, we recommend the development of a comprehensive curriculum for faculty development, which would also construct a solid ground for a diploma in medical education. Further studies regarding other aspects of faculty development programs, such as the current problems and needs of faculty members, contributing factors to achieve faculty development goals, barriers and obstacles impeding achieving such goals, and the effectiveness of existing faculty development programs, should be conducted. These studies are important to explore the needs and difficulties in implementing faculty development programs.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: all authors; Data curation: HA, BS, LA; Formal analysis: HA, BS, AT, JN; Funding acquisition: HA, JN; Methodology, Investigation: all authors; Resources, Software: HA; Supervision, Validation: HA, JN; Project administration: HA, BS, LA; Visualization: HA, BS; Writing-original draft: HA, BS, JN; Writing-review & editing: all authors.

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Mineralization-inducing potentials of calcium silicate-based pulp capping materials in human dental pulp cells

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Background: This study was performed to provide a long-term bacterial seal through the formation of reparative dentin bridge, calcium silicate-based pulp capping materials have been used at sites of pulpal exposure. The aim of this study was to evaluate the mineralization-inducing potentials of calcium silicate-based pulp capping materials (ProRoot MTA [PR], Biodentine [BD], and TheraCal LC [TC]) in human dental pulp cells (HDPCs).
Methods: Specimens of test materials were placed in deionized water for various incubation times to measure the pH variation and the concentration of calcium released. The morphology of HDPCs cultured on the specimens was examined using a confocal laser scanning microscope (CLSM). Alizarin red S staining and alkaline phosphatase assays were used to evaluate mineralization-inducing potentials of the capping materials.
Results: BD showed the highest calcium release in all test periods, followed by PR and TC. (p<0.05). All experimental groups showed high alkalinity after 1 day, except at 14 days. BD showed the highest cell viability compared with PR and TC after 1 and 3 days, while TC showed the lowest value (p<0.05). The CLSM analysis showed that cells were well adhered and expressed actin filaments for all pulp capping materials. Mineralization by PR and BD groups was higher than that by TC group based on alizarin red S staining. BD showed significantly higher alkaline phosphatase activity than PR and TC, while TC showed the lowest value (p<0.05).
Conclusion: Within the limitations of the *in vitro* study, BD had higher mineralization-inducing potential than PR and TC.

Keywords: Biocompatibility testing; Dental material; Dental pulp capping; Dentin

Introduction

At sites of pulpal exposure, dentinal continuity may be restored through the formation of a dentin bridge across the exposure. There have been reports regarding dentin bridging after pulp capping with agents such as calcium hydroxide. Calcium hydroxide is a preferable material to manage pulp exposure because of its antibacterial characteristic and ability to induce reparative dentin formation [1]. However, it has been reported that calcium hydroxide dissolves over time, causing tunnel defects in dentin bridges, and these bridges allow communication between the pulp and capping material [2].

These findings highlight the need to use materials capable of providing a long-term bacterial seal over capped pulps. Among them, mineral trioxide aggregate (MTA) has a better capping effect by stimulating the formation of the perfect reparative dentin bridge without any toxic chemical effects. Previous studies showed that MTA was more effective than calcium hydroxide in

long-term vital pulp therapy [3,4]. However, high prices, difficulties in handling and application, and longer binding duration remain disadvantages of MTA. Long setting times are an obstacle to using MTA as a pulp capping material since MTA needs to be layered with other materials while it is still fresh [5].

By adding accelerators and modifiers, several researchers attempted to decrease the setting reaction time and increase the effectiveness of MTA for direct pulp capping. One calcium silicate-based pulp capping material is Biodentine (BD; Septodont, Saint-Maur-des-Fosses, France), which has the advantage of a shorter setting time of 12 minutes. BD is a powder consisting of tricalcium silicate, dicalcium silicate, calcium carbonate, calcium chloride, and zirconium oxide as a radiopacifier. Previous studies showed that BD works similarly to MTA in both *in vitro* and *in vivo*. In addition, BD has a positive effect on pulp cells and helps them form reparative dentin [6,7]. However, research data on the mineral-inducing potential of BD is still lacking.

TheraCal LC (TC; Bisco Inc., Schaumburg, IL, USA) is a light-cured, resin-modified calcium silicate-based material designed for use in direct and indirect pulp capping and as a protective liner under various filling materials. The light-cured set permits immediate placement and condensation of the restorative material. It contains approximately 45 percentage by weight (wt%) mineral material (type III Portland cement), 10 wt% radiopaque component, 5 wt% hydrophilic thickening agent (fumed silica), and approximately 45 wt% resin [8]. In previous studies, TC showed good sealing abilities [8] and was well-tolerated by immortalized odontoblast cells [9]. It is necessary to evaluate whether that material has a mineral-inducing potential that can form a reparative dentin bridge. However, its mineral-inducing potential has not been studied yet.

This study aimed to evaluate the mineralization-inducing potentials of calcium silicate-based pulp capping materials on human dental pulp cells (HDPCs), by the following five outcome measures: (1) the amount of calcium release from the capping materials, (2) the pH values of aqueous medium exposed to the extracts of the capping materials which stimulate the pulp cell differentiation, (3) the cell viability by an MTT assay, (4) cytoskeletal organization of the HDPCs cultured on the extract of the capping materials and viewed with a microscope, and (5) alizarin red S staining images and alkaline phosphatase (ALP) activity of odontoblasts cultured on the capping materials.

Materials and methods

1. Specimen preparation

Premixed specimens of ProRoot MTA (PR; Dentsply, Tulsa, OK, USA), BD, and TC were made according to the manufacturers' instructions (Table 1). Discs (10-mm diameter and 2-mm thickness) were made using a stainless-steel frame as a mold. Each disc was allowed to set for 24 hours followed by polishing with #400, 600, and 1,200 grit lapping film (3M lapping film; 3M, Maplewood, MN, USA). The colors of disc obtained by digital camera show the white color of MTA and TheraCal, and Biodentine has the Ivory color. The specimens were placed in a 48-well tissue culture plate, kept under an ultraviolet clean bench for 24 hours, and further sterilized by ultraviolet irradiation (Figs. 1, 2).

2. Primary culture of human dental pulp cells

HDPCs were provided by the Department of Oral Pathology (School of Dentistry, Kyungpook National University, Daegu, Korea). Fragments of pulp tissue acquired from an extracted human third molar were cultured in minimal essential medium alpha (MEM-α; Invitrogen, Carlsbad, CA, USA) containing 10% fetal bovine serum (FBS; Invitrogen), 100 U/mL penicillin, and 100 U/mL streptomycin (Invitrogen). The cultures were stored in a

Table 1. Materials used in this study

Product	Concentration
ProRoot MTA (Dentsply, Tulsa, OK, USA)	
Portland cement	75%
Bismuth oxide	20%
Calcium sulfate	5%
Biodentine (Septodont, Saint-Maur-des-Fosses, France)	
Powder: tricalcium silicate, dicalcium silicate, calcium carbonate, zirconium oxide, calcium oxide, iron oxide	Packaged in capsule (0.7 g)
Liquid: calcium chloride, a hydrosoluble polymer, water	Packaged in pipette (0.18 mL)
TheraCal LC (Bisco Inc., Schamburg, IL, USA)	
Portland cement type III	< 60%
Polyethylene glycol dimethacrylate	< 50%
Barium zirconate	< 10%

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humidified atmosphere of 5% CO_2 at 37°C.

3. Measurement of calcium release from pulp capping materials

The calcium release of each specimen was measured to evaluate the mineralization-inducing potentials. The disc specimen was placed in 10 mL of deionized water for 1 and 7 hours and 1, 4, 7, 14, and 21 days. The amount of calcium ion released from the capping materials in the water was measured by inductively coupled plasma atomic emission spectroscopy (ICP; Optima 7300DV, PerkinElmer, Shelton, CT, USA). ICP is a technique for detecting trace metals. It excites atom and releases ions from electromagnetic radiation at characteristic wavelengths of a particular element.

4. Measurement of pH value

The pH values of each specimen were measured to assess the amount of eluted hydroxide ions, which stimulate the pulp cell differentiation. The disc specimen was placed in 10 mL of deionized water for 1 and 7 hours and 1, 4, 7, 14, and 21 days. The pH value of the aqueous medium, which was exposed to the extracts of the capping materials, was measured by a pH meter (Orion 3 Star, Thermo Scientific, Singapore). The pH apparatus was calibrated with solutions of pH 7.0 and 4.0. The electrode was washed with ultrapure water and dried after every measurement.

5. Cell viability test

An MTT assay was conducted to evaluate the effects of the capping materials on cell viability. The amount of HDPCs on each specimen was measured by a colorimetric immune assay that is based on measuring bromodeoxyuridine (BrdU) incorporated during DNA synthesis. BrdU enzyme-linked immunosorbent assay (ELISA; Roche Molecular Biochemicals, Nutley, NJ, USA) was performed according to the manufacturer's instructions. Cells were seeded at a density of 2×10^4 cells per well onto a 48-well plate and were cultured for 1 and 3 days with each specimen. Then, the BrdU-labeling solution was added to each well. The solution was applied to the cells in a CO_2 incubator at 37°C for 4

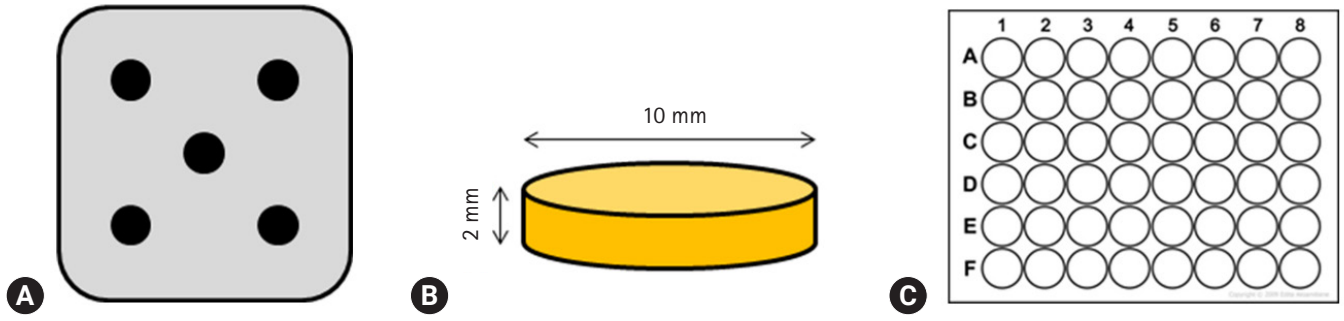

Fig. 1. (A) Stainless-steel frame with five holes, (B) schematic diagram of the specimen, (C) 48-well cell culture plates, having flat bottom which matches the specimen in size.

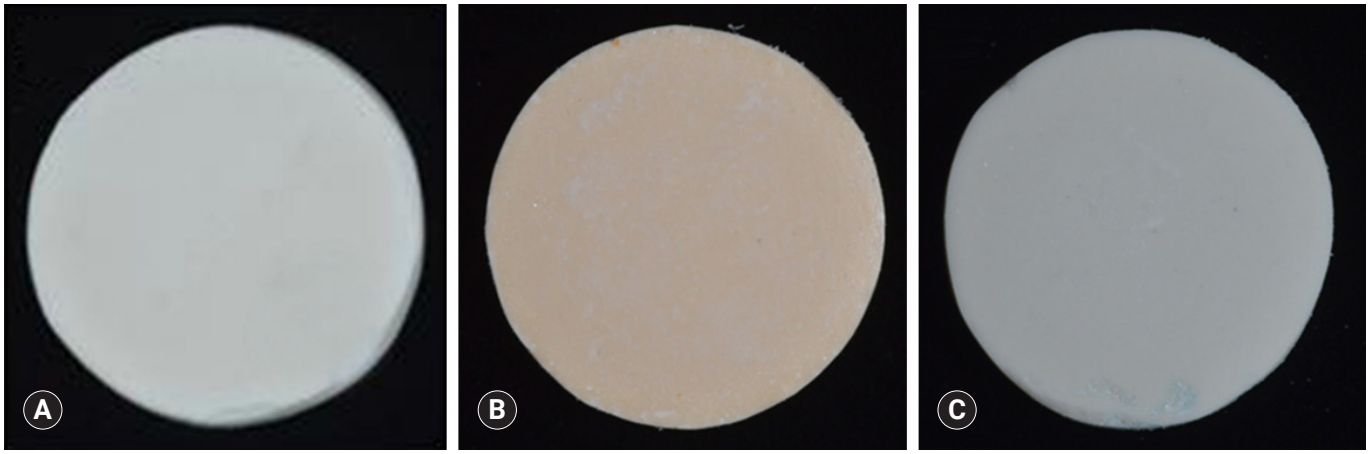

Fig. 2. Images of specimens. (A) ProRoot MTA, (B) Biodentine, (C) TheraCal LC.

hours. The supernatant of the cell solution was removed by pipetting and were washed with phosphate-buffered saline (PBS) twice. After treating the cells with 0.25% trypsin-ethylenediaminetetraacetic acid (EDTA; Gibco, Tokyo, Japan), the cells were harvested by centrifugation at 1,000 rpm for 15 minutes. For fixing and denaturing DNA, the harvested cells were mixed with FixDenat (ELISA; Roche Molecular Biochemicals) solution and then incubated for 30 minutes. Diluted anti-BrdU peroxidase (dilution ratio of 1:100) was added to the cells, which was then incubated at 20°C for 2 hours. The unbound antibody conjugate was removed, and 100 μL substrate was added to the 48-well plate. Then, the cells were incubated for 20 minutes. The reaction was finished by adding 25 μL of H_2SO_4 solution (1 M) to the cells. The solution was moved to a 96-well plate, and the absorbance of the solution was measured using an ELISA plate reader (EL 9800; Roche Molecular Biochemicals) for 5 minutes at 450 nm with a reference wavelength of 690 nm. The blank reading corresponded to 100 μL of culture medium with or without BrdU.

6. Cytoskeletal organization

To assess the cytoskeletal organization of HDPCs, which were treated with the extracts of the capping materials, double staining was performed. Briefly, a prepared specimen of each cement was stored in 10 mL MEM-α contained 10% FBS for 3 days to produce the extracts used for the treatment of HDPCs. The cells were seeded onto a 48-well plate (2×10^4 cells/mL) and were cultured for 1 day with the extracts of the specimen. The cells were fixed with 4% paraformaldehyde in PBS and washed with a PBS solution containing 0.05% Tween-20. After permeabilization with 0.1% Triton X-100 in PBS for 15 minutes at 25°C, the cells were incubated for 30 minutes in PBS containing 1% bovine serum albumin. Subsequently, 5(6)- tetramethyl-rhodamine isothiocyanate-conjugated phalloidin (Millipore, Temecula, CA, USA) was added to the 48-well plate, and the cells were incubated for approximately 1 hour. The plates were washed three times (10 minutes each) using the buffer solution and incubated with 4′,6-diamidino-2-phenylindole (Millipore) for 5 minutes. The scaffolds were washed three times (10 minutes each) with the buffer solution, and fluorescence images were visualized by a CLSM (model 700; Carl Zeiss, Oberkochen, Germany).

7. Alizarin red S staining

Mineralized nodules from differentiated cells were visualized through alizarin red S staining to evaluate the mineralization-inducing potentials of each specimen. Cells were seeded at a density of 2×10^4 cells per well onto a 48-well plate and were cultured for 14 days with each specimen. Then, mineralization of the cells was evaluated through alizarin red S staining (Sigma-Aldrich, St. Louis, MO, USA). Briefly, cells were fixed with 4% formalin for 1 hour at 4%, washed three times with deionized water, and then stained with 40 mmol/L of alizarin red solution (pH = 4.2). The stained cell plate was washed with deionized water, and the stained image was obtained with the scanner. To remove the stain, the samples were treated with 10% cetylpyridinium chloride solution (pH = 7.0) for 15 minutes, and absorbance was measured at a wavelength of 540 nm with a standard solution for the quantitative assessment.

8. Alkaline phosphatase activity assay

ALP is the marker of early differentiation and extracellular matrix mineralization. Cells were seeded at a density of 2×10^4 cells per well onto a 48-well plate and were cultured for 14 and 21 days with each specimen. Then, the cells were scraped into cold PBS and sonicated with a cell disruptor (Heat System Ultrasonics, Plainview, NJ, USA) in an ice-cold bath. ALP activity in the supernatant was determined using p-nitrophenyl phosphate as a substrate. Absorbance was measured at 410 nm using an ELISA plate reader.

9. Statistical analysis

Statistical analysis of the data from calcium ion release, pH, MTT assay, and ALP activity test was performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). One-way ANOVA, followed by the Tukey test, was performed. The level of significance was established at 0.05.

Results

1. Measurement of calcium release

BD showed significantly higher calcium release compared to PR and TC in all test periods ($p < 0.05$) (Fig. 3). Calcium release from PR was significantly higher than TC ($p < 0.05$). The amount of calcium released from both BD and PR constantly increased with increased immersing time. However, the calcium release from TC slowly increased up to 4 days and thereafter almost stopped.

2. Measurement of pH value

After 1-day immersion, PR and BD had similar pH values, but TC showed lower pH value compared with others (Fig. 4). In the early stage, PR showed the highest pH value compared with others. All experimental groups showed high alkalinity near pH 11.0 after 1 day, except at 14 days. There was no significant difference in pH values between PR, BD, and TC after 1 day, except at 14 days ($p > 0.05$).

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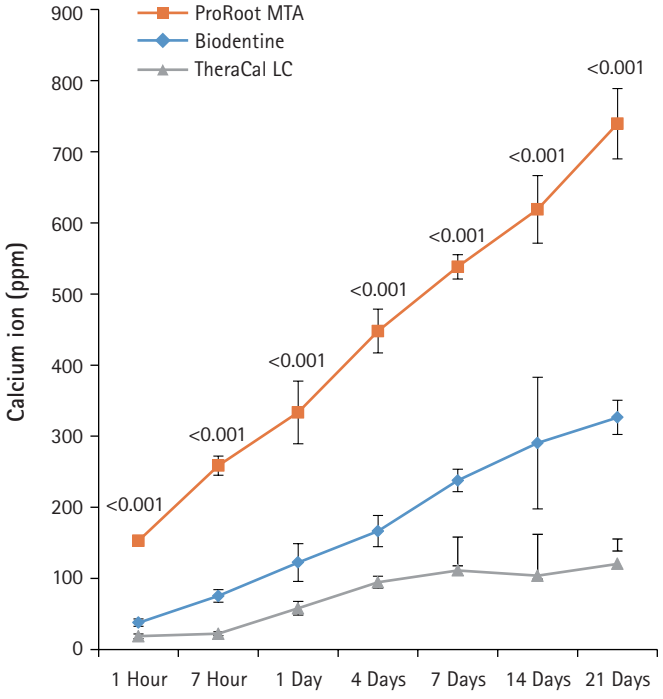

Fig. 3. The amount of calcium released from ProRoot MTA, Biodentine, and TheraCal LC in deionized water as a function of immersion time. The amount of calcium released from ProRoot MTA and Biodentine increased constantly with the immersion time, whereas the released calcium from TheraCal LC had a tendency to increase until day 4, and almost stopped increasing. For each of the three types of samples, five samples were used at each time of the experiment. Error bars indicate standard errors of the means.

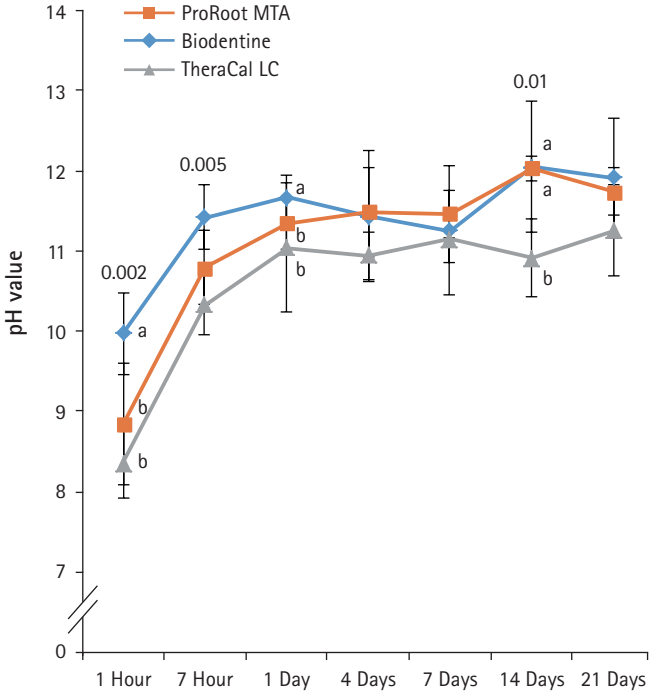

Fig. 4. pH values of aqueous medium exposed to the extracts of the capping materials as a function of immersion time. pH values for ProRoot MTA, Biodentine, and TheraCal LC were stable in near 11.0 after 1 day, except at 14 days. Values not sharing a common letter (a, b) are significantly different (p<0.05). For each of the three types of samples, five samples were used at each time of the experiment. Error bars indicate standard errors of the means.

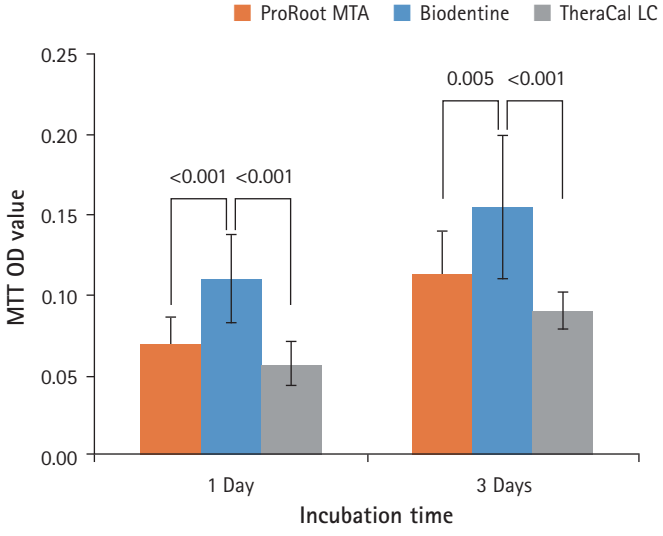

Fig. 5. Effects of ProRoot MTA, Biodentine, and TheraCal LC on cell viability measured by MTT assay. On both 1 and 3 days, the cell viability for Biodentine was highest. However, ProRoot MTA and TheraCal LC showed no significant difference (p<0.05). For each of the three types of samples, six samples were used at each time of the experiment. Error bars indicate standard errors of the means. MTT OD value: cell viability absorbance (490 nm).

3. Cell viability test

As shown in Fig. 5, BD showed the highest cell viability compared with PR and TC on both 1 day and 3 days. TC showed significantly lower cell viability than BD, but there was no significant difference between PR and TC ($p < 0.05$).

4. Cell morphologic analysis

Cells were observed by confocal laser scanning microscopy to evaluate cell growth and morphology. As shown in Fig. 6, cells are well adhered in the shape of the fusiform and expressed actin filaments for all pulp capping materials.

5. Alizarin red S staining and alkaline phosphatase activity test

There was a high increase in mineralization in the PR and BD groups compared with the TC group based on alizarin red S staining for calcium (Fig. 7). However, there was no difference in mineralization between PR and BD. In terms of ALP activity, there was a significant difference between the three groups. BD showed

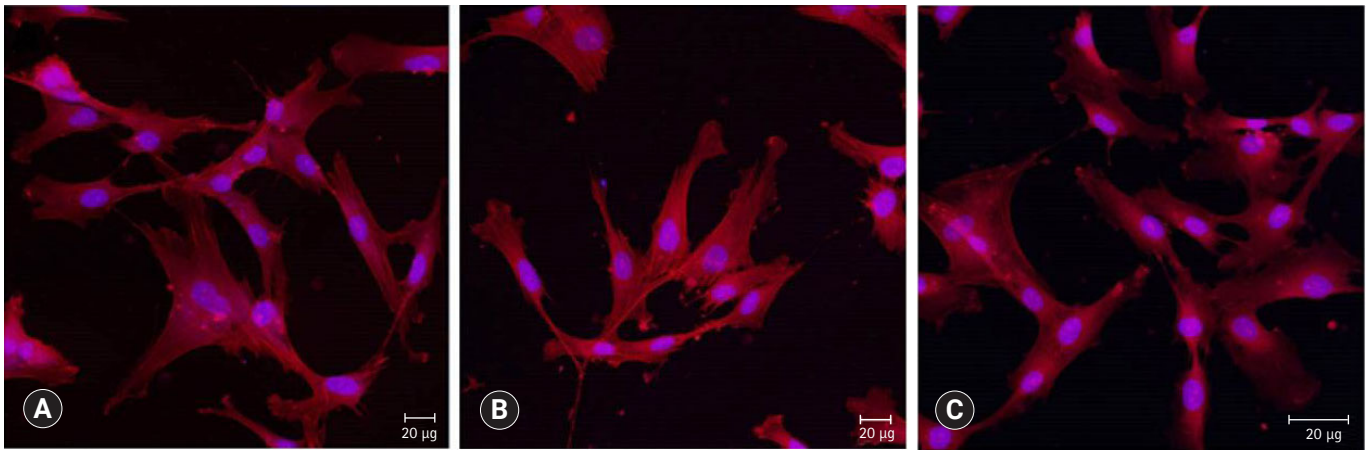

Fig. 6. Confocal laser scanning microscopic images (actin [red], nucleus [blue]) of HDPCs cultured on (A) ProRoot MTA, (B) Biodentine, and (C) TheraCal LC which were incubated in the extract of the materials for 3 days. Cells were well adhered and expressed actin filaments for all pulp capping materials (×200).

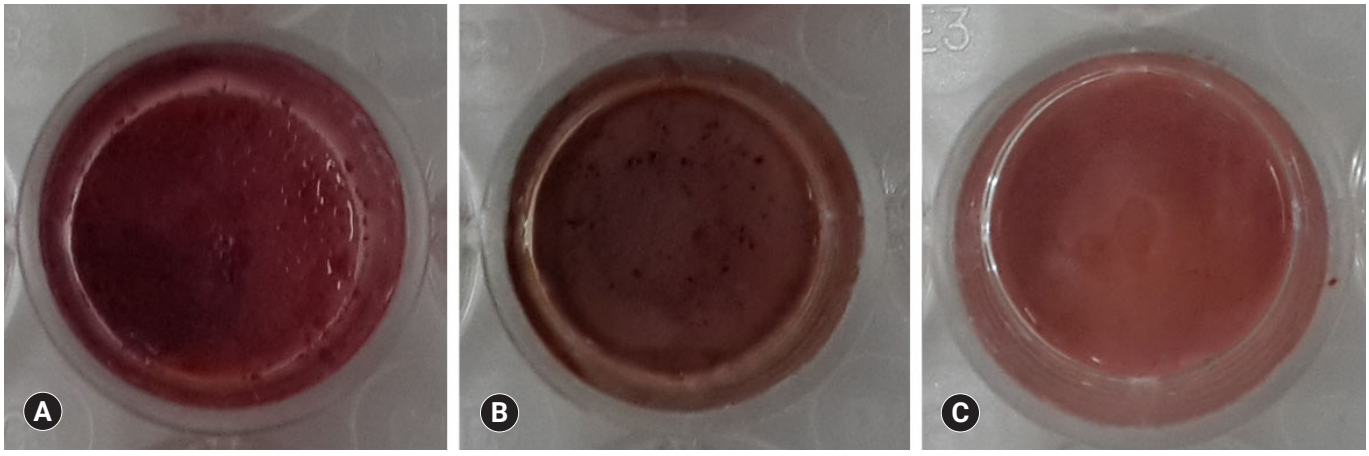

Fig. 7. Alizarin red S staining images of odontoblasts cultured on (A) ProRoot MTA, (B) Biodentine, and (C) TheraCal LC for 14 days. There was a high increase in mineralization in the ProRoot MTA and Biodentine groups compared with the TheraCal LC group based on alizarin red S staining for calcium.

a significantly higher value than PR and TC, while TC showed the lowest activity compared to the others ($p < 0.05$) (Fig. 8).

Discussion

This study was designed to investigate the mineralization-inducing potentials of pulp capping materials on cultured HDPCs.

In regards to the calcium ion release, BD showed a markedly higher release of free calcium ions compared with PR and TC. The increased calcium release from BD has been considered to be correlated with the presence of a calcium silicate component, calcium chloride, and low solubility (11.93%). This is likely linked to a superplasticizer that is commonly used to reduce the amount of water required (L/P 0.257) to disperse the particles and to enhance the fluidity, making the cement self-consolidating. In addition, the fast hydration reaction of tricalcium silicate can be correlated with the low solubility and high calcium release at early endpoints [8]. In another previous study, BD exhibited advanced hydration both *in vitro* and after pulp capping. This was evident from the densely hydrated product in the cement matrix and the absence of unhydrated cement particles after 14 days of hydration [10].

In contrast, TC exhibited the lowest calcium ion leaching. This result can be attributed to the fact that the release of calcium ions is limited due to the presence of a resin-modified matrix in the structure of TC after setting. The restriction of fluid absorption

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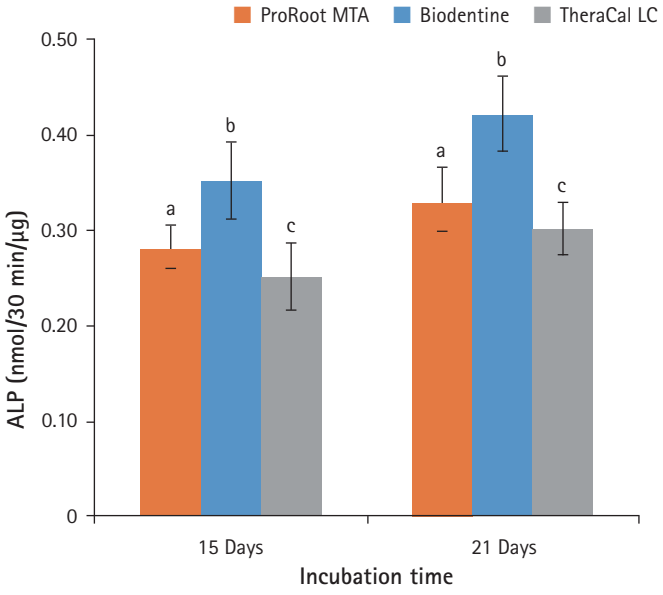

Fig. 8. Alkaline phosphatase (ALP) activity of odontoblasts cultured on pulp capping materials for 14 and 21 days. The ALP activity of odontoblasts in Biodentine group was highest on both observation days. However, the odontblasts in TheraCal LC group showed the lowest ALP activity ($p<0.05$). For each of the three types of samples, five samples were used at each time of the experiment. Values not sharing a common letter (a, b, c) are significantly different ($p<0.05$). Error bars indicate standard errors of the means.

causes calcium ions to scarcely move along the resin matrix [10].

The release rate of calcium ions is a key factor for successful endodontic and pulp capping therapies because the mineralization of cells (osteoblasts, cementoblasts, pulp cells, and odontoblasts) are influenced by calcium ions [7]. Calcium ions specifically modulate osteopontin and bone morphogenetic protein-2 levels during pulp calcification [11]. In addition, eluted calcium ions increase the proliferation of HDPCs in a dose-dependent manner [12], and calcium release enhances the activity of pyrophosphatase, which helps to maintain dentine mineralization and the formation of a dentin bridge [13].

To assess the amount of eluted hydroxide ions from the pulp capping materials, pH values of the aqueous medium, which was exposed to the extracts of the test materials, were measured. All materials showed similar alkaline activity. The pH values of all the test material reached a maximum of 11 after 7 hours, showing a plateau since 1 day immersion. This is in accordance with the results of previous studies [14,15].

The high alkalinity of calcium hydroxide seems to result in mild stimulation of cell differentiation. Hydroxide ions stimulate the release of ALP and bone morphogenetic protein 2, which participate in the mineralization process [16,17].

The release of calcium hydroxide is mainly the result of the stimulation of odontoblast activity and subsequent mineralization. The pulp capping materials that are based on tricalcium silicate all allegedly release calcium hydroxide as a by-product of hydration. This has been demonstrated for MTA [18] and BD [19]. Calcium, as well as hydroxyl ions released from the capping materials, regulate the event leading to tertiary dentinogenesis. For the biological effects of calcium hydroxide, the release of bioactive molecules, either through direct stimulation of cells or by solubilization of dentin extracellular matrix, is vital. Calcium silicate cement, together with microcrystals deposited on its surface, provides a biologically active substrate for the adsorption of biomolecules and adhesion of odontoblasts [2].

In this study, the number of calcium ions released from the capping materials and pH value of the medium were measured in deionized water rather than simulated body fluid in order to standardize the test conditions and hence allow a comparison of the data with other future studies.

Prior to investigating the mineralization-inducing potentials of the materials, the biocompatibility was compared by evaluating the effects of the capping materials on cell morphology and cell viability in this study. BD showed better cell viability than PR and TC on the MTT assay. The result of the current study corresponded with an investigation by Poggio et al. [20], which showed BD induced a more favorable cell response due to high mitochondrial activity compared with MTA and TC during the 72 hours of incubation. Meanwhile, other researchers reported that BD showed similar cell viability to MTA [5,21].

Confocal laser scanning microscopic images were used to compare cell morphology and cytoskeletal organization. When HDPCs were cultured on the capping materials for 1 day, the cultured cells appeared flat and showed well-defined cytoplasmic extensions, indicating all materials allowed cell attachment and growth. The actin microfilament cytoskeleton is involved in cell processes, cell shape, and cell attachment. As the cell adheres to a substrate material, filopodia are formed. They are moved into place by actin acting upon the plasma membrane. The actin is observed in the filopodia as directed tight parallel bundles. Contractile stress fibers are seen once the filopodia are attached [22]. Our results showed that the cytoskeletal organization of cells was observed, as shown in Fig. 6. The phenotype of differentiation-induced HDPCs is known to resemble several crucial characteristics of odontoblasts, such as increased ALP activity, mRNA expression of differentiation markers genes, and the formation of mineralized matrix *in vitro* [23].

ALP is the most frequently used marker of odontoblastic cell

differentiation because ALP activity is greatest just before cell mineralization begins. In this study, odontoblastic differentiation of HDPCs was evaluated using an ALP activity assay. There was a significant increase in the ALP activity of the cells for BD, followed by PR and TC. This result is consistent with that of a previous study reporting the up-regulation of osteogenic or odontogenic genes by BD in HDPCs [24]. BD and PR promoted the odontoblastic differentiation with the development of mineralized nodules, which is the nucleation of the calcium phosphate layer on the surface of the material, whereas nodules were rarely observed in TC. Nowicka et al. [25] reported that the reparative tissues induced by two materials were homogeneous with the BD group, showing the dentin bridge of better quality. It was also reported that BD exerted significantly higher stimulatory activity on pulp cells in comparison with MTA after direct pulp capping to animal teeth, resulting in thicker reparative dentin bridges and greater incidence of ectopic pulp calcification in developing teeth [26].

In this study, TC showed relatively low odontoblastic differentiation compared with PR and BD. This result could be explained by several reasons. First, TC may undergo a complicated setting reaction by setting light-cured resin initially and hydrating tricalcium silicate, thereafter [27], inducing insufficient hydration. Moreover, TC is a resin-modified capping material, and it does not use water as mixing fluid. According to a previous study conducted by Camilleri et al. [10], the hydration of TC depends on fluid uptake through the resin matrix from the environment. Although there is calcium ion release from hydrating TC, no calcium hydroxide is formed, as has been verified by X-ray diffraction analysis in previous research. Instead, calcium phosphate was deposited over the TC surface [19]. Further study may be needed to reveal the precise setting mechanism of TC.

Next, cytotoxicity of the unpolymerized monomers could cause adverse effects on cellular metabolism [28]. Poggio et al. [20] reported that TC had slight cytotoxicity in comparison with BD and MTA-Angelus, which showed no cytotoxicity. Some resin monomers, especially 2-hydroxyethyl methacrylate (HEMA) and triethylene glycol dimethacrylate (TEGDMA), are commonly identified in eluates of polymerized composite resins [29]. According to Kwon et al. [30], the ALP activity of HDPCs was reduced by TEGDMA and HEMA at noncytotoxic concentrations. The mRNA expression of dentin sialophosphoprotein, osteocalcin, and osteopontin was also downregulated by resin monomers. Therefore, exposure to TEGDMA and HEMA for certain period leads to the suppression of the differentiation of HDPCs via different signaling pathways. Since TC is known to contain HEMA and TEGDMA, the degree of conversion and the amount of unpolymerized monomers of TC after light curing need to be investigated in further studies.

A limitation of this study is the lack of previous studies analyzing the precise setting mechanism of TC and the biological effects of TC. Although our results are promising, further studies are required to analyze the influence of other factors such as gene expression analysis by real-time polymerase chain reaction and protein expression analysis by western blotting. Furthermore, research on the effects of the immunological system and pulp tissue *in vivo* is also required.

Within the limitations of this *in vitro* study, it was found that BD had higher mineralization-inducing potentials than PR and TC; therefore, BD is potentially suitable for use as a pulp capping material. TC showed similar biocompatibility to PR, while less effective on mineralization-inducing potentials.

Acknowledgments

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Notes

This paper is based on the author's doctoral dissertation (The Graduate School of Kyungpook National University, 2016).

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Synchronous ileal inflammatory fibroid polyp and Meckel's diverticulum found during laparoscopic surgery for adult intussusception

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We present a rare case of synchronous ileal inflammatory fibroid polyp and Meckel's diverticulum detected during laparoscopic surgery for adult intussusception. A 48-year-old woman presented with sudden onset of severe abdominal pain. Abdominal computed tomography revealed a segment of ileocecal intussusception. Thus, laparoscopic exploration was performed, which revealed an ileal mass with an outpouching closed luminal structure in the distal ileum. Two abnormal structures were resected via mini-laparotomy, and the patient was discharged without postoperative complications. Histopathological examination confirmed an ileal inflammatory fibroid polyp and Meckel's diverticulum with ectopic pancreatic tissue.

Keywords: Intestinal obstruction; Intestinal polyps; Intussusception; Meckel diverticulum

Introduction

Intussusception rarely causes intestinal obstruction in adults and accounts for approximately 1%–5% of all cases of bowel obstruction [1]. In contrast to pediatric intussusception, most cases of adult intussusception are secondary to an underlying pathology, such as primary/metastatic malignancies or benign tumors that serve as the leading point of intussusception [2].

An inflammatory fibroid polyp (IFP) is a benign tumor usually localized to the gastric antrum, although it can occur throughout the gastrointestinal tract [3]. Meckel's diverticulum (MD) is a remnant of the omphalomesenteric duct occurring in approximately 2% of the population [4]. Both IFP and MD can act as leading points in adult intussusception. We present a rare case of synchronous ileal IFP and MD noted during laparoscopic surgery for adult intussusception.

Case

A 48-year-old woman was referred to our emergency department due to a sudden onset of severe abdominal pain. Her vital signs were stable on physical examination, and direct tenderness in the right lower quadrant without rigidity or distention was observed on abdominal examination. The patient reported a history of total laparoscopic hysterectomy for early-stage endometrial cancer, 4 years prior to the presentation. Abdominal radiography revealed a stepladder sign with several small bowel loops. Blood tests were within normal limits. Abdominal computed tomography (CT) revealed ileocecal intussusception with proximal small bowel obstruction (Fig. 1).

Urgent laparoscopic exploration was performed using 3 trocars (a 12-mm supraumbilical port for the camera and two 5-mm ports placed in the left middle and lower quadrants of the abdo-

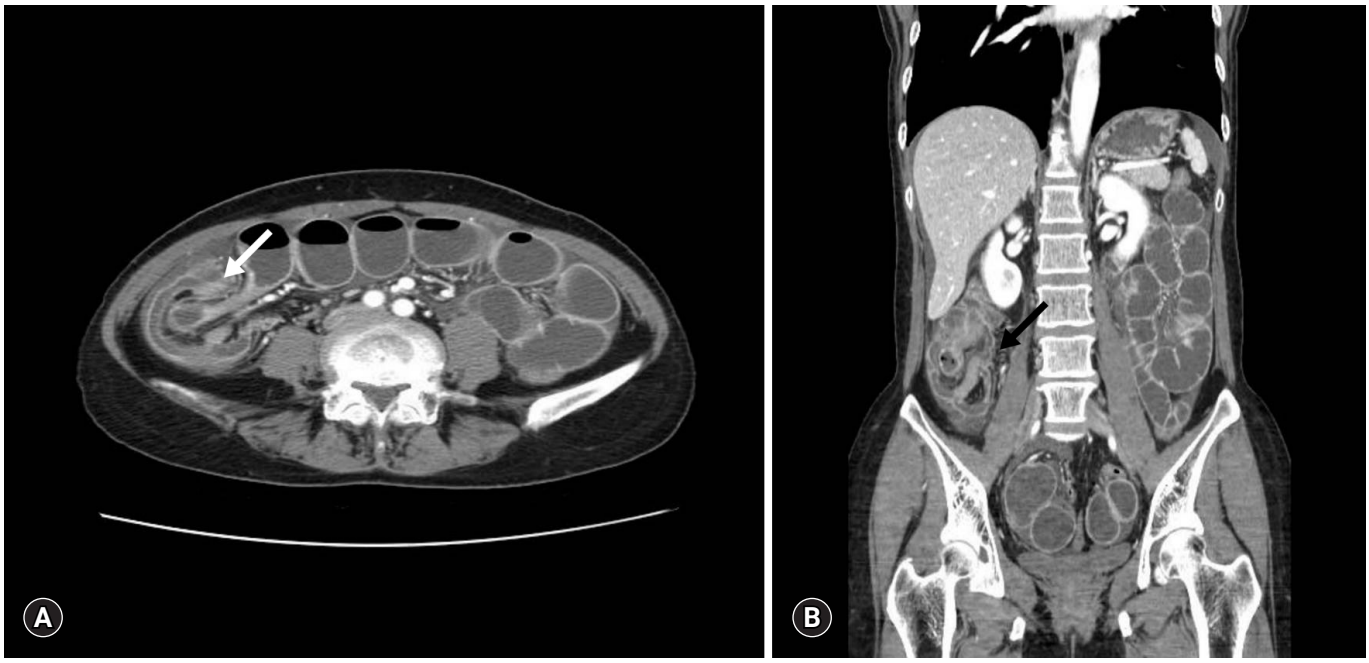

Fig. 1. Abdominal computed tomography scan shows ileocecal intussusception (arrow) with proximal small bowel obstruction. (A) Axial view. (B) Coronal view.

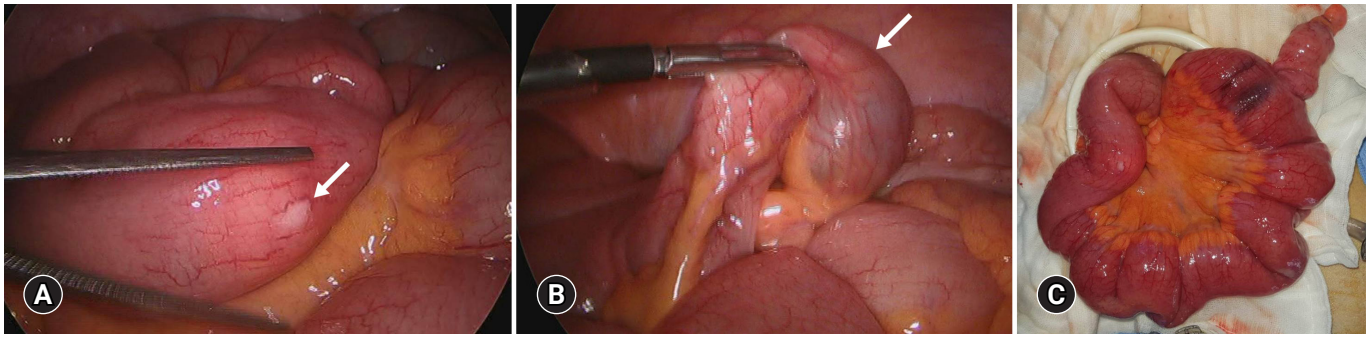

Fig. 2. Intraoperative laparoscopic images. (A) An intraluminal mass (arrow) is observed in the distal ileum approximately 30 cm from the ileocecal valve. (B) An outpouching closed luminal structure (arrow) is observed on the anti-mesenteric side wall of the ileum, located approximately 70 cm from the ileocecal valve. (C) The affected ileum is retracted via mini-laparotomy.

men), which revealed spontaneous resolution of intussusception. However, an intraluminal mass was found in the distal ileum, located approximately 30 cm from the ileocecal valve (Fig. 2A). Further bowel exploration revealed an outpouching closed luminal structure on the antimesenteric side wall of the ileum, located approximately 70 cm from the ileocecal valve (Fig. 2B). Umbilical mini-laparotomy, approximately 4 cm in length including the supraumbilical port site, was performed, and the affected ileum was retracted (Fig. 2C). The intraluminal tumor was resected via enterotomy followed by primary closure. The ileal outpouching was resected, and ileal side-to-side anastomosis was performed. The total operative time and estimated blood loss were 90 minutes and 20 mL, respectively.

The patient was discharged on the 4th postoperative day following an uneventful recovery. Histopathological examination confirmed an IFP measuring 2.5 × 1.5 cm (Fig. 3) as well as MD with ectopic pancreatic tissues measuring 5.5 × 2.5 cm (Fig. 4).

Discussion

IFP is a benign gastrointestinal tract lesion and usually asymptomatic. It develops in the submucosa and is composed of mononuclear spindle-shaped cells and prominent eosinophils [1,3]. However, small bowel IFPs tend to be symptomatic and present with bleeding or abdominal pain secondary to bowel obstruction, but less commonly occur as compared with gastric IFP [5-7]. Al-

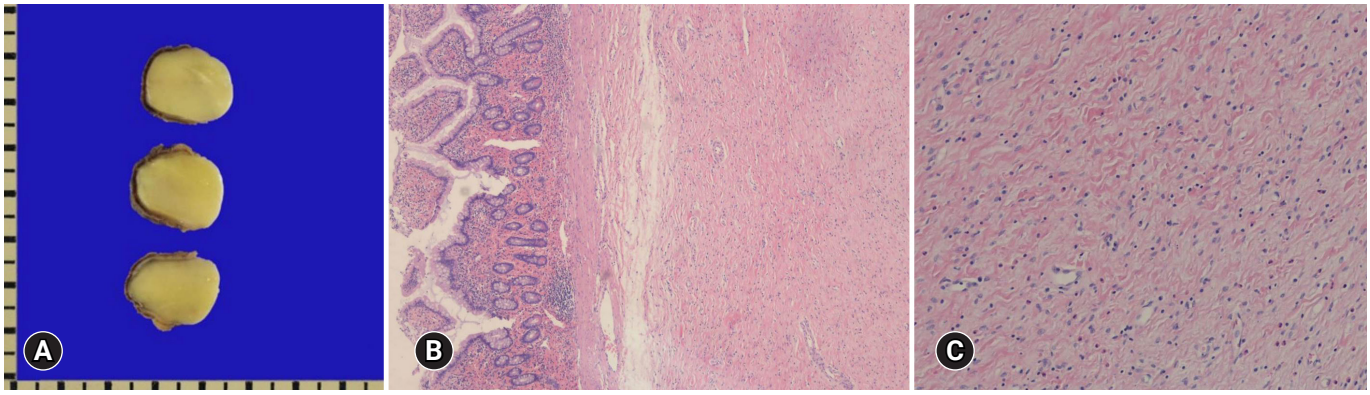

Fig. 3. Gross and microscopic findings of inflammatory fibroid polyp. (A) A well-demarcated submucosal mass is present. (B) It shows loose myxoid fibrous tissue and (C) proliferation of oval to spindle-shaped cell and scattered eosi nophils (hematoxylin and esoin stain, ×40 [B] and ×100 [C]).

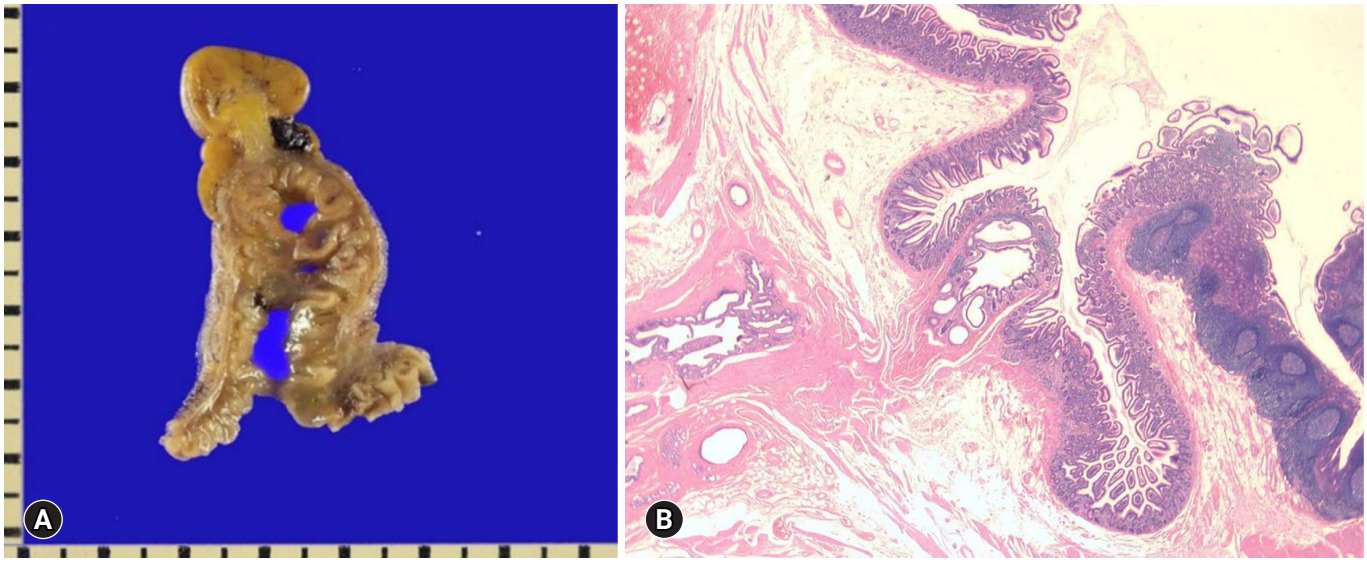

Fig. 4. Gross and microscopic findings of Meckel's diverticulum. (A) Meckel's diverticulum with an outpouching, closed luminal structure is present in the distal ileum. (B) It shows small intestinal mucosal lining with submucosal pancreatic tissue (hematoxylin and eosin stain, ×10).

though MD is usually asymptomatic in adults, abdominal pain secondary to obstruction, stricture, or MD-induced intussusception is the predominant characteristic of symptomatic cases [3].

The incidence of adult intussusception secondary to IFP and MD is extremely low. Notably, < 100 cases of intussusception secondary to ileal IFP and 4%–14% of adult intussusception attributed to intussusception are reported in the existing literature [1,8,9]. Moreover, to our knowledge, no report has described the synchronous occurrence of IFP and MD discovered during a surgery for adult intussusception to date.

Intussusception is usually diagnosed by imaging studies because its clinical manifestations and history were nonspecific. CT is preferred over ultrasonography for the differential diagnosis of intussusception because adult intussusception usually present with tumors (including malignancies). In our case, ileocecal intussusception was diagnosed with CT. However, because of the overlapping ileocolic wall, as well as edematous and dilated small bowel loops, CT did not reveal any apparent lesions that might have served as a leading point in this case.

Surgical resection is the primary treatment for adult intussusception, and some patients require radical surgery due to the malignant potential of the tumor within the leading point [10]. Laparoscopic surgery for adult intussusception has been increasingly performed in recent years due to its proven advantages such as faster recovery, less pain, and minimal scarring [10-12]. In addition, laparoscopic exploration is effective even for the confirmative diagnosis of adult intussusception to avoid unnecessary incision.

Therefore, diagnostic laparoscopy was performed first, because

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no pathologic data has confirmed whether the tumor was malignant or benign. In addition, a leading point that caused the ileocolic intussusception was not identified in radiologic examinations. During the laparoscopic exploration, a small ileal mass and MD were detected. However, we could not determine whether one of them was the leading point of intussusception because the ileocolic intussusception resolved spontaneously. However, surgical resection of the two abdominal lesions was performed because both of them were considered as leading points of intussusception.

In conclusion, we report a rare case of synchronous occurrence of ileal IFP and MD detected during laparoscopic surgery for adult intussusception, which was successfully treated with a laparoscopic approach.

Acknowledgments

Conflicts of interest
No potential conflict of interest to this article was reported.

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Impressive effect of cisplatin monotherapy on a patient with heavily pretreated triple-negative breast cancer with poor performance

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Systemic therapy for metastatic triple-negative breast cancer (TNBC) still remains challenging because there are no targeted agents or endocrine therapies currently available. The present case report documents the successful use of cisplatin monotherapy to manage a heavily pretreated TNBC patient showing poor response to therapy. The patient was a 51-year-old woman who had already undergone several lines of systemic chemotherapy for widespread TNBC. Although the mutation analysis performed on DNA isolated from blood cells and progressed lesion samples confirmed the tumor to be germline *BRCA* wild-type, cisplatin monotherapy was administered based on the increasing evidence of safety and efficacy of platinum for breast cancer. After three cycles of cisplatin treatment, the patient's metastatic lesions dramatically improved without any major toxicity, and she completed 17 cycles with good response. This case study indicates that patients with heavily pretreated TNBC can potentially achieve a good response to cisplatin monotherapy.

Keywords: Antineoplastic agents; Cisplatin; DNA repair; Triple negative breast neoplasms

Introduction

Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) [1]; TNBC accounts for 15%–20% of all breast cancers [2]. Generally, it has been well known that TNBC appears at a younger age and has a more aggressive clinical course than other breast cancer subtypes [3]. Although several clinical trials for TNBC have suggested a potential survival benefit using targeted agents, such as poly ADP-ribose polymerase (PARP) inhibitors or immune modulating agents, there are limitations in using these agents in daily practice due to domestic guidelines [4,5]. Thus, cytotoxic chemotherapy still remains the main therapeutic strategy for metastatic TNBC along with palliative radiotherapy and/or surgery [6,7]. However, to date, the treatment response of patients with advanced TNBC has been unsatisfactory [8].

In the presence of germline breast cancer susceptibility gene (*BRCA*) 1/2 mutations, PARP inhibitors or platinum agents can be considered as palliative regimens after the failure of taxanes, anthracyclines, antimetabolites, and microtubule inhibitors. Platinum is a cytotoxic agent and one of the most widely used drugs for treating solid tumors. Cisplatin, a bifunctional DNA cross-linking agent, induces cell apoptosis by causing DNA damage and inter-

fering with the DNA repair mechanism [9]. The side effects of cisplatin include myelosuppression, nephrotoxicity, neurotoxicity, and nausea/vomiting.

However, compared to other regimens, including taxanes and anthracyclines, the side effects of cisplatin are generally mild-to-moderate and manageable. While cisplatin is not usually included in the adjuvant or neoadjuvant chemotherapy for breast cancer, cisplatin-based combination therapy has recently been reported to be highly efficacious in metastatic breast cancer patients with a germline *BRCA* mutation [10,11]. However, the clinical impact of cisplatin monotherapy as a palliative treatment for *BRCA*-negative metastatic TNBC patients with a poor general condition has not yet been fully evaluated.

When selecting a therapeutic agent for advanced breast cancer with multiple metastases, it is important to carefully determine a regimen with minimal adverse effects to preserve the patients' quality of life. Therefore, in this case report, we describe our successful experience of administering cisplatin monotherapy to treat a 51-year-old woman who previously underwent multiple systemic chemotherapies for widespread *BRCA*-negative TNBC.

Case

A 51-year-old woman was transferred from a nearby hospital after receiving heavy pretreatment for disseminated breast cancer. At the time of admission to our hospital in July 2017, the patient's general condition was poor, with an Eastern Cooperative Oncology Group (ECOG) performance status of 4. She complained of widespread skin metastases with discharge and generalized edema (Fig. 1). According to her medical history, the patient was diagnosed with inoperable advanced TNBC and underwent 10 cycles of palliative chemotherapy with docetaxel and doxorubicin from May to December 2015, resulting in a partial response. However, the treatment was terminated owing to intolerance of the cumulative doxorubicin dose. Thereafter, the patient underwent a palliative modified radical mastectomy in December 2015. With ongoing disease progression, she received palliative radiotherapy and multiple lines of chemotherapy, including paclitaxel, gemcitabine, capecitabine, vinorelbine, and eribulin, before visiting our hospital.

At the time of admission, the patient's vital signs were stable and she was alert. Her chest computed tomography (CT) scan demonstrated a diffuse infiltrative mass lesion in the anterior chest

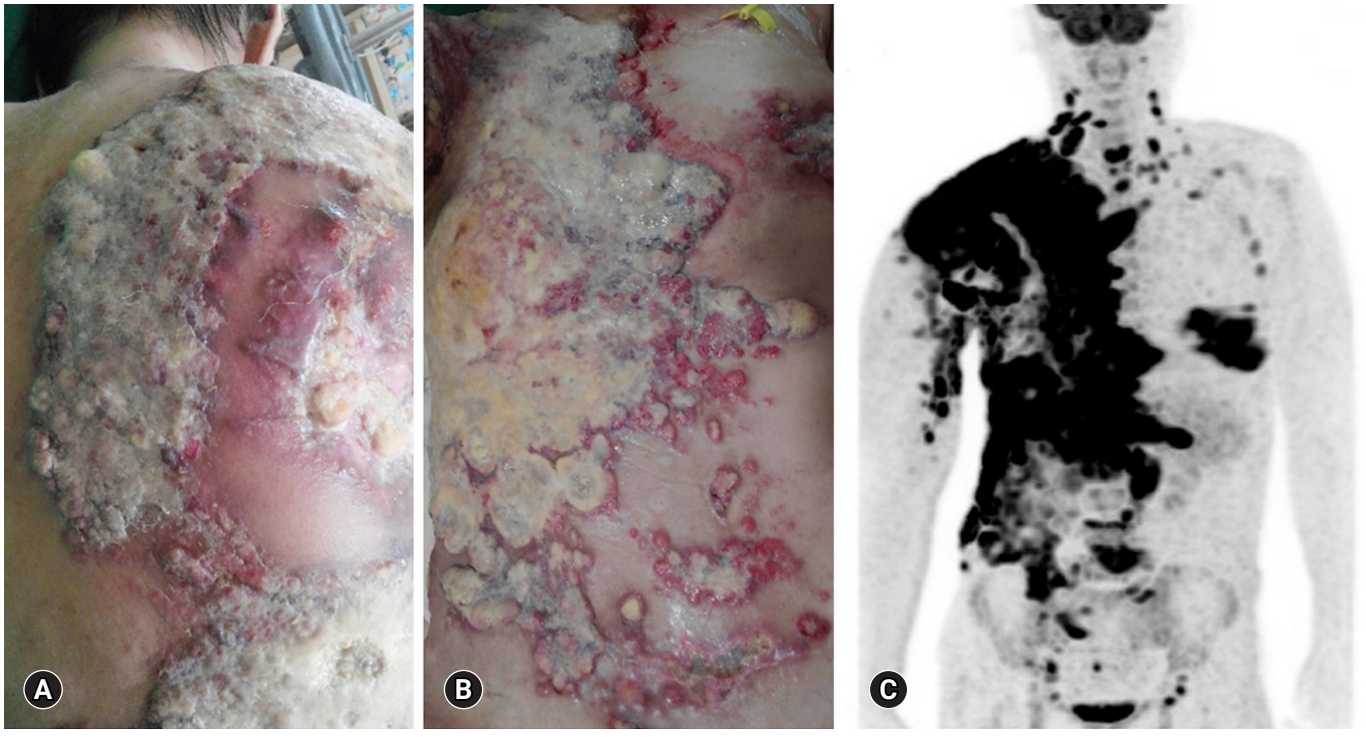

Fig. 1. Heavily pretreated breast cancer with widespread skin metastases on July 2017. At the time of admission to our hospital, the patient was suffering from severe skin metastases with discharge (A, B). Positron emission tomography-computed tomography shows breast cancer with multiple metastases in the chest wall, liver, bone, and lymph nodes (C). The patient provided written informed consent for publication of clinical details and images.

wall with bilateral pleural effusion and multiple metastatic lymphadenopathies in both the neck and axilla. The abdomen-pelvis CT scan revealed multiple liver, lymph nodes, and abdominal wall metastases. Tissue biopsy of the right chest wall tumor mass identified the tumor as a triple-negative-type invasive ductal carcinoma (Fig. 2). Cisplatin monotherapy was selected based on the results of several pilot studies, which revealed a remarkable efficacy of cisplatin for TNBC [12,13]. We also took into consideration the patient's poor general condition and the mild cisplatin-induced toxicity. The patient received 75 mg/m^2 of cisplatin every 3 weeks, along with standard hydration and antiemetic prophylaxis. Chemotherapy was administered in an in-patient setting because of the patient's poor general condition and the extensive dressing care needed for the metastatic skin lesions. After three cycles of cisplatin, the occurrence of skin ulcerative lesions was remarkably decreased. As the patient's ECOG performance status was dramatically improved to 1, the treatment was continued in an outpatient setting. After six cycles of the regimen, responses were further noted in both the liver and skin lesions (Fig. 3). With regard to adverse events, transient neutropenia and mild nausea were identified, yet both were manageable. The patient recently completed her 17th cycle of cisplatin with a good performance and minimal peripheral neuropathy (Fig. 4).

Although she has no family history of breast or ovarian cancer, germline and somatic *BRCA* mutation tests were performed in the peripheral blood and primary/residual malignant tumor tissues for the potential use of a PARP inhibitor. However, no pathogenic *BRCA* mutation was identified (Table 1).

The patient provided written informed consent for publication of clinical details and images.

Discussion

The National Comprehensive Cancer Network (NCCN) guidelines currently suggest platinum monotherapy as an alternative for metastatic TNBC based on the results of two small single arm phase II clinical trials [7,14,15]. In the TBCRC009 trial, although the tolerable response rate to platinum monotherapy was 25.6% in metastatic TNBC, progression-free survival was only 2.9 months, which was a disappointing result with respect to consid-

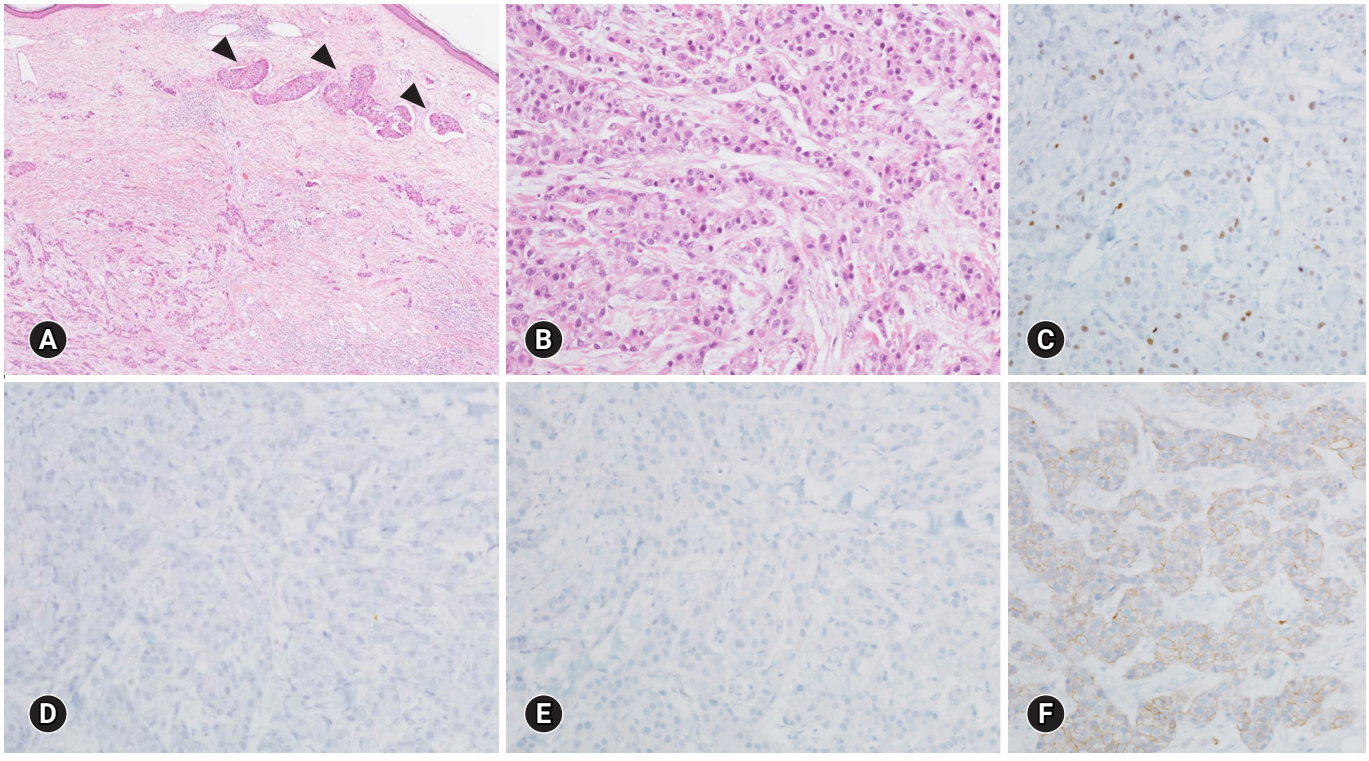

Fig. 2. Representative histological features and immunohistochemical (IHC) findings of the metastatic carcinoma. The metastatic tumor shows the histologic grade 3, according to the modified Nottingham grading system (tubule formation 3, nuclear pleomorphism 3, and mitotic activities 2), and frequent lymphovascular emboli (A, arrowheads) within the dermal area (A, B). The tumor cells shows 10% Ki-67 labeling index (C), loss of estrogen receptor (D), and progesterone receptor (E). The expression of HER2 was classified as 2+ (F) on IHC, subsequently proven HER2 negativity on HER2 silver *in situ* hybridization (not shown) (hematoxylin and eosin stain, ×40 [A, B]; IHC stain, ×200 [C–F]).

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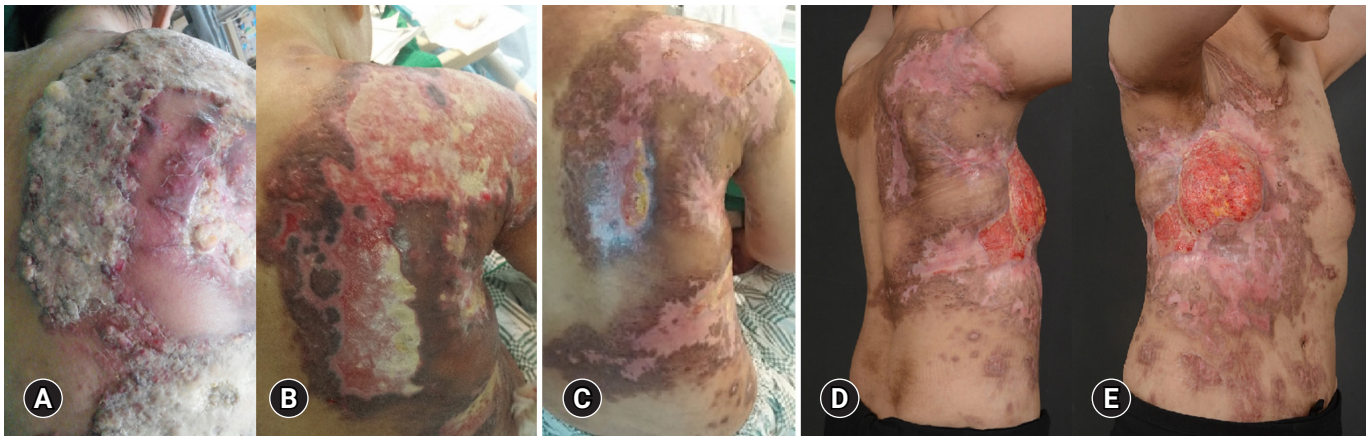

Fig. 3. Before the cisplatin treatment, the patient complained of widespread skin metastases with discharge and generalized edema (A). She received 75 mg/m^2 of cisplatin every 3 weeks, along with standard hydration and antiemetic prophylaxis. After three cycles of cisplatin, skin ulcerative lesions were remarkably decreased (B). After six cycles of the regimen, responses were further noted in skin lesions as well as liver, chest wall, and lymph nodes (C). The patient completed her 17th cycle of cisplatin with dramatic metastatic skin lesion improvement (D, E). The patient provided written informed consent for publication of clinical details and images.

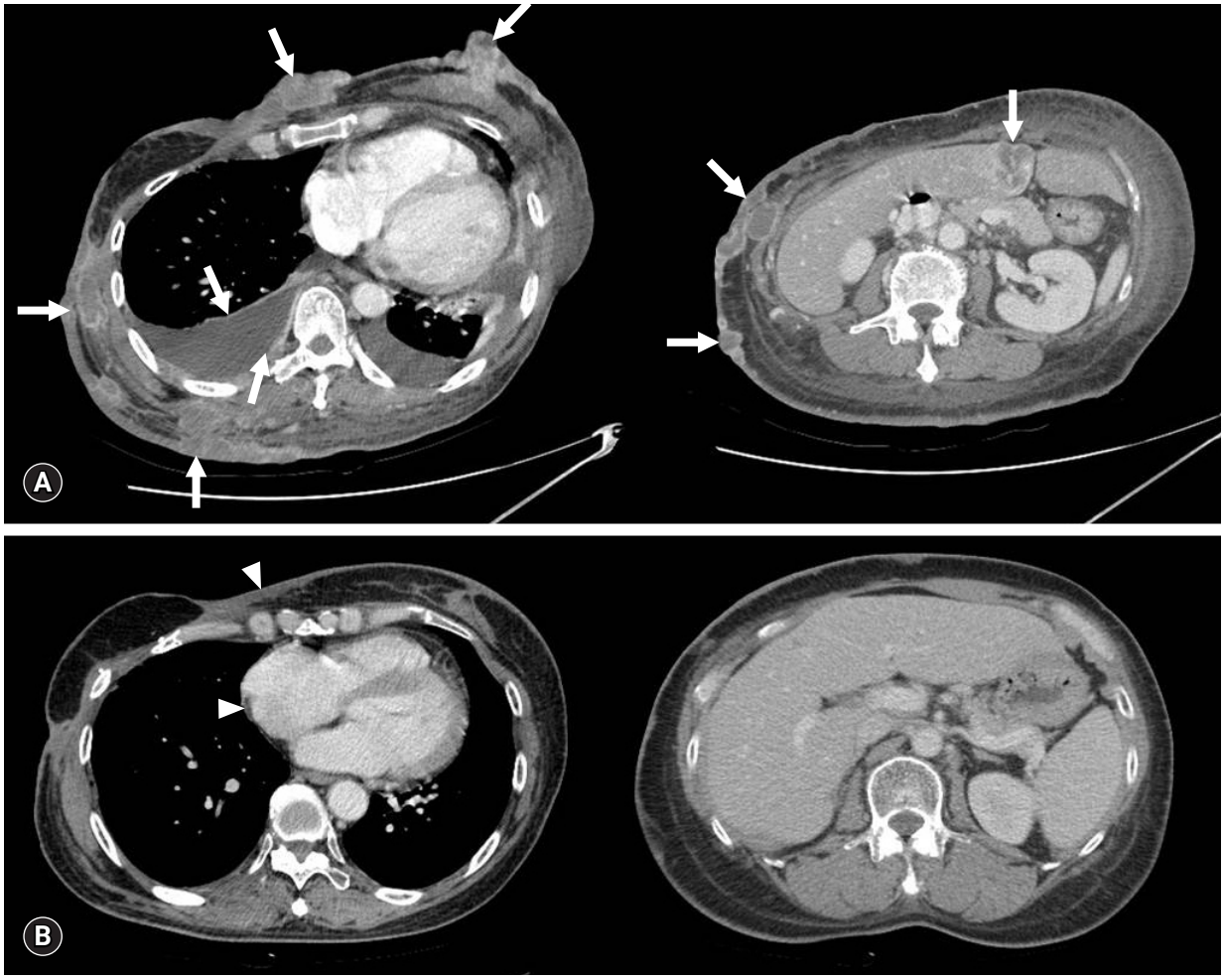

Fig. 4. Computed tomography (CT) shows the impressive response of cisplatin monotherapy. Before the cisplatin monotherapy, multiple metastases with bilateral pleural effusion (arrows) were found in the chest and abdomen CT (July 2017) (A). Pleural effusion and metastatic lesions were dramatically improved (arrowheads) after the cisplatin treatment (December 2018) (B).

Table 1. Summary of *BRCA* mutation assay results (no pathogenic mutation was identified)

	Germline (blood)			Breast tumor at diagnosis			Skin lesion prior to cisplatin monotherapy		
	Nucleotide	Amino acid	SNP no.	Nucleotide	Amino acid	SNP no.	Nucleotide	Amino acid	SNP no.
BRCA1				c.5383C>T	p.Leu1795Phe	rs878854958			
	c.4837A>G	p.S1613G	rs1799966	c.4837A>G	p.Ser1613Gly	rs1799966	c.4837A>G	p.Ser1613Gly	rs1799966
	c.4308T>C	p.S1436=	rs1060915	c.4308T>C	p.Ser1436=	rs1060915	c.4308T>C	p.Ser1436=	rs1060915
	c.3548A>G	p.K1183R	rs16942	c.3548A>G	p.Lys1183Arg	rs16942	c.3548A>G	p.Lys1183Arg	rs16942
	c.3113A>G	p.E1038G	rs16941	c.3113A>G	p.Glu1038Gly	rs16941	c.3113A>G	p.Glu1038Gly	rs16941
	c.2612C>T	p.P871L	rs799917	c.2612C>T	p.Pro871Leu	rs799917	c.2612C>T	p.Pro871Leu	rs799917
	c.2311T>C	p.L771	rs16940	c.2311T>C	p.Leu771=	rs16940	c.2311T>C	p.Leu771=	rs16940
	c.2082C>T	p.S694=	rs1799949	c.2082C>T	p.Ser694=	rs1799949	c.2082C>T	p.Ser694=	rs1799949
				c.441+36_441+38delCTT		rs147856441	c.441+36_441+38delCTT		rs147856441
				c.-19-115T>C		rs3765640	c.-19-115T>C		rs3765640
BRCA2	c.1114A>C	p.N372H	rs144848	c.1114A>C	p.Asn372His	rs144848	c.1114A>C	p.Asn372His	rs144848
	c.3807T>C	p.V1269=	rs543304	c.3807T>C	p.Val1269=	rs543304	c.3807T>C	p.Val1269=	rs543304
				c.4563A>G	p.Leu1521=	rs206075	c.4563A>G	p.Leu1521=	rs206075
				c.6513G>C	p.Val2171=	rs206076	c.6513G>C	p.Val2171=	rs206076
				c.7393G>A	p.Ala2465Thr				
				c.7397C>T	p.Ala2466Val	rs169547	c.7397C>T	p.Ala2466Val	rs169547

SNP, single-nucleotide polymorphism.

ering platinum as a first-line treatment [14]. However, this case showed that cisplatin monotherapy can be safe and effective for managing heavily pretreated TNBC patients without any major toxicities; thus, cisplatin monotherapy represents a possible palliative therapeutic option, although the current international guidelines do not recommend its routine use, especially for patients without germline *BRCA 1/2* mutations [7].

BRCA1 plays a key role in the homologous recombination (HR) DNA repair system by initiating the repair of DNA double-strand breaks and thereby maintaining DNA stability, which makes it a potential predictive biomarker for DNA-damaging agents, such as platinum [16]. Moreover, a specific TNBC subtype harboring *BRCA* mutations has been shown to be more sensitive to cisplatin than taxane [17]. Nevertheless, in the current case, whole-genome sequencing of the blood and tumor tissue samples showed no pathogenic somatic or germline *BRCA* mutation. Interestingly, the germline *BRCA* mutation status was not found to play any predictive role in carboplatin efficacy in the GeparSixto trial, although carboplatin did generate a higher response rate in the TNBC subgroup [18]. Additionally, a preclinical study reported that, similar to the *BRCA1*-mutant cell type, a non-*BRCA1* mutant basal-like cell line had a considerably high sensitivity to cisplatin treatment. Therefore, such an inconsistency in the efficacy of platinum agents against breast cancer with *BRCA* mutations suggested that *BRCA* mutation status might be insufficient for showing HR DNA repair abnormalities.

Instead of identifying the existence of *BRCA* mutations, "BRCAness" can be an alternative explanation for the existence of HR DNA repair abnormalities. For instance, homologous recombination deficiency (HRD) score, which is a measurement of BRCA promoter methylation, loss of heterozygosity, large-scale state transitions, or telomeric allelic imbalance, using next-generation sequencing can indicate BRCAness. In various small-sized retrospective and post hoc analyses, the HRD score has been highly correlated with the response to platinum-based treatment of TNBC patients with or without *BRCA* mutations [19]. However, in the TNT trial, no statistically significant difference in the response has been identified according to HRD score; long-term studies for estimating the advantages of platinum for TNBC patients are still warranted [20]. Although the DNA repair mechanism is extremely complex, a comprehensive genomic alteration test should be conducted to understand the actual efficacy of DNA-targeting agents for DNA repair and facilitate the exploration of alternative mechanisms underlying cancer progression and resistance to chemotherapeutic agents.

In this case report, a dramatic and durable response to cisplatin monotherapy was observed in a heavily pretreated TNBC patient with a poor performance status. Although platinum agents have shown effective clinical outcomes for *BRCA*-mutated TNBC, they should also be considered as an option for treating advanced

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TNBC without *BRCA* mutations.

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Conflicts of interest
No potential conflict of interest relevant to this article were reported.

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Jejunogastric intussusception prone to misdiagnosis as gastric cancer

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The authors report a case of a 78-year-old female with a history of gastric surgery 35 years ago. She was initially misdiagnosed as gastric cancer bleeding and underwent an emergency laparotomy under the diagnosis of jejunogastric intussusception (JGI), 23 hours after the onset of symptoms. We also reviewed 116 JGI case reports and analyzed clinical features and outcomes. Compared to the past, diagnosis of JGI is easier with diagnostic examinations such as an endoscopy, computed tomography, and the upper gastrointestinal series. And a good prognosis can be expected with proper fluid resuscitation and surgical reduction, even if the symptoms persist more than 48 hours.

Keywords: Gastroenterostomy; Intussusception; Jejunogastric intussusception

Introduction

Jejunogastric intussusception (JGI) occurs in only about 0.1% of gastro-enteric anastomosis and was first reported by Bozzi in 1914 [1,2]. In literature, approximately 300 cases have been reported and the interval from previous gastric surgery to JGI occurrence varies from days to decades [3,4]. Unawareness about the disease entity of JGI among clinicians causes an increase in mortality rate due to late diagnosis or misdiagnosis of JGI as gastric malignancy or bezoar. In the present case, we introduce a JGI patient who was misdiagnosed with gastric cancer bleeding and underwent surgical reduction 23 hours after onset of symptoms. We also reviewed previously published JGI case reports that were able to identify basic clinical information. We analyzed the clinical features and outcomes of 116 JGI case reports in the discussion section.

Case

This study was approved by the Institutional Review Board of Yeungnam University Hospital (IRB No: 2020-01-004).

A 78-years-old female visited the emergency room of the local hospital due to sudden and continuous epigastric pain from the previous evening. On abdominal computed tomography (CT), gastric distension with intragastric mass was found (Fig. 1) and old bloody drainage through Levin tube was seen. Under diagnosis of gastric cancer bleeding, she was transferred to the emergency room of Yeungnam University Hospital for further evaluation and management.

At the time of arrival, the patient's vital signs were stable and the color of drainage through Levin tube was yellowish. She had medical history of hypertension, diabetes mellitus, pneumonia (1 month back) and surgical history of distal gastrectomy (35 years back).

Physical examination revealed a soft and mild distended abdomen with upper midline scar. There was a palpable mass and mild tenderness on left upper abdomen. There was no rebound tenderness or guarding sign. The laboratory examination showed leukocytosis (white blood cell count, 23.07 K/μL; neutrophil, 93.4%)

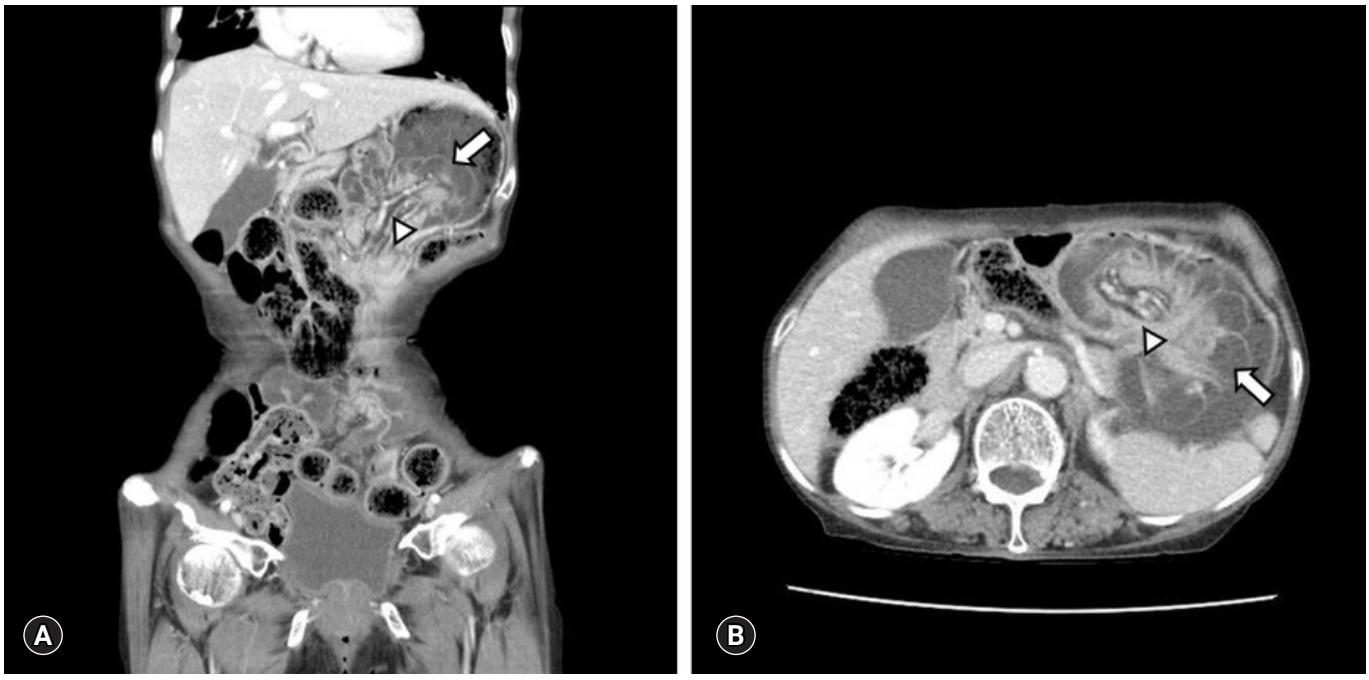

Fig. 1. Computed tomography findings of the jejunogastric intussusception patient. Both coronal (A) and axial view (B) show the intussuscepted jejunal loop (arrow) with the entrapped mesenteric vessel and fat (arrowhead) in the dilated stomach.

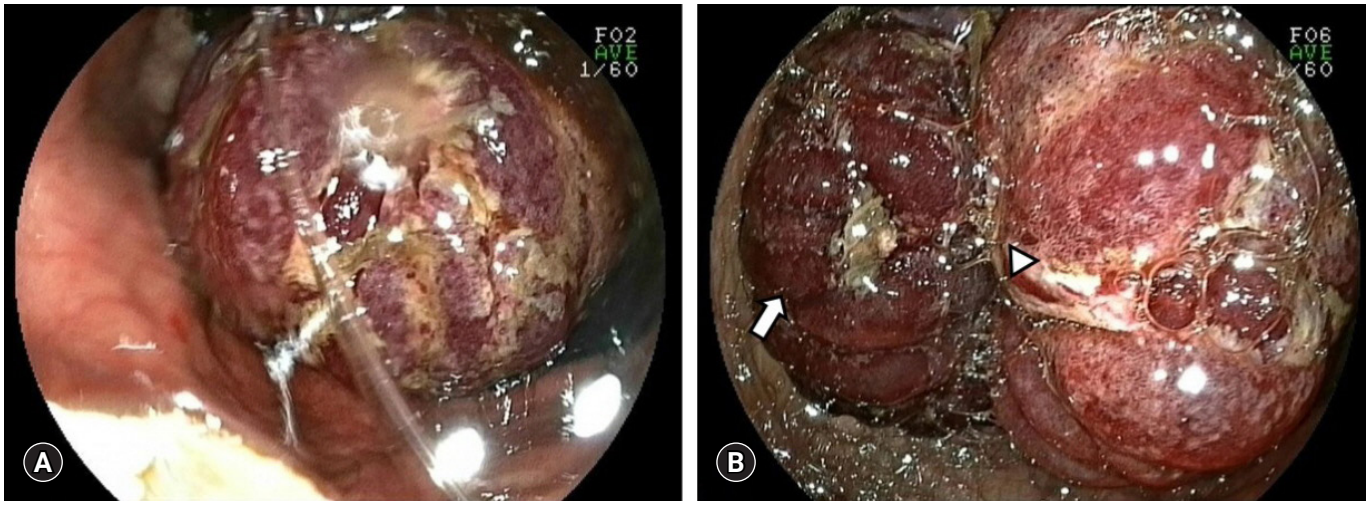

Fig. 2. Endoscopic findings of jejunogastric intussusception patient. (A) A bulky and congestive mass is seen (B) edematous mucosal fold (arrow) and the lumen (arrowhead) of intussuscepted jejunum is seen.

and other findings including hemoglobin within normal range.

The emergency medicine doctor in author's center also misdiagnosed JGI as gastric cancer bleeding and consulted an internal medicine doctor for endoscopy. After 6 hours, internal medicine doctor performed endoscopy and recommended consulting general surgery department for gastric malignancy (Fig. 2). Initially, authors were not aware of the disease entity of JGI. However, continuous abdominal pain and leukocytosis without anemia could not be regarded as mere symptoms of gastric cancer. After reviewing findings of endoscopy and CT, we performed an emergency laparotomy under the diagnosis of JGI.

The afferent loop was dilated and about 60 cm of efferent loop was intussuscepted into dilated stomach through gastro-jejunostomy site. After manual reduction and warm saline irrigation, there was no leading point and distal half of intussuscepted jejunum was not viable. Segmental resection of necrotic bowel was

performed. And efferent loop was fixed to distal body of remnant stomach and mesentery of transverse colon to prevent recurrence of JGI. Due to postoperative pneumonia, patient was discharged on the 26th day of surgery.

Discussion

The mean age of 100 JGI patients was 55 years (range, 27–83 years). There were 68 males (65.4%) and 36 females (34.6%). There were 83 cases (87.4%) that had a previous surgery for benign disease (80 cases of peptic ulcer, three cases of morbid obesity) and 12 cases (12.6%) had previous surgery for malignant disease (11 cases of gastric cancer, and one case of gall bladder cancer). The mean interval from previous surgery to diagnosis of JGI was 12.4 ± 10.6 years (range, 2 days to 55 years; n = 107) (Table 1). Shackman [5] classified JGI into three types according to the intussuscepted limb, type I (antegrade intussusception of the afferent limb, 16%), type II (retrograde intussusception of the efferent limb, 74%), type III (combined form, 10%). Brynitz and Rubinstein [6] classified JGI into four types by adding type IV (intussusception through Braun's side to side anastomosis). In our results, the percentage of each type was slightly different, but type II was most common type as shown. Among 116 cases, there were five cases (4.3%) of type I, 98 cases (84.5%) of type II, five cases (4.3%) of type III, and eight cases (6.9%) of type IV (Table 1). The author's case was type II, which is the most common type of JGI.

The pathogenesis of JGI remains unclear. But it is thought that mechanical factors and functional factors affect the occurrence of JGI [7]. Functional factors include hyperperistalsis due to hyperacidity or spasm and retrograde peristalsis due to jejunitis or increased abdominal pressure [8]. Mechanical factors include postoperative adhesion, dilatation of bowel following gastrectomy, and long afferent loop or mesentery [9].

There were 100 cases (86.2%) of JGI with acute symptoms, seven cases (6%) of JGI with chronic symptoms, and nine cases (7.8%) of JGI with acute on chronic symptoms. Most JGI shows acute manifestations, but some appear to be chronic and may change to acute if the diagnosis is delayed (Table 1). In the author's case, patient complained of sudden and continuous epigastric pain and physical examination showed a palpable mass on the upper abdomen. Severe colicky epigastric pain, hematemesis, presence of a palpable mass, and vomiting are acute symptoms of JGI [10]. Of the 101 cases that mentioned specific symptoms, there were 89 cases (88.1%) with abdominal pain, 96 cases (95%) with vomiting, and 52 cases (51.5%) with hematemesis. Hematemesis (51.5%) and palpable mass (34.5%) were not as common as abdominal pain (88.1%) and vomiting (95%) (Table 1). The color of vomit might change from clear to coffee color with the progression of ischemia of intussuscepted limb. If clinicians know

Table 1. Clinical features of jejunogastric intussusception patients

Variable	Value
Age (yr, n = 100)	55.0 ± 14.2 (27–83)
Sex (n = 116)	
Male	68 (65.4)
Female	36 (34.6)
N/M	12
Type (n = 116)	
I	5 (4.3)
II	98 (84.5)
III	5 (4.3)
IV	8 (6.9)
Previous disease (n = 116)	
Benign	83 (87.4)
Malignant	12 (12.6)
N/M	21
Interval (yr, n = 107)	12.4 ± 10.6 (2 days–55 years)
Symptom (n = 116)	
Acute	100 (86.2)
Chronic	7 (6.0)
Acute on chronic	9 (7.8)
Duration of acute symptom (hr, n = 34)	45.7 ± 43.4 (1–168)
Abdominal pain (n = 116)	
Negative	12 (11.9)
Positive	89 (88.1)
N/M	15
Vomiting (n = 116)	
Negative	5 (5.0)
Positive	96 (95.0)
N/M	15
Hematemesis (n = 116)	
Negative	49 (48.5)
Positive	52 (51.5)
N/M	15
Palpable mass (n = 116)	
Negative	57 (65.5)
Positive	30 (34.5)
N/M	29
Laboratory findings (n = 116)	
Non-specific	32 (66.7)
Leukocytosis only	5 (10.4)
Anemia only	3 (6.3)
Both	8 (16.7)
N/M	68

Values are presented as mean±standard deviation (range) or number (%).
JGI, jejunogastric intussusception; N/M, not mentioned.

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the disease entity of JGI, it becomes easier to diagnosis JGI with acute symptoms with endoscopy or CT. But if the intussusception of limb is intermittent and self-reversible, patient may complain of vague and chronic symptoms like recurrent bouts of epigastric area and nausea [11]. Diagnosis of JGI with chronic manifestation is difficult and can be performed by timely examination when the symptoms are present [10]. Of the 48 cases that mentioned laboratory findings, there were 32 cases (66.7%) with non-specific findings, five cases (10.4%) with leukocytosis, three cases (6.3%) with anemia, eight cases (16.7%) with anemia and leukocytosis (Table 1). Therefore, even if the laboratory finding is within normal limit, the diagnosis of JGI cannot be ruled out.

Endoscopy and abdominal CT are diagnostic examinations of JGI [12,13]. During endoscopy, intussuscepted jejunum is visualized. And the nature of intussuscepted jejunum can be various from small intussuscepted jejunum with viable mucosa to bulky congestive mass according to the length of jejunum and degree of ischemia. On the axial and coronal view of CT, intussuscepted jejunal loop with entrapped mesenteric vessel and fat is seen in dilated stomach. Several signs such as claw sign on axial view and target sign on sagittal view are also helpful in the diagnosis of JGI [14]. Of the 79 cases with mention of diagnostic examinations, there were 46 cases (58.2%) endoscopy, 36 cases (45.6%) with CT, 26 cases (32.9%) with upper gastrointestinal (UGI) series, and 12 cases (15.2%) with ultrasonography. Although UGI series and ultrasonography were not as commonly performed diagnostic test as endoscopy and CT, but they also were useful in diagnosis of JGI. In most JGI cases before 1970, JGI was clinically diagnosed with reference to an abdominal X-ray or UGI series (Table 2).

The treatment of choice for JGI is the surgical reduction of intussuscepted bowel with correction of dehydration and electrolyte disturbance [10]. Also, fixation of intussuscepted limb to adjacent tissues such as parietal wall, transverse colon mesentery, and stomach is required to prevent recurrence of JGI [14]. Authors fixed efferent loop to remnant stomach and transverse colon mesentery. In addition to manual reduction and fixation, bowel resection might be required according to viability of intussuscepted jejunum [15]. There were 82 cases (85.4%) with a surgical treatment. Among these cases, 41 cases (52.6%) had an additional bowel resection and 22 cases (32.4%) had fixation to adjacent tissue. There were six cases of recurrence after surgical treatment, of which two cases had a fixation procedure during previous surgery. Therefore, it is hard to say that the fixation can completely prevent the recurrence of JGI (Table 2).

Endoscopic reduction of JGI is a possible option in the treatment of JGI through which general anesthesia and surgical complications such as pneumonia and wound infection can be avoided [16]. Nevertheless, endoscopic reduction of JGI has a significant risk of recurrence and should not be performed in situation where bowel ischemia or peritoneal irritation sign is suspected [17]. There were six cases (6.3%) of endoscopic reduction, of

Table 2. Diagnosis, treatment, and outcomes of jejunogastric intussusception patients

Variable	No. (%)
Upper gastrointestinal series (n = 116)	
Not done	53 (67.1)
Done	26 (32.9)
N/M	37
Ultrasonography (n = 116)	
Not done	67 (84.8)
Done	12 (15.2)
N/M	37
Endoscopy (n = 116)	
Not done	33 (41.8)
Done	46 (58.2)
N/M	37
Computed tomography (n = 116)	
Not done	43 (54.4)
Done	36 (45.6)
N/M	37
Treatment method (n = 116)	
Spontaneous reduction	3 (3.1)
Surgical reduction	80 (83.3)
Endoscopic reduction	6 (6.3)
Surgery after endoscopy	2 (2.1)
No reduction	5 (5.2)
N/M	20
Bowel resection (n = 82)[a]	
Not done	37 (47.4)
Done	41 (52.6)
N/M	4
Fixation (n = 82)[a]	
Not done	46 (67.6)
Done	22 (32.4)
N/M	14
Recurrence (n = 108)[b]	
Negative	80 (90.9)
Positive	8 (9.1)
N/M	20
Prognosis (n = 116)	
Well recovered	88 (91.7)
Died	8 (8.3)
N/M	20

N/M, not mentioned.
[a]Number of cases with surgical reduction. [b]Number of death cases excluded.

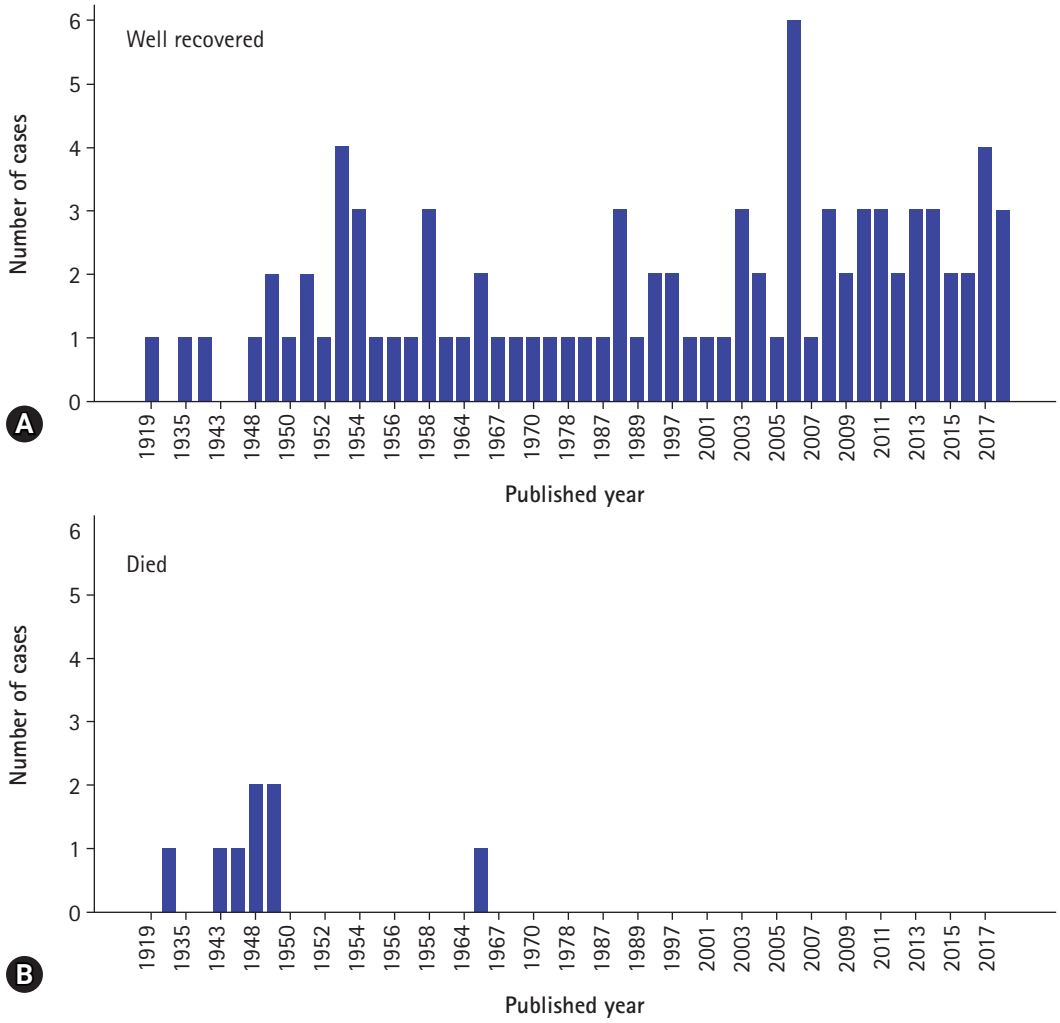

Fig. 3. Numbers of well recovered (A) and died (B) jejunogastric intussusception cases are demonstrated by published year.

which two cases recurred. The recurrence rate of an endoscopic reduction (2 out of 6, 33.3%) was higher than the recurrence rate of a surgical reduction (6 out of 82, 7.3%) (Table 2).

In this case, due to initial misdiagnosis, the surgical reduction was performed 23 hours after occurrence of sudden epigastric pain. It has been reported that if surgical treatment is performed within first 48 hours, the mortality rate of JGI patient can be about 10%, if not, may increase over 50% [18]. In our results, only 34 out of 100 acute JGI cases mentioned the duration of the symptoms. The mean duration of acute symptom was 45.7 ± 43.4 hours and ranged 1 hour to 7 days (Table 1). The mortality rate was 8.3% (8 out of 96) and all mortality cases were reported before 1970s. Interestingly, all JGI case reports after 1970 had endoscopic or surgical reduction and had good prognosis regardless of the duration of the symptoms (Table 2, Fig. 3).

If clinicians are aware of the disease entity of JGI, JGI is easily diagnosed by various examinations such as endoscopy, CT, and the UGI series. And a good prognosis can be expected even if the symptoms persist more than 48 hours, provided adequate fluid resuscitation and surgical reduction are performed.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contributions

Conceptualization: YEP, SWK; Data curation, Formal analysis: YEP, SWK; Writing-original draft, Writing-review & editing: YEP.

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Spontaneous resolution of serous retinal detachment caused by choroidal mass after a first trimester abortion

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Pregnancy-related ocular diseases develop mostly in the third trimester of pregnancy. Here, we describe a case of a pregnant woman with a choroidal mass that caused a serous retinal detachment during the first trimester of pregnancy. The patient's condition resolved spontaneously after an abortion.

Keywords: Choroidal neoplasm; Choroidal osteoma; First trimester; Pregnancy

Introduction

During pregnancy, cardiac output increases and hormone levels fluctuate. These physiological changes in pregnant women often cause retinal and choroidal diseases or worsen preexisting retinal and choroidal conditions [1,2]. For example, the incidence of central serous chorioretinopathy (CSC) and circumscribed choroidal hemangioma (CCH) increase during pregnancy [3,4]. Specifically, these diseases become exacerbated during the third trimester and spontaneously regress after childbirth [5,6]. Here, we present a case of a pregnant woman with a choroidal mass causing serous retinal detachment (SRD) during the first trimester of pregnancy that resolved spontaneously after an abortion.

Case

This study was approved by the Institutional Review Board of the Keimyung University Dongsan Hospital (IRB No: DSMC 2020-02-070). The patient provided written informed consent for publication of clinical details and images.

A 40-year-old woman was referred to our hospital with a 3-day history of visual disturbance in her left eye. The patient was a primigravida who was in her first trimester of pregnancy (7 weeks) at the time of referral. She did not have gestational hypertension or diabetes. Her left eye initially had a best-corrected visual acuity (BCVA) of 20/50 (according to the Snellen chart) and an intraocular pressure (IOP) of 15 mmHg. Her right eye had a BCVA of 20/20 and an IOP of 17 mmHg. Examination of the fundus revealed an orange-red retina in the left eye with posterior pole elevation (Fig. 1A).

Optical coherence tomography (OCT; DRI OCT Triton, Topcon, Tokyo, Japan) revealed a thick (> 500 μm) elevated choroid, an SRD, compression of the choriocapillaris, and a choroidal mass located between the choriocapillaris and the outer choroidal tissue in the left eye (Fig. 1B). We avoided fluorescein angiography (FA) and indocyanine green angiography (ICGA) because of their possible teratogenicity. The patient was diagnosed with a choroidal mass. The appearance of the mass suggested possible

CCH. We decided to closely monitor the changes in the patient's BCVA and the progression of her SRD.

One month later, the patient revisited our clinic after having had an abortion during her 9th week of pregnancy. Her left-eye BCVA was 20/20 and her IOP was 14 mmHg. Examination of the fundus showed that the elevated retinal height had decreased and that the retinal surface exhibited a patchy yellowish discoloration (Fig. 2A). OCT revealed a decreased SRD with visible fine lamellar lines of the choroidal lesion (Fig. 2B). FA (HRA-2; Heidelberg Engineering, Dossenheim, Germany) revealed patchy hyperfluorescence in the area corresponding with the previously elevated retina during the arteriovenous phase (Fig. 3A) with late-phase staining (Fig. 3B). ICGA revealed early hypofluorescence (Fig. 3C), followed by diffuse confluent fluorescence during the late phase (Fig. 3D). We requested that the patient visit the hospital 3 months later, however she was lost during this follow-up period.

Discussion

CCH appears as an indistinct, round-to-oval, orange-red mass located posterior to the equator of the eye [6]. CSC is characterized as an accumulation of subretinal fluid that causes circumscribed neurosensory retinal detachment [7]. Distinguishing between these diseases during pregnancy is difficult because using either FA or ICGA is discouraged during this period owing to their possible teratogenicity [5]. In this case, at 7 weeks of pregnancy, we

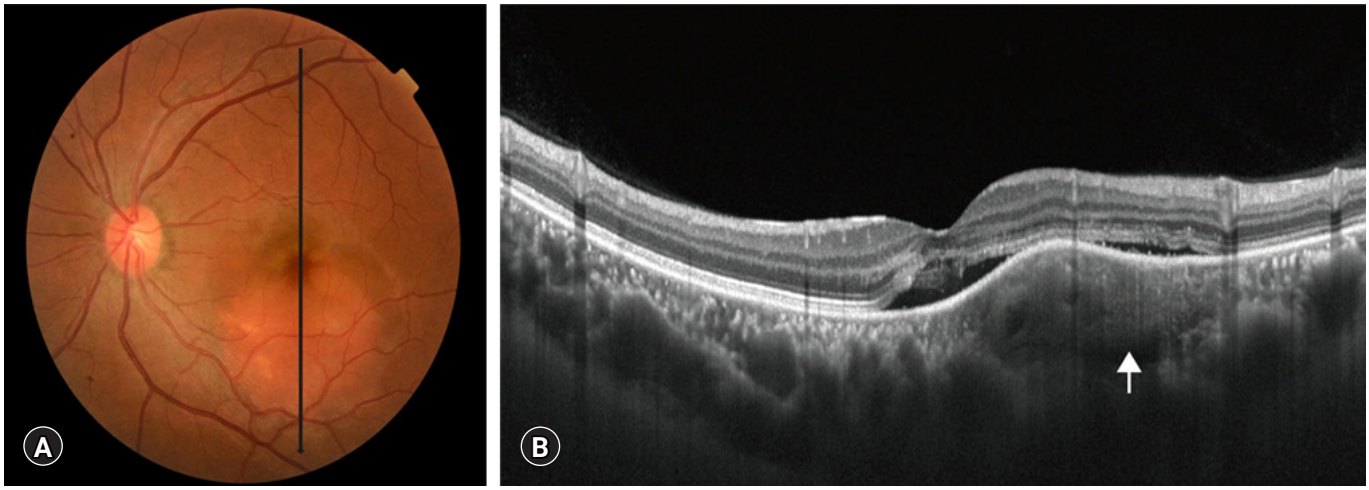

Fig. 1. Fundus photograph and optical coherence tomography of the left eye obtained on the initial visit. (A) An elevated orange-red retina is visible at the posterior pole. (B) Optical coherence tomography reveals a thick choroid, compression of the choriocapillaris, and serous retinal detachment with a choroidal mass (arrow).

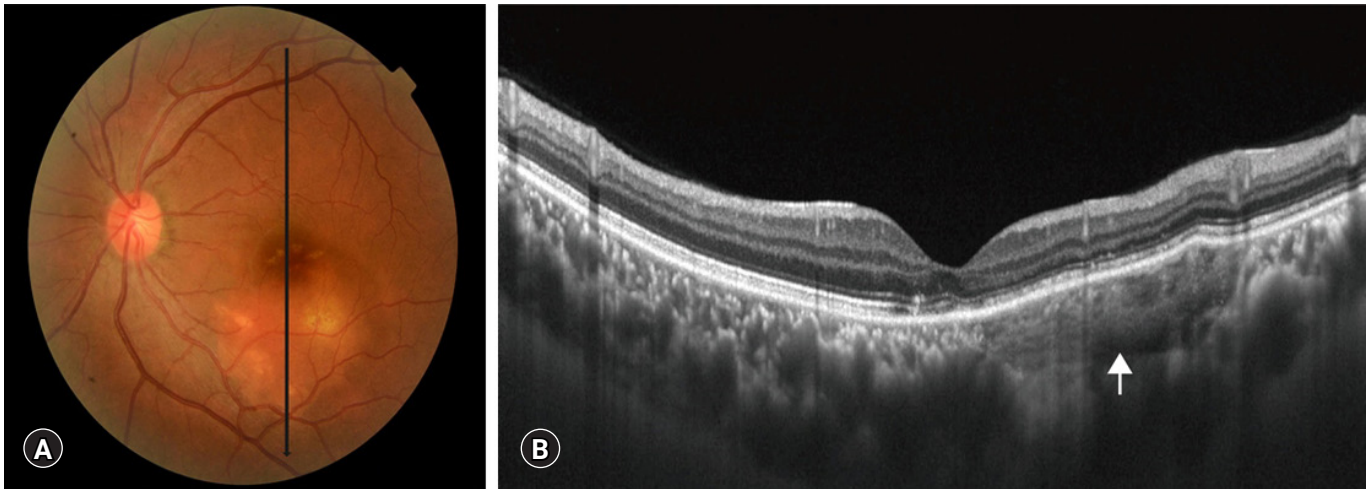

Fig. 2. Fundus photograph and optical coherence tomography of the left eye obtained 1 month after the initial visit. (A) The height of the elevated retina is reduced and patchy yellowish discoloration is seen. (B) The serous retinal detachment is resolved and fine lamellar lines within the choroidal lesion are visible (arrow).

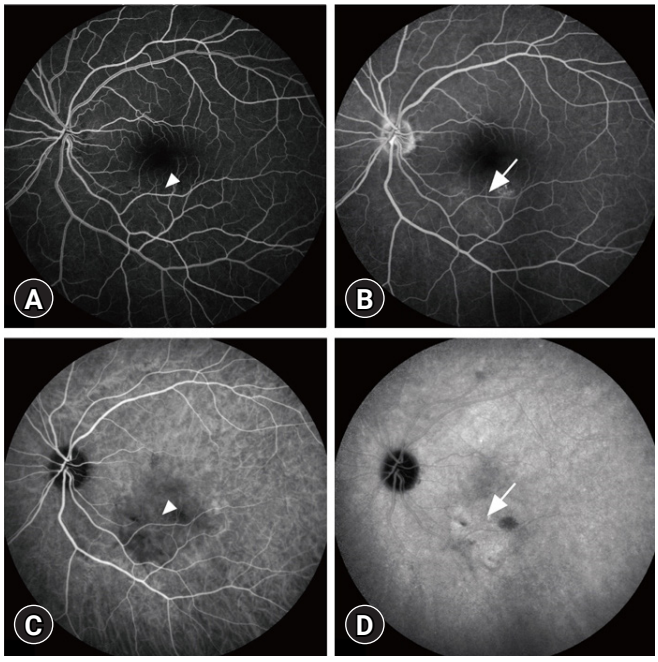

Fig. 3. Fluorescein angiography and indocyanine green angiography of the left eye obtained 1 month after the initial visit. Fluorescein angiography (A, arteriovenous phase; B, late phase) reveals early hyperfluorescence (arrowhead) with late-phase staining (arrow). Indocyanine green angiography (C, early phase; D, late phase) reveals early hypofluorescnece (arrowhead) followed by diffuse confluent fluorescence in the late phase (arrow).

initially suspected CCH because of the lesion's orange-red elevated appearance, the presence of SRD, and the presence of a thick and elevated choroid with an associated mass. Additionally, we eliminated the possibility of CSC as it typically develops in women with pre-eclampsia [8]. FA and ICGA were performed after the patient's abortion. FA revealed early patchy hyperfluorescence with late-phase staining, and ICGA revealed early hypofluorescence with later diffuse confluent fluorescence. The FA findings are consistent with the CCH diagnosis, as CCH is characterized by a stippled choroidal hyperfluorescence followed by increasing hyperfluorescence and progressive staining of the tumor. However, these FA characteristics are not pathognomonic for CCH. Unlike the FA findings, the ICGA findings are inconsistent with the CCH diagnosis, as CCH manifests as extreme early hyperfluorescence that decreases in the later phases (known as the "washout" phenomenon) [9]. Compression of the choriocapillaris was visible upon the initial OCT, however CCH typically develops in the absence of choriocapillaris compression [10].

Choroidal osteomas are benign, rare, ossifying choroidal tumors that typically affect the juxtapapillary and macular areas of young healthy females [11]. The color of the choroidal osteoma depends on the depigmentation of the retinal pigment epithelium [12]. In our case, an orange-red lesion in the fundus was seen at an early stage, which is in line with the diagnostic features of CCH. The fine lamellar lines found within the choroidal mass during OCT after the patient's abortion indicated the possible presence of an early choroidal osteoma. Moreover, ICGA of choroidal osteoma usually reveals early hypofluorescence and late-phase hyperfluorescence [13]. However, we did not perform B-scan ultrasonography in this case, which was consistent with a previous study [14]. After the patient's abortion her decreased visual acuity improved and her SRD resolved, which implies that her pregnancy was directly related to the growth of the choroidal mass. While the mechanism remains unclear, we postulated that the increase in maternal cardiac output during the first trimester may have caused hyperpermeability of the vascular channels within the choroidal mass, which may have led to its exaggerated appearance [15].

In conclusion, it is possible for SRD to develop in first trimester of pregnancy along with an associated choroidal mass. This SRD will most likely resolve spontaneously after an abortion or the termination of pregnancy. Our finding highlights the direct correlation between pregnancy and choroidal masses, which may help physicians and specialists anticipate these issues in pregnant patients.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: YHL, YCK; Data curation: YHL; Formal analysis: YCK; Supervision: YCK; Writing-original draft: YHL; Writing-review & editing: YCK.

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Gastric cancer and adenomatous colorectal polyp concomitant with pyogenic liver abscess and bacteremia

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Synchronous gastric cancer and adenomatous colorectal polyp in patients with *Klebsiella pneumoniae*-induced pyogenic liver abscess (KP-PLA) and bacteremia is a rare presentation. A 58-year-old man with a 6-month history of diabetes mellitus (DM) presented with febrile sensation and dull abdominal pain in the right upper quadrant of the abdomen. Subsequent to laboratory test results and abdominal computed tomography findings, KP-PLA with bacteremia was diagnosed. After intravenous antibiotic administration, his symptoms improved, and upper endoscopy and colonoscopy were performed to evaluate the cause of KP-PLA. Biopsy specimens of the prepyloric anterior wall revealed a moderately differentiated adenocarcinoma. Endoscopic mucosal resection of the colon revealed high-grade dysplasia. Early gastric cancer (EGC) and adenomatous colorectal polyps with high-grade dysplasia concomitant with KP-PLA and bacteremia were diagnosed in our patient who had DM. Intravenous antibiotic treatment for KP-PLA, subtotal gastrectomy for EGC, and colonoscopic mucosal resection for the colon polyp were performed. After 25 days of hospitalization, subtotal gastrectomy with adjacent lymph node dissection was performed. Follow-up ultrasound imaging showed resolution of the abscess 5 weeks post-antibiotic treatment, as well as no tumor metastasis. Upper gastrointestinal endoscopy and colonoscopy should be performed to evaluate gastric cancer in patients with PLA or bacteremia, accompanied with DM or an immunocompromised condition.

Keywords: Adenomatous polyps; Klebsiella pneumoniae; Pyogenic liver abscess; Stomach cancer

Introduction

Pyogenic liver abscess (PLA) is defined as a mass of cystic lesions in the liver with clinical manifestations, including fever, chills, and abdominal pain, which can be caused by either bacterial, fungal, or parasitic organisms [1-3]. The most common causative pathogen of PLA is *Klebsiella pneumoniae* (KP). KP can invade the liver via many routes, including the biliary tract, hepatic arteries, and portal vein and through direct invasion from an adjacent infected organ [4-6]. Hematogenous PLA is closely associated with colonic mucosal injuries such as colon cancer, intestinal tuberculosis, colonic diverticulitis, and inflammatory bowel disease (IBD) [3,7]. However, there are few reported cases of PLA with gastric cancer [3,7].

Herein, we present a rare case of early gastric cancer (EGC) and adenomatous colonic polyp with high-grade dysplasia concomitant with KP-induced PLA (KP-PLA) and bacteremia in a patient with diabetes mellitus (DM).

Case

This study was approved by the Institutional Review Board of the Yeungnam University Hospital (IRB No: 2019-10-031). All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

A 59-year-old man with a history of continuous dull pain in the right upper quadrant of the abdomen and chilling sensations for the previous 2 days visited our hospital. He had a 6-month history of DM and 2-year history of hypertension, for which he had not been prescribed any medication. His vital signs were as follows: blood pressure, 142/86 mmHg; heart rate, 98 beats/min; respiratory rate, 22 breaths/min; and body temperature, 39.6°C. Physical examination revealed tenderness in the right upper quadrant of the abdomen without a positive Murphy's sign. Blood chemistry results were as follows: white blood cell count, 15,520/μL (neutrophil count 82.8%, lymphocyte count 6.8%); hemoglobin, 11.8 g/dL; platelets, 188×10^3/μL; erythrocyte sedimentation rate, 120 mm/hr (range, <25 mm/hr); C-reactive protein, 32.3 mg/dL (range, <0.5 mg/dL); total bilirubin, 1.16 mg/dL; aspartate aminotransferase, 102 IU/L; alanine aminotransferase, 87 IU/L; alkaline phosphatase, 130 IU/L; gamma-glutamyl transferase, 56 IU/L; albumin 3.66 g/dL; and creatinine, 0.7 mg/dL. Abdominal computed tomography revealed a low attenuated lesion measuring approximately 2.1 × 1.8 cm in size with an irregular margin in the eight segments of the liver with no intrahepatic biliary abnormalities (Fig. 1). The patient was diagnosed with PLA, and antibiotics, including intravenous ceftriaxone and metronidazole, were preemptively administered. His clinical symptoms improved, and after KP was identified in blood cultures, ceftriaxone monotherapy was administered.

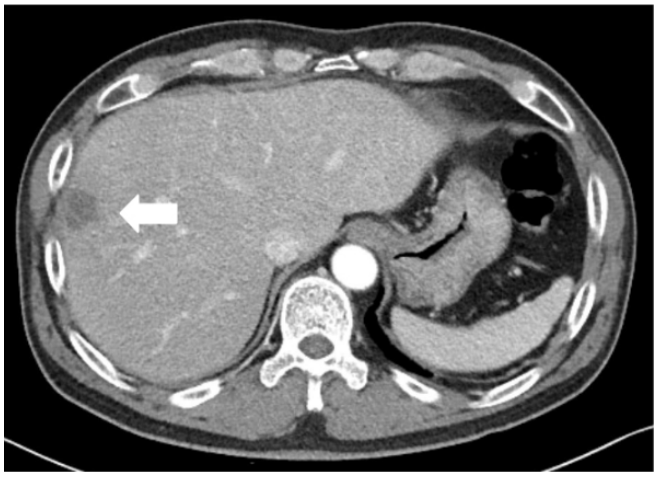

Fig. 1. Initial abdominal computed tomography shows a low attenuated lesion (arrow) measuring approximately 2.1×1.8 cm in size with an irregular margin in the right liver lobe in the portal phase.

After 15 days of hospitalization, upper endoscopy and colonoscopy were performed to determine the cause of KP-PLA. Upper endoscopy and colonoscopy revealed ill-defined nodular lesions measuring approximately 2 cm in size from the anterior wall to the lesser curvature of the prepyloric antrum and a pedunculated polyp in the sigmoid colon measuring approximately 1.5 cm in size (Fig. 2A, 2B). Biopsy specimens of the prepyloric anterior wall revealed a moderately differentiated adenocarcinoma. Endoscopic mucosal resection of the colon revealed high-grade dysplasia (Fig. 2C, 2D). After 25 days of hospitalization, the patient underwent subtotal gastrectomy with adjacent lymph node dissection. His final diagnosis was a moderately differentiated adenocarcinoma in type 1 EGC (pT1aN0) that was classified by the American Joint Committee on Cancer. Follow-up ultrasound imaging showed resolution of the abscess 5 weeks post-antibiotic treatment and no tumor metastasis.

Discussion

Liver abscesses, characterized by the spreading of various infec-

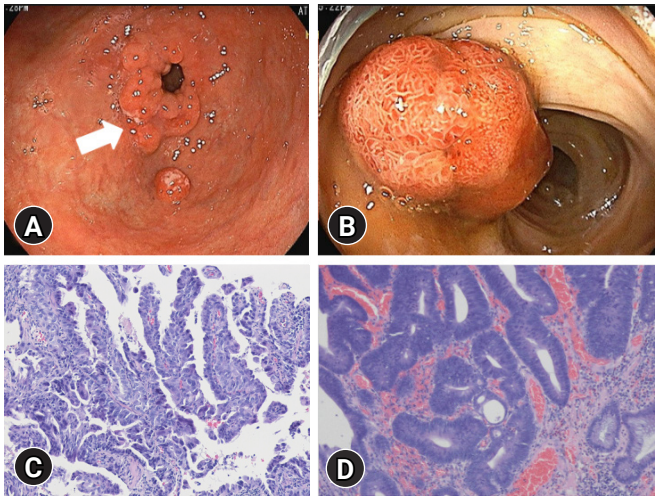

Fig. 2. (A) Upper gastroscopy shows several nodular lesions (arrow) measuring 2 cm in size with an irregular margin with erosion from the anterior wall to the lesser curvature of the prepyloric antrum. (B) Colonoscopy shows a pedunculated polyp measuring approximately 1.5 cm in size at the sigmoid colon. (C) The prepyloric nodular lesions show moderately differentiated adenocarcinoma (hematoxylin and eosin [H&E] stain, ×100). (D) The resected colon polyp shows tubular adenoma with high-grade dysplasia. Tumor cells have hyperchromatic nuclei, with cribriform pattern (H&E stain, ×100).

tious pathogens via either the biliary tract, portal vein, or hepatic artery; infection from an adjacent organ; or the accumulation of exudate, are grouped into either PLA or amebic liver abscess [1,2]. The recent improvement in public health in Korea has resulted in reducing the prevalence of amebic liver abscess, whereas PLA accounts for 73%–96% of liver abscesses, with KP being the primary causative pathogen [8]. In particular, immunocompromised patients with KP-PLA and conditions such as DM or cancer are at a risk of severe complications, including bacteremia, septic shock, and multiple organ failure [8].

Classically, PLA pathogenesis develops because of an ascending bacterial infection acquired via the biliary tract and typically originates from pylephlebitis accompanied by appendicitis and cholangitis owing to biliary tract surgery or gallbladder stones [5,6,8]. Hematogenous PLA is acquired from the hepatic portal vein or artery, which occurs because of a mucosal injury owing to colon cancer, colonic diverticulitis, or IBD [9,10]. Through this same mechanism, gastric cancer can lead to PLA via the hematogenous spread of infection from the hepatic portal vein [3,7].

However, because gastric acid eliminates the main causative pathogens, including KP, PLA rarely occurs despite the disruption of mucosal barriers caused by conditions such as gastric ulcers in immunocompetent hosts. Therefore, immunosuppressive conditions, including DM or malignant tumors, may accompany PLA and allow for the migration of pathogens via the compromised gastric mucosa, leading to distant-site infections such as KP-PLA [11].

In our study, mucosal injury owing to EGC enabled the hematogenous spread of KP via the portal vein, leading to KP-PLA with bacteremia. The putative mechanisms underlying KP-PLA with bacteremia are concomitant immunosuppressive conditions such as DM and gastric cancer. As previously mentioned, immunosuppressive conditions may be related to reduced eradication rates of stomach bacteria and reduced opsonized functions of the reticular endothelial systems such as Kupffer cells in the liver [7]. Finally, the decreased phagocytic activity associated with a weakened immune system may have led to the development of PLA with bacteremia in our case.

This study had some limitations. First, adenomatous colorectal polyps with high-grade dysplasia as precancerous lesions are associated with the ascending hematogenous spread of bacterial infection via the portal vein. However, definite evidence of mucosal injury of the colon polyp unlike EGC was not documented in the pathology report. Second, it is unclear whether the major cause of PLA is DM or mucosal injury, and it is difficult to explain the cause-and-effect relationship. It is clear that DM alone is a trigger for PLA. Despite the short duration of DM, mucosal injury in patient with DM is thought to accelerate the formation of PLA.

To the best of our knowledge, this is the first English-written case of EGC and adenomatous colorectal polyp with high-grade dysplasia concomitant with KP-PLA and bacteremia. Based on our case findings, upper gastrointestinal endoscopy can be performed for immunocompromised patients or patients with DM and PLA or bacteremia to screen for gastric cancer. However, further studies are needed to establish the association between PLA and gastric cancer in patients with PLA.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: MKK, MCK; Data curation: all authors; Formal analysis: MCK; Methodology: MKK, MCK; Investigation: MCK; Project administration, HJK; Visualization: HJK; Writing-original draft, Writing-review & editing: MKK, MCK.

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Web resources

Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after fem-

oral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf

Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process

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