Aims and scope

Journal of Yeungnam Medical Science is a peer-reviewed and open access journal in the medical field published in English four times a year (January 31, April 30, July 31, and October 31). The journal’s publishers are the Yeungnam University College of Medicine and Yeungnam University Institute Medical Science. The abbreviated title is J Yeungnam Med Sci (JYMS). Its regional focus is mainly Korea, but it welcomes submissions from researchers all over the world.

JYMS aims to communicate new medical information to medical personnel, and to facilitate the development of medicine and the propagation of medical knowledge by publishing high quality evidence-based articles. It covers all fields of medical science, including clinical research and basic medical science.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, Resident Fellow Section (RFS; clinical vignette, teaching images), and imagery. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and for the communication of valuable information about all medical fields.

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Photograph by Yeung Man Kim, Daegu, Korea.

The "Imagery" section of Journal of Yeungnam Medical Science (JYMS) is devoted to the artistic and imaginative qualities of our readers. JYMS invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.
Although pain is not a matter of life and death, it is a common cause of poor quality of life for people [1,2]. It is also the primary reason why patients visit hospitals. Therefore, clinicians should pay particular attention to the presence of a patient’s pain and effectively control it.

Pain occurs primarily because of degeneration or damage to musculoskeletal structures. A herniated disc, spinal stenosis, rotator cuff disease, adhesive capsulitis, myofascial pain syndrome on the cervical or lumbar areas, knee and hip osteoarthritis, and musculoskeletal or nervous system injuries are common causes of pain, and clinicians are familiar with diagnosing and treating these diseases. However, clinicians are often unaware of pain in patients suffering from diseases of relatively low incidence. In this special issue, Kwak [3] reviews the pain patterns and pain management in patients with amyotrophic lateral sclerosis (motor neuron disease). In addition, Park and Chang [4] describe the methodology of ultrasound-guided intervention to treat thoracic spine and chest wall pain. Motor neuron disease is uncommon; furthermore, pain in patients with motor neuron disease is often overlooked because clinicians focus on and treat the patient’s main symptoms, including muscle weakness. In addition, the incidence of thoracic spine and chest wall pain is relatively low compared to that of the above-mentioned common diseases causing musculoskeletal pain, and thoracic spine and chest wall pain are often not actively treated by clinicians because of the risk of developing lung puncture during pain control interventions. This special issue allows clinicians to improve their understanding of pain in patients with motor neuron disease and implement interventions safely and confidently in patients with thoracic spine and chest wall pain.

In clinical practice, corticosteroid injections are mainly used to control musculoskeletal pain [5]. Although corticosteroid injections can effectively control various musculoskeletal disease-associated pain, several side effects, such as allergic reaction, flushing, hyperglycemia, immunosuppression, menstrual changes, and adrenal suppression may occur [6]. Thus, several methods have been assessed as corticosteroid injection replacements. Among these methods, PRF stimulation and PRP injections are known to have some pain control effects that are equivalent to those of corticosteroid injections [6,7]. Moreover, this special issue deals with pain treatment using pulsed radiofrequency (PRF) stimulation and platelet-rich plasma (PRP) injection. Park and Chang [8] review studies on mechanisms of PRP stimulation for controlling pain, and Thu [9] reviews studies related to PRP injection in the management of musculoskeletal pain. With the help of these review papers, we hope that clinicians can effectively use PRF stimulation and PRP injections to control pain in patients, thereby enhancing the therapeutic effectiveness of pain control.

We also expect that this special issue will serve as a bridge to advanced research on neglected pain-causing diseases, PRF stimulation, and PRP injections.
Notes

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

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References

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative condition characterized by loss of motor neurons, resulting in motor weakness of the limbs and/or bulbar muscles. Pain is a prevalent but neglected symptom of ALS, and it has a significant negative impact on the quality of life of patients and their caregivers. This review outlines the epidemiology, clinical characteristics, underlying mechanisms, and management strategies of pain in ALS to improve clinical practice and patient outcomes related to pain. Pain is a prevalent symptom among patients with ALS, with a variable reported prevalence. It may occur at any stage of the disease and can involve any part of the body without a specific pattern. Primary pain includes neuropathic pain and pain from spasticity or cramps, while secondary pain is mainly nociceptive, occurring with the progression of muscle weakness and atrophy, prolonged immobility causing degenerative changes in joints and connective tissue, and long-term home mechanical ventilation. Prior to treatment, the exact patterns and causes of pain must first be identified, and the treatment should be tailored to each patient. Treatment options can be classified into pharmacological treatments, including nonsteroidal anti-inflammatory drugs, antiepileptic drugs, drugs for cramps or spasticity, and opioid; and nonpharmacological treatments, including positioning, splints, joint injections, and physical therapy. The development of standardized and specific assessment tools for pain-specific to ALS is required, as are further studies on treatments to reduce pain, diminish suffering, and improve the quality of life of patients with ALS.

Keywords: Amyotrophic lateral sclerosis; Motor neuron disease; Non-motor symptoms; Pain; Palliative care

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative condition characterized by loss of motor neurons in the cerebral motor cortex, brainstem, and spinal cord. It is typically heralded by motor weakness in the limbs and/or bulbar muscles and results in progressive muscle weakness beyond the site of initial symptoms, resulting in a fatal outcome generally within 2 to 4 years from the onset of disease [1]. Diagnosis of the disease is based on clinical and electrophysiological evidence of upper motor neuron (UMN) and lower motor neuron (LMN) involvement and the distribution of clinical signs of the disease (e.g., craniobulbar, cervical, thoracic, and lumbosacral regions) [2-4]. Notably, ALS should be considered a syndrome with a broad spectrum rather than a single disease entity because its symptoms and clinical course are very diverse (e.g., UMN vs. LMN predominance, bulbar vs. limb [spinal] predominance, rapid vs. slow progression, and the extent of concomitant cognitive impairment) [5]. ALS was once considered a pure motor disorder with ‘3 Ps’ (progressive, painless, and paralysis); however, a growing body of evidence indicates that ALS is a multisystem disease with early and diverse non-motor symptoms including cognitive and behavioral changes,
neuropsychiatric disturbances, sleep disruption, excess secretions, metabolic abnormalities, bowel and bladder dysfunction, changes in bone health, olfactory and somatosensory impairment, and pain [6]. These non-motor symptoms of ALS have attracted research attention over the last decade, with the identification of a repeat expansion of the C9orf72 gene in some patients and many shared pathologies across the spectrum of ALS and frontotemporal dementia in these patients [7,8].

The active study of pain in ALS, as well as other non-motor symptoms, began approximately 10 years ago, although there were earlier observations [9-11]. Previous studies revealed that these symptoms are prevalent among patients with ALS and negatively impact the lives of these patients and their caregivers, physically, psychologically, socially, and spiritually [12-15]. In addition, the two major guidelines on the management of ALS (from the American Academy of Neurology [AAN] and European Federation of Neurological Societies [EFNS]) include the treatment of pain in these patients [16,17], and there has been a Cochrane review on this subject [18]. However, a more thorough understanding of the prevalence, clinical characteristics, underlying mechanisms, and effective management of pain in this population is required to improve clinical practice and patient outcomes. In this review, the epidemiology of pain in patients with ALS, its clinical characteristics, and suggested underlying mechanisms of pain will be discussed before summarizing the assessment and treatment strategies for pain in ALS.

Epidemiology of pain in amyotrophic lateral sclerosis

The prevalence of pain in patients with ALS varies greatly from as low as 15% to as high as 85% [10,13,15,19-24]. These differences are thought to arise from the different study designs and settings, definitions of pain, and tools used to assess pain. A recent meta-analysis on the prevalence of pain in ALS estimated the pooled prevalence to be 60% (95% confidence interval [CI], 50%–69%) with a high degree of heterogeneity ($I^2 = 94\%, p < 0.001$) [25]. This meta-analysis also found that studies using tailored measures (e.g., clinical interviews, unvalidated questionnaires, or retrospective reviews of the medical record) to assess pain tended to show a lower pooled prevalence of 47% (95% CI, 34%–60%) and greater heterogeneity ($I^2 = 90\%, p < 0.001$) compared to those using tailored measures ($I^2 = 82\%, p = 0.002$, respectively), while studies using only validated measures showed a pooled pain prevalence of 65% (95% CI, 56%–73%, similar to the overall pooled prevalence of 60%) and lower heterogeneity. This demonstrates the importance of appropriate assessment tools for pain. Nevertheless, the two major guidelines for the management of ALS do not suggest which assessment tools should be selected. Another study showed that less than 20% of ALS clinics used questionnaires involving pain rating scales other than just open-ended questions [19]. Therefore, the establishment of a standardized assessment tool for pain in ALS is necessary to better manage pain in patients with ALS.

Currently, the most frequently used formal assessment tool is the Brief Pain Inventory questionnaire [13,15,19,22,24], which assesses current pain, its intensity over the previous week, and the extent of interference with mood, sleep, and physical, working, and social activities. Other validated assessment tools include the Neuropathic Pain Scale, short-form McGill Pain Questionnaire, Neuropathic Pain Symptom Inventory, and Neuropathic Pain Diagnostic Questionnaire [20,23]. However, although these tools are validated and are useful in discriminating and describing pain, it is unclear how useful they are for assessing pain in patients with ALS, who often have more than one type of pain [26]. Therefore, the development of standardized assessment tools for the diagnosis and monitoring of pain in ALS is important for improving patient care and outcomes.

In addition, the attention that physicians and patients pay to pain might also result in an inconsistency in its reported prevalence [26]. For example, a recent study conducted by Åkerblom et al. [12] indicated that some patients with ALS who were experiencing pain did not report it to their physician because they thought pain was not as important as other symptoms of the disease, they had received insufficient attention from the physician, or they believed there was no effective pain treatment, just as there was no effective disease treatment. Considering these points, it is important not only to evaluate pain at every visit using a structured assessment tool but also to train healthcare professionals accordingly.

Characteristics of pain

Primary pain in patients with ALS includes neuropathic pain and pain from spasticity or cramps. Secondary pain is mainly nociceptive, occurring with the progression of muscle weakness and atrophy, prolonged immobility causing degenerative changes in joints and connective tissue, and long-term home mechanical ventilation (HMV) either noninvasively by mask interface or invasively by tracheostomy (Fig. 1) [26,27].

Pain in ALS is largely nociceptive in nature, although it cannot explain all types of ALS pain. Neuropathic pain has not been reported to be prevalent among patients with ALS [16,26,28-30]. Previous studies have indicated a prevalence of neuropathic pain of 9% [28], 1% [29], and 5% [30] using Douleur Neuropathique 4
(DN4) as a screening tool; these values are not higher than those of the general population, ranging from 6.9% to 10.0%, as reported in a previous systematic review [31]. However, a recent study indicated that 62.5% of patients with ALS experienced neuropathic pain, described as electric shock, burning, dull, stabbing, throbbing, painful cold, sharp, or shooting [32]. However, that study did not adopt a validated measure for neuropathic pain. Although neuropathic pain seems to be rare in ALS, this finding might result from the fact that DN4 is only a screening tool for neuropathic pain and may not be a definite measure to diagnose neuropathic pain in ALS [28]. Furthermore, the low prevalence of neuropathic pain might have occurred because a large number of patients were already taking neurotropic medications such as riluzole, the only drug approved by the U.S. Food and Drug Administration for ALS treatment, which blocks the presynaptic release of glutamate [33] and thereby might reduce neuropathic pain [29,34,35]. Some neuropathic pain might be due to spinal disorders, at least partially, considering that the peak incidence of ALS occurs between 58 and 63 years of age [1], an age group in which spinal disorders are common. Although it has been reported that 14% to 32% of the diagnostic delay in ALS is due to the misdiagnosis of ALS as a spinal disorder such as myelopathy or radiculopathy [36-42], no study has evaluated the exact prevalence of spinal disorders in patients with ALS.

Other sources of primary pain include cramps and spasticity. Muscle cramp refers to a sudden and involuntary muscle contraction originating from the peripheral nerves [43] and is reported to be a major source of pain in patients with ALS, affecting approximately two-thirds of patients [11,44]. In a previous study, which followed 41 patients with ALS for up to 21 months, 95% of the patients had experienced cramps over the course of the disease [45]. Muscle cramps in patients with ALS are believed to originate from instability of the affected motor unit and are typically associated with denervation of the muscles [43]; patients with limb-onset ALS are more frequently affected by them [43,45]. Spasticity is a velocity-dependent increase in muscle tone, which results from the loss of inhibitory control of UMN, causing stiffness and spasms in the affected muscles as well as difficulties in fine motor control [46]. According to a recent study conducted in a tertiary hospital in France, the prevalence of spasticity was 36% in patients with

Fig. 1. Types of pain in amyotrophic lateral sclerosis. Most reported types of pain are secondary in nature (mainly nociceptive; blue shading), but there is some evidence for primary forms of pain (green shading), such as neuropathic pain, spasticity, and cramps. NIV, noninvasive ventilation. Reprinted from Chiò et al. [26] with permission from Elsevier.
ALS, and approximately half (42.5%) of those patients had mild pain. However, 16.7% of patients with spasticity had moderate to severe pain, with numeric rating scale scores of ≥ 4 [47].

Secondary pain is mainly nociceptive, which means it arises from nonneuronal tissue damage or the activation of peripheral nociceptors as a result of mechanical or other noxious stimuli [48]. Secondary pain is known to develop as ALS progresses. Joint pain, which is prevalent in patients with ALS, develops when weakened and wasting muscles are unable to provide support to the joint [26,49]. It has been reported that shoulders and hips are the most frequently affected joints [13,50]. Immobility might cause skin pressure, which might be perceived as pain, although pressure sores do not occur frequently despite the poor mobility of patients with ALS [51]. Long-term HMV may be another source of pain. In patients undergoing noninvasive ventilation (NIV), skin problems due to mask interfaces, especially on the nasal bridge, can cause pain [26]. In invasively ventilated patients with a tracheostomy who remain in the same position over a period of time during HMV, irritation of the throat from the weight of the circuits (tubes) and suctioning of the secretions can result in significant discomfort and pain, which are often unnoticed by caregivers or medical professionals [52].

In terms of the localization of pain, previous studies have not found a specific pattern, and pain can involve any part of the body, including the proximal and distal sites of the upper and lower extremities and the back, or it could be diffuse [13,15,19,22,23,53]. A recent meta-analysis, which analyzed a total of 393 patients with ALS who reported 715 locations of pain, reported that the most commonly reported location was the upper limbs (including shoulders and extremities) (41.5%), followed by the lower limbs (33.7%), and the head, neck, trunk, and back (24.8%) [25].

The intensity of pain was also reported in the same study; among 1,426 patients who reported pain intensity, 78.8% reported moderate pain, 17.5% reported severe pain, and only 2.0% and 1.7% reported mild and very severe pain, respectively [25], which is consistent with previous reports [23,29]. However, other studies have indicated that the intensity was mainly mild [14,22]. Again, this inconsistency might result from the different study designs and settings, the definition of pain, and the assessment tools for pain, as well as the cross-sectional nature of the aforementioned studies. A recent longitudinal study indicated that at least moderate average pain was reported in about two-thirds of patients who completed a 1-year follow-up [54], indicating that moderate to severe pain might be persistent in patients with ALS.

Several studies have indicated the occurrence of pain early in the disease course [9,15,19,26,32,55]. In a study including 424 patients, 34% of patients with ALS reported pain in the early stage of disease [19], and a recent epidemiological study revealed that patients with ALS had been prescribed more drugs for neuropathic pain (hazard ratio, 1.84; 95% CI, 0.99–3.42) up to 2 years before the onset of ALS [56]. The question of whether pain worsens with ALS progression varies widely among studies [13-15,22,23,53], probably because of the cross-sectional nature of these studies [26]. A longitudinal study indicated that pain intensity increased by 1 point on the visual analog scale from the first visit to the last, with a median follow-up period of 104 days (range, 35–846 days) [57]. Similarly, a recent study including 151 patients at baseline also revealed that the intensity and quality of pain and the impairment it causes did not change significantly over time [54], which is consistent with findings from another longitudinal study [58].

### Treatment of pain in amyotrophic lateral sclerosis

Currently, there is little high-quality evidence regarding the pharmacological treatment of pain in ALS, as there are no randomized or quasi-randomized treatment trials of pain in ALS. However, several guidelines on the clinical management of ALS include management of pain, cramps, and spasticity [16,17,59], and there are Cochrane reviews [18,60]. Prior to treatment, the exact patterns and causes of pain must first be identified; then, the treatment should be tailored to each patient. Treatment options can be classified into pharmacological and nonpharmacological treatments, for which pharmacological treatment is known to be more effective for the primary pain, whereas nonpharmacological approaches are regarded as more effective for secondary pain in ALS [26]. A summary of interventions for the management of pain according to its etiology is presented in Table 1, including both self-treatment and professional treatment.

#### 1. Treatment of primary pain in amyotrophic lateral sclerosis

As stated earlier, neuropathic pain does not appear to be prevalent in patients with ALS; however, this type of pain is significant because it can be controlled according to pharmacological management pathways for neuropathic pain [61]. The most widely used drugs for the treatment of neuropathic pain are gabapentin, pregabalin, and tricyclic antidepressants [49]. Although opioids are not recommended as first-line therapy, they can be used when pain is not controlled or in advanced stages in cases of increased pain or with symptoms related to respiratory insufficiency, such as dyspnea and sleep disturbance [62]. However, there is little evidence to support the safety and efficacy of opioid use [18].

Quinine sulfate is the most frequently prescribed drug in Euro-
Table 1. Interventions for the management of pain in patients with amyotrophic lateral sclerosis according to the etiology of pain

<table>
<thead>
<tr>
<th>Etiology of pain</th>
<th>Self-management</th>
<th>Professional management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle cramps</strong></td>
<td>Massage, stretching</td>
<td>Quinine sulfate</td>
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<tr>
<td>Aromatherapy</td>
<td>Magnesium</td>
<td></td>
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<tr>
<td>Drink tonic water (contains quinine)</td>
<td>Vitamin E</td>
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<tr>
<td>Bananas, oranges, and citrus fruit juices (to address magnesium imbalance)</td>
<td>Vitamin D</td>
<td></td>
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<tr>
<td>Heat</td>
<td></td>
<td></td>
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<tr>
<td><strong>Spasticity</strong></td>
<td>Positioning</td>
<td>Physiotherapy</td>
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<tr>
<td>Passive exercise</td>
<td>Tizanidine</td>
<td></td>
</tr>
<tr>
<td>Active within limitations</td>
<td>Baclofen</td>
<td></td>
</tr>
<tr>
<td>Heat</td>
<td>Hydrotherapy</td>
<td></td>
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<tr>
<td>Pressure above and below joint</td>
<td>Botulinum toxin</td>
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<tr>
<td>Stretching</td>
<td></td>
<td></td>
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<tr>
<td><strong>Constipation</strong></td>
<td>Review of dietary intake</td>
<td>Laxatives</td>
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<tr>
<td>Review of fluid intake</td>
<td>Movicol</td>
<td></td>
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<tr>
<td>Review of current medications</td>
<td>Senna and lactulose</td>
<td></td>
</tr>
<tr>
<td>Passive exercise</td>
<td>Dulcolax</td>
<td></td>
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<tr>
<td>Regular review of bowel habits, monitor or change</td>
<td>Laxatives on commencement of opioids</td>
<td></td>
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<tr>
<td>Abdominal massage</td>
<td></td>
<td></td>
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<tr>
<td>Linseed seeds</td>
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<tr>
<td><strong>Spasm</strong></td>
<td>Passive exercise</td>
<td>Baclofen</td>
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<tr>
<td>Positioning</td>
<td>Dantrolene</td>
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<td></td>
<td>Diazepam</td>
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<tr>
<td></td>
<td>Sublingual lorazepam</td>
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<tr>
<td></td>
<td>Tizanidine</td>
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<tr>
<td><strong>Skin pressure</strong></td>
<td>Positioning</td>
<td>Pressure mattresses/cushions</td>
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<tr>
<td>Regular turning</td>
<td>Appropriate beds/chairs</td>
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<tr>
<td>Correct moving and handling techniques</td>
<td>Use of hoists</td>
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<tr>
<td>Preventative measures</td>
<td>Diclofenac sodium</td>
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<td></td>
<td>Morphine</td>
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<td></td>
<td>Amitriptyline</td>
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<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Passive exercise prior to transfer for immobile individuals, range of motion</td>
<td>Physiotherapy</td>
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<tr>
<td>Preventative measures</td>
<td>Hydrotherapy</td>
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<tr>
<td>Positioning</td>
<td>NSAIDs</td>
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<tr>
<td>Correct moving and handling techniques</td>
<td>Paracetamol</td>
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<td></td>
<td>Tramadol</td>
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<td></td>
<td>Joint injections</td>
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<td></td>
<td>Morphine</td>
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<td></td>
<td>Orthotics, splints</td>
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<td></td>
<td>Collars</td>
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<td>TENS</td>
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<td></td>
<td>Complementary/alternative therapy</td>
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</table>

NSAIDs, nonsteroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation.

pean countries, although its use for cramps is proscribed by the U.S. Food and Drug Administration [26,63]. It should also be noted that quinine sulfate can cause serious side effects, such as thrombocytopenia and drug interactions [49]. Mexiletine at a dose of 300 mg per day and dronabinol at a dose of 5 mg twice daily could be used as first-line therapies; gabapentin and levetiracetam are suggested as second-line therapies in the guidelines [16,17].
Spasticity can be effectively managed with appropriate medication. Although there are no controlled clinical trials in patients with ALS, baclofen, tizanidine, benzodiazepines, dantrolene, and carbamazepine can be used to reduce spasticity [49]. However, undesirable side effects, such as weakness, daytime somnolence, or excessive fatigue, are common with these medications. Therefore, careful dose titration and appropriate physiotherapy are required [50,64,65]. In cases of refractory spasticity, intrathecal baclofen pump placement was proposed as an option, and a previous study indicated an average reduction of 54% in pain intensity after the procedure. However, these findings should be interpreted with caution considering the open-label study design and lack of follow-up evaluation [66].

2. Treatment of secondary pain in amyotrophic lateral sclerosis
Musculoskeletal pain secondary to progressive wasting and weakness of the muscles should be managed with careful positioning, regular gentle range of movement exercises, joint injections, and medications [11,26]. The timely and proper use of assistive devices is also an important point of care, which includes the use of special mattresses and pillows, custom-fitted wheelchairs, and neutral-position splints for the hands and ankles to prevent joint contractures [64,65].

If pain is not controlled by positioning, splints, joint injections, or physical therapy, regular administration of analgesics should be considered using the World Health Organization analgesic ladder originally developed for the management of cancer-related pain, as suggested by the AAN Practice Parameters and EFNS guidelines [16,17]. However, the use of this strategy in patients with ALS is still debatable [67,68].

Conclusion
Pain is an important issue in ALS, with a pronounced impact on quality of life and suffering. The ultimate goal of pain treatment is to reduce its intensity, diminish suffering, and improve the quality of life of patients. To achieve this goal, thorough and timely assessments are vital. However, there is currently no assessment tool specific to this population. Therefore, a consensus should be reached regarding the timing, intervals, and contents of pain assessments in ALS. In addition, specific guidelines on the treatment of pain in ALS should be developed because successful pain treatment can improve the quality of life of patients and their caregivers, even in the absence of a disease cure. Further research on this topic is needed, considering the gaps between current care standards and patient requirements. In particular, careful consideration of the study design is required [26], considering that a classic double-blind, placebo-controlled study might not be feasible owing to the nature of the disease (rare, rapidly progressing, and incurable). Until more robust evidence is available, strategies for managing pain in ALS should be tailored to the needs of individual patients, based on good clinical practices and information from the management of nonmalignant chronic pain.

Notes

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34. Moon ES, Karadimas SK, Yu WR, Austin JW, Fehlings MG. Riluzole attenuates neuropathic pain and enhances functional re-


Ultrasound-guided interventions for controlling the thoracic spine and chest wall pain: a narrative review

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Ultrasound-guided injection is useful for managing thoracic spine and chest wall pain. With ultrasound, pain physicians perform the injection with real-time viewing of major structures, such as the pleura, vasculature, and nerves. Therefore, the ultrasound-guided injection procedure not only prevents procedure-related adverse events but also increases the accuracy of the procedure. Here, ultrasound-guided interventions that could be applied for thoracic spine and chest wall pain were described. We presented ultrasound-guided thoracic facet joint and costotransverse joint injections and thoracic paravertebral, intercostal nerve, erector spinae plane, and pectoralis and serratus plane blocks. The indication, anatomy, sonoanatomy, and technique for each procedure were also described. We believe that our article is helpful for clinicians to conduct ultrasound-guided injections for controlling thoracic spine and chest wall pain precisely and safely.

Keywords: Anatomy; Diagnostic imaging; Injections; Pain; Thoracic vertebrae; Thoracic wall

Introduction

Thoracic spine and chest wall pain is less prevalent than lumbar or cervical area pain, but it has been reported to affect 13% to 15% of the total population [1]. Encountering patients with thoracic spine and chest wall pain in actual pain clinics is not rare in clinical practice. Moreover, persistent thoracic spine and chest wall pain could impair activities of daily living and cause decline in the quality of life [2]. Clinicians generally do not prefer injection to the thoracic structures due to the risk of pneumothorax caused by puncturing a lung with the needle during the procedure. Even with fluoroscopy-guided thoracic procedures, the lungs cannot be viewed directly, meaning any procedure-related risk of pneumothorax is unavoidable [3]. Rather than perform such procedures, clinicians prescribe anti-inflammatory analgesics and physical therapy to patients with thoracic spine and chest wall pain and monitor their progress; however, in several cases, pain is not often controlled sufficiently.

Ultrasound offers the advantage of being able to perform a procedure with real-time viewing of major structures, such as the pleura, vasculature, and nerves, which cannot be viewed by fluoroscopy [4-7]. Therefore, the ultrasound-guided injection procedure not only prevents procedure-related adverse events but also enables accuracy.

This study aimed to describe ultrasound-guided interventions that could be applied for patients with thoracic spine and chest wall pain. In this study, the ultrasound image was obtained using an ultrasound machine (RS80A, Samsung Medison Corp., Ltd.,...
Seoul, Korea) with 1 to 7 MHz curved and 3 to 12 and 2 to 9 MHz linear array transducers.

**Thoracic facet joint injection**

1. **Indication**
The thoracic facet joint injection procedure is indicated for patients with painful conditions due to the involvement of the thoracic facet joints.

2. **Anatomy**
The thoracic facet is composed of the inferior and superior articular processes. The superior articular processes of the thoracic vertebrae face anteriorly, while the inferior processes face posteriorly [8]. The thoracic facet joints are angled at 60° to the axial plane and 20° to the frontal plane [9]. This allows for rotation and some flexion/extension and lateral flexion. The facet joints are synovial joints, which have a smooth contact surface called articular cartilage [8,9]. Each facet joint is also surrounded by a capsule. An irritated and inflamed facet joint produces mid back pain and thoracic facet-origin pain with reference to the trunk or rib cage [10].

3. **Sonoanatomy and technique**
The facet joint in the thoracic vertebrae has a high coronal plane, which makes it difficult to perform the procedure since the facet joint is not readily visible under fluoroscopy. However, the thoracic facet joint in the coronal plane could be well viewed on ultrasound images, and needle insertion is actually more convenient with ultrasound guidance. The patient is placed in a prone position. After the probe (1–7 MHz curved array transducer) is slightly moved laterally over the lamina, between two hyperechoic lines, that are the inferior and superior articular processes, the thoracic facet joint is visualized in the paramedian sagittal image (Fig. 1A). With the probe in one hand and the syringe in the other, insertion is performed longitudinally toward the proximal region, in-plane below one- or two-finger width below the probe (Fig. 1B).

To find the level of the posterior joint being targeted by ultrasound, the probe placed longitudinally in the inferior aspect is slowly moved superiorly to locate the 12th rib, which is the first rib visualized. By moving the probe superomedially along the 12th rib, the 12th costotransverse articulation could be seen. By slightly moving inferomedially from this point, the T12 spinous process can be seen past the T12 lamina, which could be used as the starting point. When slightly moving superolaterally from this starting point, the first posterior joint encountered is the T11–T12 facet joint, and the T10–T11 facet joint could be found by moving superiorly. By counting in this manner, the probe could be moved superiorly up to the target joint to perform the procedure. Usually, 1 to 2 mL of local anesthetic is injected per each facet joint.

**Costotransverse joint injection**

1. **Indication**
The costotransverse joint injection procedure is indicated for patients with painful conditions because of the costovertebral joints.

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**Fig. 1.** (A) The thoracic facet is formed by the union of the inferior articular process (IAP) and superior articular process (SAP). After the probe is slightly moved laterally over the lamina, between two hyperechoic lines, which are the IAP and SAP, the thoracic facet joint is visualized in the paramedian sagittal image. Dotted arrow indicates the pathway of the needle. (B) With the probe in one hand and the syringe in the other, insertion is performed longitudinally toward the proximal region, in-plane below 1- or 2-finger width below the probe.
2. Anatomy
The costotransverse joint is the articulation that connects the ribs with the transverse processes [11]. This joint significantly contributes to the stability and movement of the thoracic spine and ribs [11].

3. Sonoanatomy and technique
The patient is placed in the prone position. For the targeted level, the same method previously described in the thoracic facet injection section is used to scan superiorly, starting from the T12 level. Using a 2- to 9-MHz linear array transducer, transverse scan is performed at the targeted thoracic level so that the transverse process, costotransverse joint, rib, and lung appear in the same plane (Fig. 2A). In an in-plane approach, the needle is pointed toward the costotransverse joint in the lateral to medial direction (Fig. 2B). Injection of 1 to 2 mL of local anesthetic is conducted per each facet joint.

Thoracic paravertebral block

1. Indication
The procedure can be used in patients with mid back pain, cancer pain on the thoracic spine and chest wall, rib fracture, refractory angina pectoralis, thoracoabdominal neuralgia, or post-thoracotomy pain [12].

2. Anatomy
The thoracic paravertebral space has a triangular shape on axial cross-section, and its borders are as follows: the base is formed by the intervertebral discs, intervertebral foramina, and posterolateral aspect of the vertebral body; the anterolateral border by the parietal pleura; and the posterior border by the superior costotransverse ligament [12]. The thoracic paravertebral space is comprised mostly of fatty tissues, where various nerves, such as the ventral ramus, dorsal ramus, intercostal nerves (ICNs), sympathetic chain, and rami communicantes, pass through [13].

3. Sonoanatomy and technique
The patient is placed in the prone position. The image center is positioned on the lateral side of the transverse process by transverse scan of the targeted thoracic level. The transverse process and ribs are visible from the medial and lateral sides, respectively, as hyperechoic lines. While maintaining the transverse scan, the probe (2–9-MHz linear array transducer) is slid into the intercostal space between the ribs. In the intercostal space, an echogenic line by the pleural interface, instead of the rib, is observed. The intercostal and thoracic paravertebral spaces are visible from the lateral and medial sides, respectively (Fig. 3A). The probe is fixed by the transverse scan in a position with a clear view of the thoracic paravertebral space, and the needle entry site is set to the lateral side of the probe for medial insertion (Fig. 3B). After confirming that the needle tip

Fig. 2. (A) The costotransverse joint is the articulation that connects the ribs with the transverse process (TP). Transverse scan is performed at the targeted thoracic level so that the TP, costotransverse joint, rib, and lung appear in the same plane. Dotted arrow indicates the pathway of the needle. (B) The injection is performed by an in-plane approach with the needle pointed toward the costotransverse joint in the lateral to medial direction.
is inside the thoracic paravertebral space, the injection material is injected into the space (Fig. 3B). The suggested volume is 15 to 20 mL of a long-acting local anesthetic [14].

**Intercostal nerve block**

1. **Indication**
The ultrasound-guided ICN block procedure is usually necessary for analgesia for multiple rib and sternal fractures, costochondritis, thoracic trauma, chest wall surgery and tumors, and chest tube procedure; postoperative pain control after complete or partial mastectomy, lumpectomy (breast-conserving surgery), or wide excision or breast reconstruction; or the treatment of pain caused by shingles or postherpetic neuralgia [15].

2. **Anatomy**
The intercostal space is the space between two adjacent thoracic ribs. There are 11 intercostal spaces on each side, and the intercostal muscles, intercostal membranes, ICNs, and intercostal vessels are presented in the intercostal space [15,16]. There are 11 pairs of ICNs (T1–T11), which are the anterior divisions of the thoracic spinal nerves [15,16]. The ICNs course through the intercostal spaces accompanied by the intercostal artery and vein [15,16]. The ICNs provide motor and sensory innervations to the thoracic and abdominal wall and sensory innervation to the peritoneum and parietal pleura [15,16]. Around the posterior axillary line, ICNs are divided into the main and collateral branches [15,16].

   In regard to the intercostal muscles, three layers consist the external, internal, and innermost intercostal muscles [15,16]. The parietal pleura is located under the innermost intercostal muscle [15,16]. From the costal angle onward, a neurovascular bundle, which consists of the main ICNs and vessels, is arranged in the vein, artery, and nerve orientation from superior to inferior [15,16]. Both neurovascular bundles are found between the internal and innermost intercostal muscles. However, the main neurovascular bundle is found near the inferior border of the upper rib of an intercostal space, while the collateral neurovascular bundle is found at the superior border of the lower rib [15,16].

3. **Sonoanatomy and technique**
To perform the effective ICN block by a single injection, an ultrasound-guided ICN block has to be performed before the ICN is divided into the main and collateral branches [15]. Therefore, the ultrasound-guided intercostal block is usually performed at the posterior to the posterior axillary lines. The ICNs in the intercostal space are often not possible to be found by ultrasound examination. However, the vessels within the main neurovascular bundle located in the lower margin of the rib may be visible using the color Doppler (3–12-MHz-linear array transducer) (Fig. 4A). Therefore, it is possible to estimate the location of the ICN by detecting the location of the vessels using a color Doppler.

   The patient can be placed in either sitting, prone, or lateral decubitus position. Using ultrasound, the intercostal space behind the
posterior axillary line has to be scanned to find the ICN before dividing it into the main and collateral branches. To identify the level of the intercostal space, start scanning at the inferior angle of the scapula, which corresponds to approximately the 7th intercostal space when the hand is hanging down on the side [13]. After finding the intercostal space, place the probe vertically and advance the needle to the inferior margin of the rib (Fig. 4B, 4C). For ICN block, the injection of 2 to 4 mL of local anesthetic is usually sufficient [16]. However, to improve the effectiveness of ultrasound-guided ICN block, hydrodissection is recommended to distinguish the intercostal muscle layers because these are difficult to distinguish by ultrasound [15].

Erector spinae plane block

1. Indication
The ultrasound-guided erector spinae plane block (ESPB) procedure is usually necessary in patients with thoracic neuropathic pain. Moreover, it is used as a postoperative analgesia method in several surgical procedures from the shoulder to the hip (C7–L4), including laparoscopic/open renal and perirenal procedures and those requiring large dermatomal blockage such as the combination of surgeries (mastectomy, breast prosthesis, and abdominoplasty), urological procedures such as bladder surgeries, radical prostatectomy, gynecological procedures, or orthopedic procedures such as hip and knee surgeries. This block serves the purpose of a paravertebral block without the risk of pleural injury [17,18].

2. Anatomy
The erector spinae is not one muscle but a group of tendons and muscles. It is divided into three columns: iliocostalis (lateral column), longissimus (intermediate column), and spinalis (medial column) muscles [19-21].

The iliocostalis muscle originates from the iliac crest, sacrum, and erector spinae aponeurosis. It has three different insertions: iliocostalis cervicis (originated from the angle of the 3rd–6th ribs and inserted to the posterior tubercle of the C4–C6 transverse processes), iliocostalis thoracis (originated from the angle of the 7th–12th ribs and inserted to the angles of the 1st-6th ribs, C7 transverse process), and iliocostalis lumborum (originated from the lateral crest of the sacrum, medial end of the iliac crest, and thoracolumbar fascia and inserted to the angles of the 5th–12th ribs, L1–L4 transverse processes) [19-21].

The longissimus muscle has three parts with different origin and insertion: longissimus thoracis (originated from the sacrum, spinous processes of the lumbar vertebrae, and transverse process of the last thoracic vertebra and inserted to the transverse processes of the lumbar vertebrae, erector spinae aponeurosis, ribs, and costal processes of the thoracic vertebrae), longissimus cervicis (originated from the T1–T6 transverse processes and inserted to the C2–C7 transverse processes), and longissimus capitis (originated from the T1–T3 transverse processes, runs through C3–C7, and inserted to the mastoid process of the temporal bone) [19-21].

The spinalis muscle has three parts: spinalis thoracis (originated from the T10–L3 spinous processes and inserted to the T2–T8 spinous processes), spinalis cervicis (originated from the T2–C6 spinous process and inserted to the C2–C4 spinous process), and spinalis capitis (originated from the spinous process at the cervical and upper thoracic levels and then inserted to the external occipital protuberance) [19-21].

3. Sonoanatomy and technique
The patient can be placed in either sitting, prone, or lateral decubitus position. Usually, to perform an ESPB at the thoracic level, a high-frequency linear ultrasound transducer probe is used. To
identify the spinous process, the probe has to be placed in a transverse orientation.

Using the previous study as a reference, ESPB can be performed at the T2 vertebral and T5 and T7 spine levels for the sensory blockade of the cervical, thoracic, and lumbar dermatomes, respectively [22].

Using a 2 to 9-MHz linear array transducer, once the level is identified according to sensory blockage level, the probe is moved approximately 3 cm laterally until the transverse process is identified. The transverse process has a square contour compared with the ribs, which has a rounded contour. The probe should be rotated 90° on the transverse process by placing it in a parasagittal plane. At the T5 vertebral level, the following three muscles must be identified as above to the hyperechoic transverse process shadow: trapezius, rhomboid major, and erector spinae (Fig. 5A). At the T7 vertebral level, however, the rhomboid major muscle disappears (Fig. 5B). The needle is usually inserted in the plane (Fig. 5C). Depending on the patient’s position or region to be treated, the procedure can be performed in the craniocaudal or opposite direction. The target of the injection must be in the fascial plane, deeper than the erector spinae muscles at the tip of the transverse process of the thoracic spine (Fig. 5C). To increase the effectiveness, a hydrodissection is recommended.

In the previous studies, 20 mL of local anesthetics spreads between three and seven levels, averaging the blockage of 4.6 levels. Usually, 20 to 30 mL of local anesthetics is applied in the thoracic spine and chest wall, whereas 30 to 40 mL of local anesthetics is applied in the lumbar areas for the dermatomal coverage of the surgical field [23]. In addition, it is probable that high volume and concentration increase the success rate of ESPB [23].

### Pectoralis and serratus plane blocks

#### 1. Indication

The pectoralis (Pecs 1 and Pecs 2) and serratus plane blocks are anterior approach chest wall blocks initially described by Blanco et al. [24] as a novel technique to provide analgesia after breast surgery [25-30]. The Pecs 1 block is targeting the lateral and medial pectoral nerves between the major and minor pectoral muscles. In the Pecs 2 block, the injection of local anesthetic is added under the serratus anterior muscle and into the interfascial space between the pectoralis minor and serratus anterior muscles in addition to the Pecs 1 block. The serratus plane block uses a more lateral and posterior approach to block the interfascial plane superficial or deep to the serratus anterior muscle.

They can be performed more safely and easily than posterior approach blocks such as thoracic epidural or paravertebral blocks under ultrasound guidance because the anatomical structures concerned are located more superficially and easy to access. Therefore, they could be used as an alternative or emergency option to the posterior approach chest wall blocks when they are not applicable. Although they are originally designed as analgesic options after breast surgery, there are several studies in which they are used for other indications such as rib fracture, thoracotomy, and insertion of a cardiac device [25-30].

#### 2. Anatomy

The pectoral and axillary regions are composed of muscles innervated by the brachial plexus and separated by multiple fascias. The Pecs and serratus plane blocks are targeting these separated interfascial spaces. There are three groups of nerves we should take into account.

![Fig. 5](https://doi.org/10.12701/jyms.2022.00192)
The first group is the lateral and medial pectoral nerves. They arise from the brachial plexus, communicate with each other through the ansa pectoralis, and run between the major and minor pectoral muscles innervating them [31,32]. The Pecs 1 block is aimed at this interfascial space between the major and minor pectoral muscles, expecting to block the pectoral nerves. The lateral pectoral nerve arises from the lateral cord of the brachial plexus, which is supplied from the C5 to C7 nerve roots, runs down in close proximity to the pectoral branch of the thoracoacromial artery, and innervates the pectoralis major muscle [33]. The medial pectoral nerve is a branch of the medial cord of the brachial plexus supplied from the C8 to T1 nerve roots. It runs under the pectoralis minor muscle and then punctures the muscle to enter the interfascial space between the major and minor pectoral muscles [33].

The second group of nerves is the ICNs, which take charge of the segmental somatic sensory innervation of the chest wall, axilla, and medial aspect of the upper arm. The Pecs 2 and serratus plane blocks are mainly targeting this set of nerves. They give off the lateral cutaneous branches just anterior to the midaxillary line. Thereafter, they run to the sternal border, turn anteriorly, and terminate as the anterior cutaneous branches. The T1 nerve generally has no lateral and anterior cutaneous branches, and most of its fibers join those from the C8 nerve. Some fibers of the T2 and T3 nerves give rise to the intercostobrachial nerve, which innervates the axilla and medial aspect of the upper arm.

The third and the last group of nerves is the long thoracic and thoracodorsal nerves. The long thoracic nerve arises directly from the C5 to C7 nerve roots, entering the axilla, and resting on and innervating the serratus anterior muscle. The thoracodorsal nerve branches from the posterior cord of the brachial plexus. It accompanies the thoracodorsal artery and innervates the latissimus dorsi muscle.

3. Sonoanatomy and technique

1) Pecs 1 block
The goal of the Pecs 1 block is to infiltrate the local anesthetic into the interfascial space between the pectoral muscles to block the lateral and medial pectoral nerves. A high-frequency linear probe (3–12-MHz linear array transducer) is selected because the involved anatomical structures are located superficially. The patient is positioned supine with the arm next to the chest or abducted at 90°. The probe is placed under the lateral third of the clavicle in a sagittal plane where the pectoral muscles and axillary vessels can be visualized. The pectoral branch of the thoracoacromial artery that is in close proximity to the lateral pectoral nerve is seen as a small pulsating structure between the pectoral muscles, and it can be confirmed using the color Doppler ultrasound (Fig. 6A). Rotating the caudal border of the probe slightly laterally, the needle can be introduced from the skin to the interfascial space using the in-plane technique from proximal and medial to distal and lateral in an oblique manner. After confirming the hydrodissection of the two pectoral muscles by the injected local anesthetic, the procedure is completed. The suggested volume is 10 mL of a long-acting local anesthetic [34].

2) Pecs 2 block
The Pecs 2 block is an extension of the Pecs 1 block to achieve the blockade of the ICNs, and it includes the Pecs 1 block. From the Pecs 1 block position, the probe is moved more laterally to the an-
terior axillary line, where the serratus anterior muscle is seen deep and posterior to the pectoralis minor muscle. At the level between the 2nd and 4th ribs, the needle is introduced into the space under the serratus anterior muscle (Fig. 6B). After injecting the anesthetic, the needle is pulled back to the interfascial space between the pectoralis minor and serratus anterior muscles under ultrasound guidance (Fig. 6B, 6C). After injecting the anesthetic, the needle is pulled back to the interfascial space between the pectoral muscles where the Pecs 1 block is performed (Fig. 6B). In that space, the remainder of the anesthetic is deposited. The two targeted interfascial compartments can be blocked with a single skin puncture by this technique, and it is easier to perform the deep block first before the Pecs 1 block. When performing the Pecs 2 block, the first injection of approximately 10 mL of a long-acting local anesthetic is performed into the space under the serratus anterior, and the second injection of 10 mL is performed between the pectoralis minor and serratus anterior muscles (total, 20 mL) [30].

3) Serratus plane block
The serratus plane block is an easier and safer modification of the Pecs blocks, which is expected to block not only the ICNs but also the long thoracic and thoracodorsal nerves. This block is also performed from the anterior approach with an in-plane technique under ultrasound guidance. The patient is in a supine position with their arm abducted. The probe is placed more laterally and posteriorly near the midaxillary to posterior axillary lines. At this location, the latissimus dorsi muscle is seen most superficially and posteriorly (Fig. 7A). The teres major is located superiorly deep to the latissimus dorsi muscle (Fig. 7A). Anteroinferiorly, the serratus anterior muscle is seen deep to the teres major and latissimus dorsi muscles (Fig. 7A). The serratus plane block can be performed superficial or deep to the serratus anterior muscle, but the superficial plane block is safer and more effective (Fig. 7A, 7B) [30]. Compared with the Pecs 2 block, the serratus anterior muscle is more superficially located and easier to identify in this technique; thus, the blockade is easy to be obtained with a low-risk profile. When performing the serratus plane block, approximately 20 mL of a long-acting local anesthetic is administered.

**Conclusion**
We believe that our article is helpful for clinicians to conduct ultrasound-guided injections for controlling thoracic spine and chest wall pain precisely and safely.

**Notes**

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

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References


Introduction

Most people experience pain due to pathologies of the nervous or musculoskeletal systems [1,2]. When the degree of pain is severe, patients' quality of life decreases, and their function in daily activities and work deteriorates [1,2]. Therefore, pain control is important in clinical practice. Corticosteroid injections are frequently used [3,4]. However, they can have various adverse effects including flushing, hyperglycemia, allergic reactions, menstrual changes, immunosuppression, and adrenal suppression [5,6]. To date, many injection materials have been suggested as substitutes for corticosteroids [7-9]. However, the effectiveness of materials that substitute corticosteroids is generally inferior to that of corticosteroids.

Electrical stimulation is thought to have a pain-reducing effect, and several types of electrical simulations have been used to alleviate pain [10-12]. Of these various stimulations, radiofrequency was found to have a pain-reducing effect similar to corticosteroid injection [13-15]. Continuous radiofrequency (CRF) exposes the target nerves or tissues to high temperatures (70°C–90°C) via continuous electrical stimulation [16]. Nerves or tissues treated with
CRF are ablated [16]. The ablation of targeted nociceptive nerve fibers is thought to be the main mechanism of pain reduction after CRF [16]. However, as experiences of CRF use were accumulated, physicians realized that the pain could be effectively controlled even not under such high temperatures [17-19]. Therefore, it was thought that the formation and action of the electrical field around the target nerves or tissues would be a more important mechanism of PRF action than ablation by high temperatures. In 1998, Sluijter et al. [20] first introduced pulsed radiofrequency (PRF). By placing a long resting phase between brief electrical stimulation, PRF does not produce sufficient heat to cause structural damage [20]. Therefore, major complications rarely occur after PRF. Since its introduction, PRF has been widely used for various types of pain, such as neuropathic, joint, discogenic, and muscular pain [21-24] (Fig. 1).

To date, several clinical studies have demonstrated its positive analgesic effect [21-24]. In addition, many researchers have attempted to identify the mechanisms of action of PRF in alleviating pain. Although the exact mechanisms have not been elucidated, several possible mechanisms have been suggested.

This review aimed to outline the pain-reducing mechanisms of PRF by reviewing previous studies on this topic.

**Basic theory of action of pulsed radiofrequency**

CRF supplies high-frequency continuous current to the targeted nerves [16]. The tip of the probe during the CRF procedure is at approximately 80°C and induces coagulative necrosis to target nerve structures around the probe tip [16]. Because the high temperature of a targeted structure decreases rapidly with distance from the electrode tip, lesions caused by the CRF procedure are well-circumscribed [16]. Therefore, other than damage to the targeted area, other tissues are rarely affected. Electrical neurolysis using CRF can inhibit the transfer of pain signals and has been proven to have a pain-reducing effect in various musculoskeletal disorders [25,26]. However, neurolysis can result in various side effects, such as sensory deficits, neuropathic pain, and skin burns [27,28].

In contrast, PRF uses a radiofrequency current comprising alternatively repeated electrical stimulation with a short duration (e.g., 20 ms) and resting phase (e.g., 480 ms) [17-20] (Fig. 2). This allows time for heat elimination and maintains the temperature of the target tissue below 42°C. Temperatures below 42°C rarely induce nerve tissue damage [17-24]. Therefore, adverse effects that can develop after the C-reactive protein procedure do not occur after the PRF procedure. PRF stimulation produces selective long-term depression (LTD) in C-fiber–mediated spinal sensitization [29,30]. LTD reduces the efficacy of neuronal synapses in C-fibers, and consequently, inhibits pain signaling from the peripheral nerve to the central nervous system [29,30]. LTD after PRF stimulation was supposed to be the main pain-reducing mechanism by Sluijter et al. [20], who invented the PRF procedure. Subsequently, several animal studies have been conducted to determine the pain-reducing mechanism of PRF, and these studies demonstrated that several mechanisms other than LTD are associated with pain reduction after the application of PRF (Table 1).

**Fig. 1.** The application of pulsed radiofrequency procedure on the lumbar dorsal root ganglion.

**Fig. 2.** The waveforms of continuous RF (CRF) and pulsed RF (PRF). While CRF is applied continuously without any resting phase, PRF has a long resting phase between brief electrical stimulation. RF, radiofrequency; Voltage, the amplitude of pulsed RF current.
The suggested pain-reducing mechanism of pulsed radiofrequency (PRF) for the treatment of neuropathic pain, as observed in the DRG and spinal dorsal horn, is primarily associated with an increase in proinflammatory cytokines, such as IL-6 and TNF-α, observed in the sciatic nerve and DRG of rats, returned to baseline values. Along with the decreased activation of proinflammatory gene expression, mechanical allodynia in the hind paw was alleviated. In 2019, Jiang et al. [36] applied PRF (pulse width, 20 ms; pulse rate, 2 Hz; duration, 2 minutes) on the ipsilateral L5 DRG or sciatic nerve in 20 rats with chronic constriction injury to the sciatic nerve. Mechanical allodynia and thermal hyperalgesia were relieved by PRF application. In addition, the authors found that IL-1β and TNF-α in the peripheral blood were downregulated. This anti-inflammatory effect of PRF appears to result in a reduction of various types of neuromuscular pain.

### Pain-reducing mechanism of pulsed radiofrequency

1. **Changes at the molecular level**

   1) Decrease of microglial activity
   
   Microglia in the dorsal horn of the spinal cord play an important role in the induction and maintenance of neuroinflammation, resulting in chronic neuropathic pain [31,32]. Activated microglia release various inflammatory cytokines and chemokines that facilitate nociceptive processing at all levels of the neuraxis, including the spinal cord and supraspinal centers. Some previous animal studies have demonstrated the downregulation of microglia in rats with neuropathic pain after the application of PRF [31,32]. In 2013, Cho et al. [31] applied PRF stimulation (voltage, 45 V; pulse rate, 2 Hz; duration, 2 minutes) to the single dorsal root ganglion (DRG) in 23 Sprague-Dawley rats with sciatica due to herniated discs. After PRF application, mechanical withdrawal thresholds significantly increased, which persisted for 40 days. At 41 days after PRF application, microglia in the spinal dorsal horn were found to be deactivated. In 2016, Cho et al. [32] applied caudal epidural PRF (pulse rate, 5 Hz; pulse width, 5 ms; duration, 10 minutes) to 35 Sprague-Dawley rats with sciatica due to herniated discs. At 14 days post-PRF, in the sections of the spinal cord from L3, L4, L5, L6, and S1, microglial activation was attenuated in rats with herniated discs. The deactivation of microglia in the spinal dorsal horn after PRF application seems to prevent the progression from acute pain to chronic pain.

   2) Reduction of proinflammatory cytokines
   
   Inflammation is associated with acute and chronic neuropathic pain. An increase in proinflammatory cytokines, such as various types of interleukin (IL) and tumor necrosis factor-alpha (TNF-α), has been observed in the DRG and spinal dorsal horn in animal models of neuropathic pain [33,34]. In 2013, Vallejo et al. [35] evaluated the effect of PRF (voltage, 45 V; pulse width, 20 ms; duration, 3 minutes) on the ipsilateral L5 DRG in six rats exhibiting sciatic nerve injury. Following PRF therapy, increased proinflammatory gene expression, such as IL-6 and TNF-α, observed in the sciatic nerve and DRG of rats, returned to baseline values. Along with the decreased activation of proinflammatory gene expression, mechanical allodynia in the hind paw was alleviated. In 2019, Jiang et al. [36] applied PRF (pulse width, 20 ms; pulse rate, 2 Hz; duration, 2 minutes) on the ipsilateral L5 DRG or sciatic nerve in 20 rats with chronic constriction injury to the sciatic nerve. Mechanical allodynia and thermal hyperalgesia were relieved by PRF application. In addition, the authors found that IL-1β and TNF-α in the peripheral blood were downregulated. This anti-inflammatory effect of PRF appears to result in a reduction of various types of neuromuscular pain.

3) Increase in the levels of endogenous opioid precursor messenger RNA and the corresponding opioid peptide

In 2012, Moffett et al. [37] investigated the molecular changes after applying PRF using cultured human dermal fibroblasts and human epidermal keratinocytes. After the application of PRF, the levels of endogenous opioid precursor messenger RNA (mRNA; proenkephalin, proopiomelanocortin, and prodynorphin) and corresponding opioid peptides were increased.

This finding suggests that PRF exerts an analgesic effect by increasing endogenous opioid precursor mRNA levels.

2. **Changes in neuronal activity**

   1) Activation of pain-inhibitory mechanism
   
   Previous animal studies have demonstrated that the noradrenergic descending inhibitory pathway plays an important role in analgesic action [38]. In addition, activation of serotonin receptors, such as 5-HT1, 5-HT2, and 5-HT3, induces analgesic effects [39,40]. In 2009, Hagiwara et al. [41] performed an animal study in rats to evaluate the mechanism of PRF action. They induced unilateral hind paw hyperalgesia by injecting 0.15 mL of Freund’s complete adjuvant and applied PRF at 37°C or 42°C for 3 minutes on the sciatic nerves. The pain-reducing effect of PRF was significantly inhibited by intrathecal injection of the alpha2-adrenoceptor antagonist (yohimbine), the selective 5-HT3 serotonin receptor antagonist (MDL72222), and the nonselective serotonin receptor antagonist (methysergid). Based on their results, they suggested that the pain-reducing effect of PRF is correlated with the enhancement of the noradrenergic and serotonergic descending pain inhibitory pathways.
2) Inhibition of the excitatory nociceptive C-fibers

In 2017, Huang et al. [29] conducted experiments in rats with neuropathic pain induced by left L5 spinal nerve ligation. After PRF stimulation (pulse rate, 2 Hz; pulse width, 25 ms; duration, 5 minutes) on the left L5 DRG, the excitation of A- and C-afferent fibers was measured by checking the A- and C-components on the evoked field potential recordings. They found that PRF significantly suppressed the C-component overtime after 30 minutes, and this suppression was sustained for at least 140 minutes after PRF. However, the A component was not significantly suppressed after PRF stimulation. Mechanical allodynia and thermal analgesia significantly reduced after 10 and 14 days, respectively. This result indicates that PRF reduces neuropathic pain by inhibiting or suppressing the excitation of nociceptive C-fibers.

3. Anatomical changes

1) Microscopic damage of the nociceptive nerve

PRF is known to control pain without causing damage to the targeted tissue because the temperature of the targeted tissue does not exceed 42°C during PRF stimulation, and the threshold of tissue destruction is known to range from 45°C to 50°C. However, Erdine et al. [42] reported tissue destruction after PRF stimulation. In 2009, Erdine et al. [42] conducted PRF stimulation (voltage, 45 V; pulse rate, 2 Hz; pulse width, 1 ms) of the sciatic nerve of rats. The temperature was not allowed to exceed 42°C. The authors evaluated microscopic alterations in the nerve tissue using electron microscopy. After the application of PRF, the destruction of membranes, mitochondria, microfilaments, and microtubules was observed in the C-fibers, A-delta, and A-beta fibers. C- and A-delta fibers are nociceptive nerve fibers. The damage to these fibers was attributed to pain reduction after PRF stimulation.

Conclusion

In this review, we discuss previous studies on the mechanism of pain reduction using PRF. LTD of pain signaling from the peripheral nerves to the central nervous system, deactivation of microglia, reduction of proinflammatory cytokines, an increase in the endogenous opioid precursor mRNA, enhancement of descending pain inhibitory pathway, and inhibition and injury of nociceptive nerve fibers were suggested to contribute to pain reduction after PRF. However, the pain-reducing mechanism of PRF has not been clearly and definitely elucidated. Further studies are warranted to clarify the pain-reducing mechanism of PRF.

Notes

Conflicts of interest

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Introduction

Among clinically associated pain conditions, musculoskeletal (MSK) pain is the most frequent [1]. MSK diseases are the most common cause of severe long-term pain and physical disability and have a major impact on the quality of life of patients [2,3]. MSK pain affects hundreds of millions of people around the world [4].

The primary goal of physiatrists is to optimize the pain management of their patients with various MSK conditions, including acute and chronic muscle, tendon, ligament, and cartilage disorders. The traditional management of MSK pain involves control with conservative “Rest, Ice, Compression, Elevation” treatment and physical therapy to corticosteroid injections coupled with specific rehabilitation exercises [5].

Although the traditional management of MSK pain may be helpful for short-term pain reduction and early recovery of function, it does not typically reverse the structural changes associated with degenerative conditions. Recently, the multidisciplinary field of tissue engineering has been expanding to enhance healing and stimulate growth in injuries of soft tissue and bone [6].

Platelet-rich plasma (PRP) is one research area that has developed rapidly in recent years. Historically, hematologists coined the term PRP in the 1970s, and platelets have been used to treat patients with hemorrhage or thrombocytopenia [6,7]. The clinical use of PRP as a cell and tissue engineering therapy has dramatically increased over the last decade [8].

PRP is a biological product defined as the plasma fraction of autologous blood with a platelet concentration above baseline after centrifugation [9]. PRP contains many biologically active factors such as platelet-derived growth factor, transforming growth factor-beta (TGF-β), insulin-like growth factor, vascular endothelial growth factor, and epidermal growth factor [10]. PRP concentrates can promote the supraphysiological release of growth factors.
to enhance healing in chronic injuries, accelerate the acute injury repair process, and reduce MSK pain [11].

**Platelet-rich plasma**

PRP is defined as the plasma fraction of autologous blood with a platelet concentration above baseline after centrifugation [9]. Platelets are irregularly shaped, non-nucleated cytoplasmic bodies derived from fragmentation of megakaryocyte precursors. Platelets are important in blood clot formation, thrombosis and hemostasis, immunity, inflammation, wound healing, hematological malignancies, and metabolic disorders [12].

PRP contains growth factors that promote cellular anabolism and enhance the release of inflammatory mediators and modulators that exert anti-inflammatory and analgesic effects [13]. PRP counteracts the inflammatory cascade [14]. PRP treatment has been shown to induce the release of hepatocyte growth factor (HGF), a major anti-inflammatory factor. Growth factors (HGF, interleukin-4, and tumor necrosis factor-alpha [TNF-α]) reduce the levels of cyclooxygenase (COX)-1, COX-2, and prostaglandin E₂, which are proinflammatory mediators. Additionally, PRP can suppress the production of nuclear factor kappa-light-chain-enhancer of activated B cells, which is highly relevant in soft tissue inflammation [15,16].

PRP promotes tissue regeneration and has gained popularity in recent decades [16]. PRP can induce the production of collagen and growth factors and might increase stem cell numbers, which consequently promotes the healing process by delivering high concentrations of alpha-granules containing biologically active moieties (such as vascular endothelial growth factor and TGF-β) to areas of soft tissue damage [17]. PRP also stimulates cell proliferation and cartilaginous matrix production by chondrocytes and adult mesenchymal stem cells (MSCs). Findings from current clinical trials suggest that PRP has the potential to enhance cartilage repair, attenuate arthritis symptoms, and improve joint function with an acceptable safety profile [13].

**Composition of platelet-rich plasma**

PRP is the plasma from autologous blood after centrifugation and contains a rich concentration of platelets and a variety of growth factors, cytokines, chemokines, and proteins [18]. The key growth factors in PRP are summarized in Table 1. The composition of growth factors promotes tissue repair and regeneration, enhances angiogenesis, and plays a vital role in anti-inflammatory and analgesic effects [19].

**Knee osteoarthritis**

Symptomatic knee osteoarthritis (OA) is a leading cause of disability globally with a significant financial impact [20]. The development of knee OA involves not only the cartilage but also the entire joint, with changes in the articular bone, synovial membrane, joint capsule, ligaments, and musculature around the joint [21].

There is no disease-modifying therapy for the management of OA; therefore, the treatment goals are to improve pain and function. Pharmacotherapy management includes topical and oral non-steroidal anti-inflammatory drugs, duloxetine, and periodic intra-articular glucocorticoid and hyaluronan injections [22].

PRP containing growth factors stimulates local angiogenesis, regulates inflammation, inhibits catabolic enzymes and cytokines, and recruits local stem cells and fibroblasts to the damaged sites. PRP also induces nearby healthy cells to synthesize greater amounts of growth factors and increase endogenous hyaluronan synthesis with few serious side effects [23-26]. In recent years, PRP has emerged as a viable treatment method for the management of knee OA [27]. Eighteen studies (all level 1) involving 811 patients undergoing intra-articular PRP injection (mean age, 57.6 years) and 797 patients undergoing hyaluronic acid injection (mean age, 59.3 years) showed that the mean improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores was significantly higher in the PRP group (44.7%) than in the hyaluronic acid group (12.6%) (p < 0.01) [28].

Many systematic reviews and meta-analyses have found positive results for PRP in relieving pain and improving function in knee OA [27-30]. Therefore, PRP can be expected to improve pain and function in the management of knee OA, although further studies are needed for the definitive assessment of knee OA treatment.

**Ankle joint osteoarthritis**

Ankle OA is rarer than OA of the hip and knee and is more common in young active individuals, with a prevalence of 3.4% in the general adult population [31,32]. The primary etiology of ankle OA is trauma, and the overall risk of developing posttraumatic ankle OA after 20 years is almost 40%. The management of ankle OA involves nonsurgical options (medications, physical therapy, orthotics and insoles, and intra-articular injections) and surgical options (joint-sparing surgery, total ankle arthroplasty, and ankle arthrodesis) [33].

Individuals with ankle OA, hemophilic arthropathy, and rheumatoid arthritis were included in 27 studies (1,085 patients). Most of these studies were observational. A case series found that PRP,
MSC, hyaluronic acid, and corticosteroid injections provided symptomatic relief, although the efficacy of corticosteroid injections was short-term [34].

PRP injections for ankle OA are valid and safe alternatives for postponing the need for surgery [31]. PRP injections are favored for the treatment of pain associated with ankle OA. However, the relative efficacy of PRP injection therapy is far from definitive and warrants further high-quality comparative trials [34].

### Temporomandibular joint osteoarthritis

The prevalence of temporomandibular (TM) joint OA is increasing, and it is more common in women. OA may cause pain in the TM joint area [35,36]. Excessive or prolonged overload of TM joints may lead to adverse remodeling, resulting in OA. The management of TM OA includes conservative treatment (medications, splints, and physiotherapy), intra-articular injections, arthrocentesis, arthroscopy, and open-joint surgery [37].

A comparative randomized study showed that maximum improvements in pain-free mouth opening and reduction in pain severity were observed in all groups (bite splint, betamethasone, sodium hyaluronate, and PRP injections in addition to using the bite splint). In the PRP group, patients with a maximum pain-free mouth opening value of 25.8 mm before treatment improved to 46.8 mm after treatment. The PRP group showed the best results after 6 months [38].

PRP injections may reduce pain and joint sound and improve the range of motion of the TM joint because PRP injections have

### Table 1. Growth factors contained in platelet-rich plasma and their major physiological actions

<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Physiological action</th>
</tr>
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| Transforming growth factor-β | Enhances undifferentiated mesenchymal cell proliferation  
                           Modulates endothelial, fibroblastic, and osteoblastic mitogenesis  
                           Modulates collagen synthesis and collagenase secretion  
                           Modulates mitogenic effects of other growth factors  
                           Enhances endothelial chemotaxis and angiogenesis  
                           Inhibits macrophage and lymphocyte proliferation |
| Fibroblast growth factor     | Enhances growth and differentiation of chondrocytes and osteoblasts  
                           Mitogenic for mesenchymal cells, chondrocytes, and osteoblasts |
| Platelet-derived growth factor A and B | Mitogenic for mesenchymal cells and osteoblasts  
                           Promotes chemotaxis and mitogenesis in fibroblast, glial, or smooth muscle cells  
                           Modulates collagenase secretion and collagen synthesis  
                           Promotes macrophage and neutrophil chemotaxis |
| Epidermal growth factor      | Enhances endothelial chemotaxis or angiogenesis  
                           Modulates collagenase secretion  
                           Enhances epithelial or mesenchymal mitogenesis |
| Vascular endothelial growth factor | Stimulates angiogenesis and vessel permeability  
                           Enhances mitogenesis for endothelial cells |
| Connective tissue growth factor | Stimulates angiogenesis  
                           Cartilage regeneration  
                           Fibrosis and platelet adhesion |
| Insulin-like growth factor 1 and 2 | Chemotactic for fibroblasts and stimulates protein synthesis  
                           Stimulates bone formation |
| Platelet factor 4            | Promotes the initial influx of neutrophils into wounds  
                           Chemoattractant for fibroblasts |
| Interleukin-8                | Proinflammatory mediator  
                           Recruitment of inflammatory cells |
| Keratinocyte growth factor  | Stimulates endothelial cell growth, migration, adhesion, and survival  
                           Angiogenesis |

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anti-inflammatory and analgesic properties. PRP restores intra-articular hyaluronic acid levels, increases chondrocyte glycosaminoglycan synthesis, and balances joint angiogenesis. However, a standardized protocol for PRP preparation and application needs to be established [37-40].

Low back pain

Low back pain (LBP) involves a spectrum of different types of pain (e.g., nociceptive, neuropathic, nociplastic, and nonspecific) that frequently overlap. LBP can be caused by lumbar spine elements (e.g., soft tissue, vertebrae, zygapophyseal and sacroiliac joints, intervertebral discs, and neurovascular structures) [41]. Therapy for LBP usually begins with self-care and medication in combination with non-pharmacological methods, such as physical therapy and psychological treatment, in appropriate patients [42].

Systematic reviews and single-arm meta-analyses showed that PRP may be effective in managing discogenic LBP, radicular pain, facet joint pain, and sacroiliac joint pain. However, the levels of evidence vary [43,44]. Intradiscal PRP injections can be a safe, inexpensive, and feasible treatment to counter the intervertebral disc degeneration associated with LBP. It is important to administer PRP early during the course of treatment to stimulate growth of the remaining cells in the disc [45,46]. PRP injections in the lumbar multifidus muscle can be a safe and inexpensive approach to treating LBP [47]. A small number of prospective trials have described that PRP injection may improve the pain or functional decline caused by facet joint arthropathy for a longer duration [48].

In 2017, a prospective comparative study including 46 patients showed statistically significant pain reduction in both groups (PRP, group A and corticosteroid/local anesthesia, group B). However, for subjective satisfaction based on the modified Mac Nab criteria, the success rate for group B remained at 20% after 6 months, while it increased over time in group A. Therefore, autologous PRP was suggested as a superior treatment option for long-duration efficacy in lumbar facet joint syndrome [49].

Twenty patients completed another prospective clinical trial. The improvements in pain scores (numerical rating scale and Oswestry Disability Index scores) were positively correlated with platelet concentrations in the PRP group [46].

In conclusion, the use of PRP in various injections, such as intradiscal, intrafacet, and intramuscular injections, has yielded significantly reduced pain and improved patient satisfaction, with a significant advantage of no major complications. However, further studies with larger sample sizes and control groups are needed to confirm its efficacy [43,44,48,50].

Myofascial pain syndrome

Myofascial pain is an important cause of disability in the whole population [51]. Emerging symptoms arise from each painful myofascial trigger point, which is a hypersensitive spot within a taut band of skeletal muscle that produces pain on compression, stretch, overload, or contraction of the tissue. The end result is usually pain that is perceived to be distant from the spot of origin. In a randomized controlled trial, there was no statistically significant difference in pain levels between the “lidocaine” and “PRP” groups before and 2 weeks after treatment; however, a statistically significant difference was found between the two groups 4 weeks after treatment ($p < 0.001$). Specifically, 4 weeks after the injection, the average pain of the patients in the lidocaine and PRP groups was 3.4 and 0.9 on the visual analogue scale (VAS), respectively [52].

There are a few studies associated with myofascial pain that were conducted only on the masticatory muscles, which are involved in the most common TM disorders. PRP injections effectively improved trigger-point symptoms in the masseter muscle at 1 and 3 months [52,53].

Lateral epicondylitis

As tendons have poor vascularity, the tissue has limited healing and the lesions are not reversible, resulting in tendinopathies due to trauma or excessive overload. This causes tendon soreness, reduced strength, pain upon exertion, and progressive reduction in function [54].

Lateral epicondylitis, also known as tennis elbow, is a common musculotendinous degenerative disorder of the extensor origin at the lateral humeral epicondyle in adults [55], with a prevalence of 1% to 3% in the general population [56]. The presenting symptoms include lateral elbow pain, pain caused by wrist extension, and weakened grip strength. The diagnosis is always made clinically through medical history and physical examinations [57]. The treatment of lateral epicondylitis includes rest, nonsteroidal anti-inflammatory medication, bracing, physical therapy, extracorporeal shock wave therapy (ESWT), and botulinum toxin injection [58].

Compared with lateral epicondyle surgery, PRP injections provide similar improvements in pain and function in patients suffering from lateral epicondylitis [59]. PRP components promote cell recruitment, proliferation, and angiogenesis. It has also been suggested that PRP induces a transient inflammatory response, resulting in a regenerative response and immunomodulatory effects on tenocytes [60].

A randomized study involving 83 patients was conducted in 2007. The study was composed of two groups: group A, local ste-
roid injection (n = 50) and group B, autologous PRP (n = 33). A significant difference between the two groups (p = 0.0001) was found in pain and function at the end of 6 months. Group B showed a 91% mean improvement (8.33–0.69) in VAS score compared to a 42.2% mean improvement (7.98–4.61) in group A. Regarding function assessment, MAYO Elbow Scores also indicated a favorable outcome in the PRP-treated patients (group B) with a 54.4% mean improvement (61.51–95.0) compared to a 1.25% mean improvement (63.92–63.12) in the steroid-treated patients (group A), a difference that was statistically significant (p = 0.0001) [61].

Many systematic reviews and meta-analyses have found that PRP can be considered a safe and effective treatment option for lateral epicondylitis with clinical improvements in pain and function, although there is a lack of quantification of specific PRP content and considerable heterogeneity among randomized controlled trials exists [62-65].

**Plantar fasciitis**

Plantar fasciitis is a common cause of heel pain and is associated with significant morbidity. It is a debilitating degenerative condition of the plantar fascia resulting from repetitive microtrauma and excessive strain on the plantar surface of the foot [66]. PRP may modulate plantar fascia degeneration because of its regenerative properties [67]. PRP also releases vascular endothelial growth factor, which increases angiogenesis and may facilitate the healing of degenerative conditions by promoting neovascularization and repair [68].

PRP has been suggested as a safe therapeutic option in the treatment of plantar fasciitis, as it reduces pain and improves function in patients with this condition, and its effect persists long term [69-71].

**Patellar tendinopathy (jumper’s knee)**

Patellar tendinopathy (PT) is referred to as “jumper’s knee,” a clinical and chronic overuse condition of unknown pathogenesis and etiology [72]. A large proportion of patients are refractory to conservative treatment, and a variety of new treatments have emerged, including PRP injections [73]. PRP-containing growth factors have been shown to play a role in tendon healing [74,75]. The growth factors in PRP have been observed to play crucial roles in the tissue healing process, collagen production, and tendon cell proliferation [76].

To compare PRP with focused ESWT among athletes with chronic PT, a randomized controlled single-center trial with 12 months of follow-up was performed. During the 12-month follow-up period, the Victorian Institute of Sport Assessment-Patella questionnaire scores for both groups improved significantly from baseline (55.3 for PRP, 56.1 for ESWT), although the PRP group showed greater improvement at 6 months (86.7 vs. 73.7, p = 0.014) and 12 months (91.3 vs. 77.6, p = 0.026). The pain scores during five single-leg squats demonstrated similar trends. At 12 months, a greater proportion of patients in the PRP group rated their response to treatment as good or excellent (PRP, 91.3% vs. ESWT, 60.8%; p = 0.035) [77].

Therefore, PRP plays a potential role in the treatment of PT, leading to a significant decrease in pain and significant improvement in knee function and quality of life over 12 months [78-82].

**Rotator cuff tendinopathy**

More than 50% of all shoulder pain cases are considered to be related to tendinopathies of the rotator cuff (RC), such as tendinosis and incomplete thickness tears of the supraspinatus [81]. In the management of RC tendinopathy, physical rehabilitation, rest, and nonsteroidal anti-inflammatory drugs are considered conventional treatments; however, the best treatment is still inconclusive [83,84].

PRP has been reported to promote the proliferation of two tendon cell types; tenocytes and tendon stem/progenitor cells. Several studies have shown that PRP can induce tenocyte proliferation in vitro [85].

For patients with RC tendinopathy, corticosteroids yield pain reduction and functional improvement in the short term (3–6 weeks), but not in the long term (over 24 weeks). In contrast, PRP may yield better long-term outcomes (more than 24 weeks) [86].

Moreover, the long-term retear rates of RC-related abnormalities were significantly decreased in patients who received PRP [87].

Many systematic reviews and meta-analyses have found that the currently available clinical evidence on PRP injections supports a beneficial effect on pain reduction and functional outcomes in RC tendinopathy [88-91].

**Adhesive capsulitis**

Adhesive capsulitis (AC) of the shoulder is a common clinical condition characterized by insidious and progressive pain resulting in loss of glenohumeral joint function [92]. However, the etiology of AC remains unclear. It has been postulated that the motion limitations of the shoulder joint are due to an imbalance between fibrosis and loss of normal collagenous remodeling after an inflammatory
healing response [93].

PRP can exert an anti-inflammatory effect at the inflammation site by releasing TNF-α, HGF, and lipoxin A4, which are potent anti-inflammatory agents [94,95].

At the 12-week follow-up in another study, a single injection of PRP was found to be more effective than corticosteroid injection in improving pain, disability, and shoulder range of movement in patients with AC [96].

PRP injections have been found to be effective in reducing pain and improving shoulder joint function due to AC [93,96,97]. These findings suggest that PRP is a therapeutic option for the management of AC.

**Adverse effects**

The most common adverse effect was mild pain and discomfort at the injection site after PRP injection [98]. Some authors have reported that PRP injections are more painful than saline injections. However, no serious adverse effects were observed [99].

**Limitations**

Although good clinical outcomes and safety profiles can be achieved with the use of PRP, there are discrepancies in the existing literature. Several variables must be considered when using PRP. However, these variables were not described herein. PRP preparation methods, types of activators, types of pathology to be treated, routes and times of administration, and the association of PRP with other treatments can influence outcomes. Although several research articles have been published on PRP, this field still requires more scrutiny because of the inconsistent results of different studies, and a definite direction remains elusive.

**Conclusion**

This review article presents available evidence supporting the clinical efficacy of PRP in patients with MSK pain, with fewer side effects. PRP leads to reductions in pain and improvements in patient’s function; however, evidence to clarify the discrepancies in PRP therapy is still needed.

**Notes**

**Conflicts of interest**

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A comparative study of the psychological impacts of tasks related and unrelated to COVID-19 on nurses: a cross-sectional study

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**Background:** This study assessed the psychological impact of the outbreak of coronavirus disease 2019 (COVID–19) on university hospital nurses. It provides an assessment of mental health issues, including depression, anxiety, distress, and burnout of nurses dealing directly and indirectly with COVID–19.

**Methods:** In a web-based, cross-sectional study, 111 nurses from Daegu Catholic University Hospital in Korea were enrolled from August 4 to August 9, 2020. Patient Health Questionnaire–9, Generalized Anxiety Disorder–7, Impact of Event Scale–Revised, and Maslach Burnout Inventory were used to assess the psychological symptoms of depression, anxiety, psychological distress, and burnout among the study participants.

**Results:** Of 111 nurses, 35 (31.5%), nine (8.1%), 26 (23.4%), and 49 (44.1%) experienced depression, anxiety, distress, and burnout, respectively. Nurses who performed COVID–19–related tasks were more likely to have moderate depression (related vs. unrelated, 52.0% vs. 25.6%; \(p = 0.037\)). There were no differences in anxiety, distress, and burnout between nurses with and without COVID–19–related tasks. More than 50% of the participants showed receptive and positive attitudes toward caring for COVID–19 patients.

**Conclusion:** Nurses who performed COVID–19–related tasks had a higher risk of depression. There were no significant differences in anxiety, distress, and burnout between the two groups. Since nurses who perform COVID–19–related tasks are more prone to psychological distress, continued psychiatric interventions are required for infectious disease outbreaks with a high mortality rate for healthcare workers who are emotionally vulnerable.

**Keywords:** Anxiety; COVID–19; Depression; Distress; Psychological burnout

**Introduction**

In December 2019, a coronavirus disease 2019 (COVID–19) outbreak occurred in Wuhan (Hubei, China) [1]. In early 2020, COVID–19 began to spread rapidly on a global scale. On March 11, 2020, the World Health Organization (WHO) officially declared COVID–19 a pandemic [2]. This rapid and unprecedented pandemic has led to significant mental health problems such as depression and anxiety among healthcare workers (HCWs) and the general population [3,4].

The WHO identified HCWs as a group particularly at risk of developing a wide range of physical and mental problems as a result of working directly or indirectly with COVID–19 patients [5]. HCWs are at the forefront of the fight against infectious diseases and in providing patient care. HCWs are exposed to severe stress, high emotional load, long working hours, the risk of being infected...
or infecting their families, inadequate support in the work environment, and the lack of effective supportive treatments, all of which affect their mental health [6,7]. HCWs may experience a variety of symptoms, including anxiety, stress, fear, and insomnia [8]. Representing almost half of the global healthcare workforce, nurses are at the forefront of providing care and services across the health spectrum [9]. Thus, their mental health is most likely to be affected. For example, a study revealed that during the peak of the 2003 severe acute respiratory syndrome (SARS) outbreak in Taiwan, nurses treating patients suffered from extreme stress, among other psychological problems [10]. Burnout was reported to be especially high among nurses who worked long hours with the Middle East respiratory syndrome (MERS) patients [11]. A meta-analysis demonstrated that young HCWs who were nurses and women during the SARS/MERS/COVID-19 epidemics/pandemics were particularly vulnerable to SARS/MERS/COVID-19–related psychological distress, including anxiety, depression, and exhaustion [4].

South Korea has been in a state of emergency since February 23, 2020 owing to the COVID-19 crisis. In the Daegu and Gyeongbuk province, a region located in South Korea, the number of people infected with COVID-19 has increased dramatically since the 31st case was confirmed. Approximately 5,300 additional cases were confirmed within 15 days, representing approximately 70% of the total number of confirmed cases. Daegu became the epicenter of the outbreak in South Korea [12]. Innumerable medical workers and resources have been devoted to the efforts to treat COVID-19. To control the spread of COVID-19, the authorities of Daegu carried out various administrative regulations. All citizens in Daegu were asked to self-quarantine and maintain social distancing. South Korea began implementing quarantine measures along with social distancing, especially considering the number of confirmed cases in Daegu since March 22, 2020. As the sporadic cases persisted, the Ministry of Health and Welfare categorized social distancing into three stages, with Stage 1 being the least intense and Stage 3 being the most stringent. Stage 3 had to be implemented on June 28, 2020, and schools and companies were urged to close. Since the explosive outbreak, Daegu has maintained a low level of social distancing in daily life.

Due to the ongoing COVID-19 pandemic, HCWs are constantly exposed to the risk of infection, and they need to maintain strict social distancing for several weeks or months. There are numerous studies on the psychological impact of the COVID-19 outbreak on frontline HCWs, particularly nurses. However, few studies have compared the impact of such outbreaks on those who perform tasks directly related to the outbreak versus those who do not. This has left gaps in the existing literature in terms of understanding the different mental health outcomes of different groups of people during such crises. The present study provides an assessment of the mental health burden of nurses working directly and indirectly with COVID-19 patients.

### Methods

**Ethical statements:** The Institutional Review Board of Daegu Catholic University Hospital (IRB No: CR-20-109) reviewed and approved this study. Informed consent was obtained from all respondents.

#### 1. Study design and participants

The study was conducted with medical nurses working at Daegu Catholic University Hospital in Korea during the COVID-19 outbreak. Since the outbreak of COVID-19, the hospital has been in charge of the diagnosis and treatment of COVID-19 (March 1 to May 6, 2020). The survey was conducted from August 4 to August 9, 2020, and data were collected through an online questionnaire distributed to HCWs via a mobile text message. Of the 1,387 HCWs, 500 were selected using a random extraction method, of which 133 responded to the questionnaire. Only one response was permitted per person. Questionnaires with missing information were excluded from the study. Accordingly, 111 participants were enrolled in the study.

#### 2. Measurements

The questionnaire was designed to identify factors that could affect the mental health of nurses. Demographic factors included age, sex, and medical history. COVID-19–related variables included quarantine experience, confirmed COVID-19 cases among family members, and exposure to COVID-19–related tasks. COVID-19–related tasks included working in the isolation ward or screening center and working directly with patients who were positive for COVID-19 or those having a high chance of being infected. Tasks not related to COVID-19 included working in a general ward (non-COVID-19), entrance visitor screening, and working in outpatient departments. These non-COVID-19–related tasks pertain to other consequences of the pandemic and do not involve coming face-to-face with infected patients.

1) Perception of COVID-19 threat

Participants were asked about their perceived threat of COVID-19. The items were adapted from those used in a previous study assessing the psychological impact of SARS on hospital employees [10], including perceived job risk, perceived stigma, perceived job stress, fear of infection, little control, worry about transmis-
sion, concern for others, and thought of the possibility of death. The survey consisted of 10 questions rated on a 5-point Likert-type scale ranging from 1 to 5 (1, strongly disagree; 5, strongly agree).

2) Measurement of depression and anxiety symptoms
Patient Health Questionnaire-9 (PHQ-9) is a 9-item self-administered instrument, used to measure depression symptoms [13,14]. Items are rated on a 4-point Likert-type scale ranging from 0 (not at all) to 3 (nearly every day). The total scores range from 0 to 27 (cutoff value ≥ 10). Generalized Anxiety Disorder-7 (GAD-7) is a tool for assessing the presence of anxiety [15-17]. Items are rated on a 4-point Likert-type scale ranging from 0 (not at all) to 3 (nearly every day). The total scores range from 0 to 21 (cutoff value ≥ 10). Cronbach’s alpha in the current study was 0.882 and 0.859 for PHQ-9 and GAD-7, respectively.

3) Impact of Event Scale-Revised
The Korean version of Impact of Event Scale-Revised (IES-R) has been used to assess psychological distress among the general population, workers, and psychiatric patients [18]. The IES-R is a 22-item, 6-point scale (0, not at all; 1, a little bit; 2, moderate; 3, quite a bit; and 4, extreme), with a Cronbach’s alpha of 0.967. The total score ranges from 0 to 88. A total score of ≥ 25 in the Korean version of the IES-R is indicative of posttraumatic stress disorder (PTSD), whereas a score of ≥ 18 indicates the presence of PTSD-like symptoms [19].

4) Maslach Burnout Inventory-General Survey
Burnout measurement was performed using the Korean version of the Maslach Burnout Inventory-General Survey (MBI-GS) developed by Maslach and Jackson [20]. The validity of the Korean version of the MBI-GS was verified by Shin [21]. Overall burnout was defined as a high score in either the emotional exhaustion or depersonalization subscale (cutoff scores: > 13 for emotional exhaustion, > 8 for depersonalization, and < 18 for personal accomplishment) [22]. Cronbach’s alpha for the current study was 0.784.

3. Statistical analysis
Pearson chi-square test or Fisher exact test was used to determine whether there was a significant difference in basic characteristics, perception of threat, and severity ratings of PHQ-9, GAD-7, IES-R, and MBI-GS between the groups depending on the assignment of COVID-19–related tasks. Statistical analysis was performed using PASW Statistics ver. 18.0 for Windows (IBM Corp., Armonk, NY, USA), and the level of significance was set at 0.05.

Results
1. Demographic characteristics
Of the 500 surveys transmitted, 111 responses (22.2%) were received. The basic characteristics of the respondents according to their participation in COVID-19 treatments are shown in Table 1. Twenty-five respondents (22.5%) performed COVID-19–related tasks. Most respondents in both groups were women in their 20s. Only 28.8% of the participants had educational training for infectious diseases. The group with participants who performed COVID-19–related tasks had more quarantine experience during the COVID-19 outbreak (related vs. unrelated, 20% vs. 5.8%; p = 0.044). Most respondents did not have family members who were infected nor did they have comorbidities.

2. Perception of COVID-19 threat
Regarding perceived threat, most respondents felt that their jobs were risky. There was no significant difference between the two groups. Over half of the respondents reported that “My job puts me at a great risk,” “I feel more stress at work,” “I accept the risk of caring for COVID-19 patients,” “I am afraid of falling ill with COVID-19,” or “I am afraid I will pass COVID-19 to others.” The items “I accept the risk of caring for COVID-19 patients,” “I feel more stress at work,” and “I am afraid I will pass COVID-19 to others” showed high proportions in all groups. However, the items “People avoid my family because of my work,” “I have little control over whether I get infected or not,” “I think of resigning because of COVID-19,” and “I have little chance of survival if I were to get COVID-19” showed low proportions in all groups (Table 2).

3. Comparison of depression, anxiety, distress, and burnout among nurses
Table 3 shows the distribution of scores within the PHQ-9, GAD-7, IES-R, and MBI-GS severity cutoffs. The prevalence of mild depression in the COVID-19–related task group was significantly lower than that in the unrelated task group (16.0% vs. 32.6%, p = 0.037). However, the prevalence of moderate to severe depression was significantly higher in the related task group (52.0% vs. 25.6%, p = 0.037). All respondents had a GAD-7 score of ≥ 5. Based on a cutoff value of 10, the prevalence of moderate to severe anxiety was 12.0% and 7% in each group, respectively. However, there were no statistically significant differences between the two groups. Twenty-six respondents (23.4%) screened positive for PTSD, 13 (11.7%) for PTSD-like symptoms, 41 (36.9%) for emotional exhaustion, 33 (29.7%) for depersonalization, 40 (36.0%) for low personal accomplishment, and 49 (44.1%) for burnout.
Table 1. Basic characteristics of respondents according to participation in COVID–19 treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 111)</th>
<th>Related group (n = 25)</th>
<th>Unrelated group (n = 86)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>111 (100)</td>
<td>25 (22.5)</td>
<td>86 (77.5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.615</td>
</tr>
<tr>
<td>Male</td>
<td>6 (5.4)</td>
<td>2 (8.0)</td>
<td>4 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>105 (94.6)</td>
<td>23 (92.0)</td>
<td>82 (95.3)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td>0.073</td>
</tr>
<tr>
<td>20s</td>
<td>60 (54.1)</td>
<td>18 (72.0)</td>
<td>42 (48.8)</td>
<td></td>
</tr>
<tr>
<td>30s</td>
<td>32 (28.8)</td>
<td>2 (8.0)</td>
<td>30 (34.9)</td>
<td></td>
</tr>
<tr>
<td>40s</td>
<td>12 (10.8)</td>
<td>3 (12.0)</td>
<td>9 (10.5)</td>
<td></td>
</tr>
<tr>
<td>50s</td>
<td>7 (6.3)</td>
<td>2 (8.0)</td>
<td>5 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Educational training for infectious diseases</td>
<td></td>
<td></td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (28.8)</td>
<td>11 (44.0)</td>
<td>21 (24.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>79 (71.2)</td>
<td>14 (56.0)</td>
<td>65 (75.6)</td>
<td></td>
</tr>
<tr>
<td>Quarantine experience</td>
<td></td>
<td></td>
<td></td>
<td>0.044</td>
</tr>
<tr>
<td>Yes</td>
<td>10 (9.0)</td>
<td>5 (20.0)</td>
<td>5 (5.8)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>101 (91.0)</td>
<td>20 (80.0)</td>
<td>81 (94.2)</td>
<td></td>
</tr>
<tr>
<td>Family member with confirmed COVID–19</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (3.6)</td>
<td>1 (4.0)</td>
<td>3 (3.5)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>107 (96.4)</td>
<td>24 (96.0)</td>
<td>83 (96.5)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td>0.681</td>
</tr>
<tr>
<td>None</td>
<td>102 (91.9)</td>
<td>24 (96.0)</td>
<td>78 (90.7)</td>
<td></td>
</tr>
<tr>
<td>Chronic disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (8.1)</td>
<td>1 (4.0)</td>
<td>8 (9.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
<sup>a</sup>Chronic diseases include hypertension, diabetes, cancer, psychiatric disease, and other conditions.

Table 2. Comparison of the perception of threat<sup>b</sup> of COVID–19 between the two groups

<table>
<thead>
<tr>
<th>Item&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Total (n = 111)</th>
<th>Related group (n = 25)</th>
<th>Unrelated group (n = 86)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My job puts me at a great risk</td>
<td>78 (70.3)</td>
<td>17 (68.0)</td>
<td>61 (70.9)</td>
<td>0.778</td>
</tr>
<tr>
<td>2. I feel more stress at work</td>
<td>78 (70.3)</td>
<td>21 (84.0)</td>
<td>57 (66.3)</td>
<td>0.135</td>
</tr>
<tr>
<td>3. I accept the risk of caring for COVID–19 patients</td>
<td>72 (64.9)</td>
<td>20 (80.0)</td>
<td>52 (60.5)</td>
<td>0.096</td>
</tr>
<tr>
<td>4. I am afraid of falling ill with COVID–19</td>
<td>67 (60.4)</td>
<td>15 (60.0)</td>
<td>52 (60.5)</td>
<td>0.967</td>
</tr>
<tr>
<td>5. I have little control over whether I get infected or not</td>
<td>26 (23.4)</td>
<td>5 (20.0)</td>
<td>21 (24.4)</td>
<td>0.791</td>
</tr>
<tr>
<td>6. I have little chance of survival if I were to get COVID–19</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>7. I think of resigning because of COVID–19</td>
<td>3 (2.7)</td>
<td>2 (8.0)</td>
<td>1 (1.2)</td>
<td>0.127</td>
</tr>
<tr>
<td>8. I am afraid I will pass COVID–19 to others</td>
<td>68 (61.3)</td>
<td>16 (64.0)</td>
<td>52 (60.5)</td>
<td>0.749</td>
</tr>
<tr>
<td>9. My family and friends are worried they might get infected through me</td>
<td>55 (49.5)</td>
<td>13 (52.0)</td>
<td>42 (48.8)</td>
<td>0.781</td>
</tr>
<tr>
<td>10. People avoid my family because of my work</td>
<td>15 (13.5)</td>
<td>3 (12.0)</td>
<td>12 (14.0)</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
<sup>b</sup>Sum of “agree” and “strongly agree.”
<sup>a</sup>Modified from Chong et al. [10].

There was no significant difference between the two groups in terms of distress and burnout.

**Discussion**

The main outcome of this study indicates that after the COVID-19 outbreak, those who performed COVID-19–related tasks were more likely to have moderate depression. There were no significant differences between the GAD-7, IES-R, and MBI distributions.

In the existing meta-analysis on the psychological impact of COVID-19 on HCWs from 13 studies, the prevalence of depression was 22.8% [23]. The prevalence of depression and anxiety in the current study was 31.5% and 9%, respectively, and nurses involved in COVID-19–related tasks showed a higher prevalence of depression than those who were not involved. Most respondents

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had mild anxiety (91.9%). This outcome was similar to that of earlier studies, which found that HCW jobs involving close contact with COVID-19 patients can be risk factors for depression and anxiety. Exposure to unspecified patients has also been associated with depression and anxiety [24]. There are some concerns that GAD-7 may not be sensitive to measuring reactive anxiety after stress. However, GAD-7 has the advantage of effectively discriminating anxiety disorders in a short period of time and has been widely used in epidemiologic studies [25].

The prevalence of PTSD-like symptoms, PTSD, and burnout among respondents was 11.7%, 23.4%, and 44.1%, respectively. There were no statistically significant differences between the two groups. Previous studies on the impact of COVID-19 on the mental health of HCWs have indicated that frontline HCWs who provide direct care to COVID-19 patients are at a higher risk of distress and burnout [26,27]. Women, nurses, and young people have greater psychological distress than men and physicians, as the former are thought to be more vulnerable to stress [24,28]. Considering reasons the results differ from those of previous studies, the participants’ receptive attitude toward the disease and educational training on infectious diseases may have acted as protective factors. In the case of the COVID-19–related task group, a significant proportion of the responses agreed with the item, “I accept the risk of caring for COVID-19 patients” and disagreed with the items, “I have little control over whether I get infected or not” and “I think of resigning because of COVID-19,” indicating that they are receptive and positive toward taking care of COVID-19 patients. Since the COVID-19–related task group was mainly engaged with high-risk infectious disease and received infectious disease education, as opposed to the other group, the effect on mental health may have been offset.

Furthermore, considering that this study was conducted during Stage 1 of social distancing norms, psychological adaptation may have occurred over time. In the Daegu-Gyeongbuk region, minor local infections have continued since the explosive spread in February 2020 [29]. Regarding SARS, a study on 1,257 HCWs reported differences in mental health across the two phases of the outbreak. In the initial phase, when the disease spread rapidly, 81% of the participants experienced anxiety. During the repair phase, when the infection was brought under control, 77% experienced anxiety. The decreasing anxiety was thought to be the result of the virus being under control and the increasing recognition that the disease was preventable [30]. A Chinese study on frontline nurses supplying care to patients with COVID-19 also recorded psychological changes over time; psychological adaptation was observed during the later stage. This might be mainly due to the familiarity of the nurses with the work environment and processes, the mutual support of team members, monetary incentives, social support, and recognition from the government and public. They felt that what they were
doing was important and valuable to the health of the people and the nation. Their energy was renewed by rediscovering the original purpose of their dedication to care, reevaluating the nursing profession, taking pride in their contributions, and having an upgraded sense of personal accomplishment [31].

This study has some limitations. First, the sample size was small and may not be representative of the psychological states of all nurses. In addition, differences in mental status according to the tenure of the nurse or the type of work were not included in the study. Further investigations with a larger sample size and detailed classification are needed. Second, the study design did not include an analysis of the causes of psychological strains, such as work-related stress. Further studies on the various factors that may affect the psychological status of nurses are needed. Third, this study was cross-sectional, so it was unable to distinguish pre-existing mental health symptoms from new symptoms. Considering the long duration of COVID-19, the psychological status of nurses can change over time. It would be ideal to reinvestigate the mental health of nurses after a period of time, including long periods of depression, anxiety, stress, and burnout. It is important to highlight the importance of designing interventions that target female nurses who work directly with infectious diseases, as they may experience higher psychological burdens.

The COVID-19 pandemic had negative psychological implications for nurses who performed COVID-19–related tasks. They showed a higher risk of depression, but anxiety, distress, and burnout were not significantly different between the two groups. Continued psychiatric interventions of emotionally vulnerable groups among HCWs are required for infectious disease outbreaks.

Notes

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

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Author contributions
Conceptualization, Formal analysis: HJK, GHL; Data curation, Methodology, Visualization, Investigation, Resources, Software: HJK; Funding acquisition, Supervision, Validation, Writing-original draft: HJK; Writing-review & editing: GHL.

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References

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Infection prevention measures and outcomes for surgical patients during a COVID-19 outbreak in a tertiary hospital in Daegu, South Korea: a retrospective observational study

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Background: The first large coronavirus disease 2019 (COVID–19) outbreak outside China occurred in Daegu. In response, we developed infection prevention measures for surgical patients during the outbreak at our hospital and retrospectively reviewed the outcomes of COVID–19–related surgical patients.

Methods: We reviewed the medical records of 118 COVID–19–related surgical patients and monitored their clinical outcomes until March 31, 2021. We also interviewed healthcare workers who participated in their perioperative care at Kyungpook National University Chilgok Hospital. The perioperative management guidelines for COVID–19–related patients were prepared through multidisciplinary discussions, including the infection control department, surgical departments, and anesthesiology department before and during the COVID–19 outbreak.

Results: One standard operating room was temporarily converted to a negative-pressure room by increasing the exhaust air volume, creating a relative pressure of −11.3 Pa. The healthcare workers were equipped with personal protective equipment according to the patient's classification of the risk of COVID–19 transmission. The 118 COVID–19–related patients underwent emergent surgery in the negative–pressure room, including three COVID–19–confirmed patients and five COVID–19–exposed patients.

Conclusion: All surgeries of the COVID–19–related patients were performed without specific adverse events or perioperative COVID–19 transmission. Our experience setting up a negative–pressure operating room and conservative perioperative protocol to prevent COVID–19 transmission will help plan and execute infection control measures in the future.

Keywords: COVID–19; Infection; Prevention; Surgery

Introduction

The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in South Korea was confirmed on January 20, 2020, and the first case in Daegu was confirmed on February 18, 2020. The famous 31st case in South Korea was a 61-year-
old woman who lived in Daegu and infected more than 1,100 people [1]. After the first confirmed SARS-CoV-2 infection case in Daegu, the cases of laboratory-confirmed SARS-CoV-2 infection increased rapidly to a maximum of 741 patients per day [2]. Daegu became the first city with a large-scale coronavirus disease 2019 (COVID-19) outbreak outside China. During the COVID-19 outbreak in Daegu, 11,037 cases were confirmed, and 222 patients died [2].

Few hospitals in Daegu were prepared to provide perioperative care for COVID-19–related patients before the COVID-19 outbreak. However, perioperative infection control in COVID-19–related patients is crucial in preventing nosocomial infections and maintaining essential hospital services during the COVID-19 outbreak. Therefore, we developed and applied COVID-19 infection control protocols for surgical patients. This study describes our experience delivering perioperative infection prevention and control measures for COVID-19–related surgical patients and retrospectively reviews their clinical outcomes.

Methods

Ethical statements: The study was approved by the Institutional Review Board (IRB) of the Kyungpook National University Chilgok Hospital (IRB No. 2020-04-038). The IRB waived patient consent because of the retrospective nature of the study. Patient confidentiality was maintained throughout the study.

This study was based on Kyungpook National University Chilgok Hospital records and interviews with frontline healthcare workers (HCWs) involved in providing care during the outbreak. A nasopharyngeal swab or sputum sample was collected for SARS-CoV-2 quantitative reverse transcription-polymerase chain reaction (RT-PCR) from the patients involved. SARS-CoV-2 RT-PCR was performed using the PowerChek 2019-nCoV Real-Time PCR kit (Kogene Biotech, Seoul, Korea) and CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA).

The perioperative management guidelines for COVID-19–related patients were prepared through multidisciplinary discussions, including the infection control department, surgical departments, and anesthesiology department before and during the COVID-19 outbreak. The electronic medical records of the COVID-19–related patients who underwent surgery were reviewed, and the clinical outcomes of the patients were monitored up to March 31, 2021, when all the patients had been discharged. We also reviewed the records on remodeling of the positive-pressure operating room (OR) to create the negative-pressure OR.

Results

1. Development of COVID-19 infection control protocols for surgical patients

Before and during the COVID-19 outbreak in Daegu, we developed COVID-19 infection control measures for surgical patients, modified from the infection control protocols for severe acute respiratory syndrome [3] and perioperative considerations for COVID-19 developed by the Anesthesia Patients Safety Foundation [4].

The strategy for perioperative COVID-19 infection control targeted three key areas: (1) classification of patients based on the risk of COVID-19 transmission, (2) protection of HCWs, and (3) reorganization of the OR.

1) Classification of surgical patients based on risk of COVID-19 transmission

We tested all surgical patients before surgery using SARS-CoV-2 RT-PCR to identify asymptomatic COVID-19 carriers. All surgical patients wore face masks (dental or KF-94, masks able to filter at least 94% of airborne particles) to prevent SARS-CoV-2 transmission. Elective surgeries for COVID-19–confirmed patients were delayed as much as possible. For COVID-19–exposed patients, the surgeries were delayed until after the 14-day incubation period [5]. For emergent surgeries, we classified the surgical patients into four groups: (1) patients who had a negative SARS-CoV-2 RT-PCR test without suspected symptoms (fever, fatigue, dry cough, dyspnea, or pulmonary consolidations on chest computed tomography [CT]) and who did not have a contact history with COVID-19 patients (surgeries were performed in a common OR for this group of patients); (2) patients who had not received their SARS-CoV-2 RT-PCR results before entering the OR or had ambiguous test results, but did not have suspected symptoms or contact history with COVID-19 patients; (3) patients who had suspected symptoms or were exposed to someone with COVID-19, but had negative test results or did not have their SARS-CoV-2 RT-PCR test results before entering the OR; and (4) patients who had a positive SARS-CoV-2 RT-PCR test (Table 1). We classified the last three groups as COVID-19–related surgical patients.

2) Healthcare worker protection

Temperature monitoring was mandatory for all HCWs in the hospital. HCWs with a temperature above 37.5°C, respiratory symptoms, or possible contact history with a confirmed COVID-19 pa-
tient without wearing personal protective equipment (PPE) were removed from duty and sent for SARS-CoV-2 RT-qPCR testing. In addition, all contact histories between HCWs and COVID-19–related patients were recorded within the OR complex.

PPE was introduced for all HCWs who usually had contact with patients in the hospital. Basic PPE, which consisted of a KF94 mask (mask able to filter at least 94% of airborne particles), eye protection goggles, and latex gloves, was provided to all HCWs in the OR. Standard PPE, which comprised an N95 respirator, surgical cap, eye protection (goggles or face shield), apron gown, and gloves, was provided to HCWs who cared for SARS-CoV-2-negative patients or patients who did not have confirmed test results with COVID-19–related symptoms. Enhanced PPE, which consisted of overall clothes with a headcover, shoe covers, goggles, surgical gloves, and a powered air-purifying respirator (PAPR), was provided to HCWs who managed SARS-CoV-2-confirmed patients, or SARS-CoV-2-exposed patients.

3) Reorganization of the operating room
We reduced elective surgeries to half capacity to limit traffic in the OR during the first 2 months after the outbreak. Surgical procedures for confirmed COVID-19 patients in the intensive care unit (ICU) were performed at the bedside, where possible. We operated on COVID-19–related surgical patients in the designated COVID-19 OR, which had been converted to a negative-pressure OR. When possible, surgeries for confirmed COVID-19 patients and SARS-CoV-2-exposed patients were performed in the last order of the day to minimize contact with other HCWs in the OR complex. These patients were transferred directly to the COVID-19 OR via dedicated paths and an elevator using a portable patient isolation unit with negative pressure (Fig. 1).

After the COVID-19–related patients entered the COVID-19 OR, anesthesiologists induced anesthesia with endotracheal intubation using the rapid sequence technique. Thirty minutes of ventilation on room air was allowed after endotracheal extubation. The patients recovered from anesthesia in the COVID-19 OR.

Table 1. Application of PPE for health care workers, according to the classification of COVID–19–related patients

<table>
<thead>
<tr>
<th>PPE composition</th>
<th>SARS-CoV–2 RT-qPCR</th>
<th>Contact history with COVID–19 patients</th>
<th>COVID–19–related symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic: goggles, KF94 mask, nitrile gloves</td>
<td>Negative or unknown</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Standard: surgical gloves, apron gowns, goggles, N95 respirator</td>
<td>Negative or unknown</td>
<td>None</td>
<td>Fever, dry cough, pneumonic consolidation on chest CT</td>
</tr>
<tr>
<td>Enhanced: two pairs of surgical gloves, overall clothes with headcover, shoe covers, goggles, PAPR</td>
<td>Negative or unknown</td>
<td>Possibly or direct</td>
<td>Any of the above</td>
</tr>
</tbody>
</table>

PPE, personal protective equipment; COVID–19, coronavirus disease 2019; SARS-CoV–2 RT-qPCR, severe acute respiratory syndrome coronavirus 2 quantitative reverse transcription–polymerase chain reaction; PAPR, powered air-purifying respirator; CT, computed tomography.

Fig. 1. (A) Transfer route for coronavirus disease 2019 (COVID–19)–related patients. The red arrows show all pathways that were closed during COVID–19–related patient transfer. (B) Patient transfer using a portable isolation unit. All healthcare workers wore enhanced personal protective equipment, including overall clothes with headcover, shoe cover, goggles, surgical gloves, and powered air-purifying respirator. OR, operating room; ICU, intensive care unit.
OR without using the post-anesthesia care unit. After the patients had fully recovered, they were sent back to the ward or ICU using a portable patient isolation unit in negative-pressure mode.

2. Setting up the negative-pressure operating room
Our hospital has 13 ORs in the main operating complex, which is a positive-pressure environment. The rooms allowed 30 air changes per hour and were managed as class 100,000 cleanrooms (less than 100,000 particles/m³). Therefore, we needed to establish a negative-pressure OR to minimize the flow of contaminated air spreading outside the OR [6]. We selected OR number 4 as the COVID-19 OR in the main operating complex because it was easy to access from outside the operating complex and had a transparent glass window.

Outside air was supplied from an inlet duct, and the air in the OR was discharged using a constant air volume unit through the outlet duct. We added a new exhaust duct with a new constant air volume unit to achieve negative pressure (Fig. 2). After this modification, the outflow air volume of OR 4 changed from 450 cubic meters per hour (CMH) to 3,380 CMH, and the room pressure was maintained at −11.3 Pa when the door was closed (below the negative-pressure room standard of −2.5 Pa [7]). Thus, during operation of the negative-pressure OR, exhaust to the clean corridor was limited.

3. Room preparation before and after surgery
Computers, telephones, monitors, and ventilators were draped with plastic film. Anesthetic drugs, fluids, and equipment needed to perform the surgery were prepared before patient arrival. Additionally, we used disposable equipment such as a laryngoscope, surgical drape, and anesthetic circuit. We installed three high-efficiency particulate air (HEPA) filters in the anesthetic circuit (the anesthesia machine’s inspiratory and expiratory limbs and the patient’s side that connects to the endotracheal tube). HCWs in the COVID-19 OR wore dedicated PPE before the COVID-19–related patient entered the OR. After the patient was removed, the room was ventilated for 30 minutes. Subsequently, the HCWs removed and disposed of their PPE in the COVID-19 OR. Surface disinfection was performed using 0.1% sodium hypochlorite. For SARS-CoV-2-confirmed cases, surface disinfection was performed twice.

4. Surgeries for COVID-19–related patients
Between February 22, 2020 and March 31, 2021, 118 COVID-19–related patients underwent emergency surgery. All patients under-

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**Fig. 2.** Ventilation system of the temporary, negative-pressure operating room. V.D., volume damper; CMH, cubic meter per hour; HEPA, high-efficiency particulate air.
went SARS-CoV-2 quantitative RT-PCR testing before surgery. A total of 102 patients who were unable to wait for the test results due to emergency surgery were included in the COVID-19–related patient group. Eight patients were negative on the preoperative test but had a COVID-19–related symptom. Six patients had fevers. Two patients had pneumonia consolidation on the preoperative CT scan. Four patients had a history of direct exposure. Two patients had a prior positive COVID-19 test but were negative at the time of surgery. Two patients were confirmed to be positive for COVID-19 upon preoperative examination.

One patient, who was negative based on the preoperative SARS-CoV-2 quantitative RT-PCR result using a nasopharyngeal swab sample, tested positive postoperatively with a sputum sample. The patient had a history of direct exposure to COVID-19 and pneumonia consolidation on preoperative chest CT. Hence, we performed surgery with enhanced PPE. The types of surgeries that the patients underwent are shown in Table 2.

All surgeries for the COVID-19–related patients were uneventful, and perioperative COVID-19 transmission was not reported during this period. We performed 75 cases of general anesthesia and 43 cases of regional anesthesia.

Discussion

SARS-CoV-2 is highly contagious and spreads rapidly. In Hubei province, China, the estimated reproduction number (R) was 4.02, but the R in Daegu, Korea was between 3.472 and 3.543 [8]. An increase in COVID-19 patients in Daegu, Korea was mainly a result of exposure among members of the Shincheonji Church of Jesus and hospital transmission [1].

The COVID-19 outbreak has underscored the importance of preventing nosocomial transmission [9]. HCWs need to be wary of COVID-19 nosocomial transmission, and hospitals should establish and maintain infection control and prevention protocols. We provided a facemask for all surgical patients. In addition, we reduced the number of elective surgeries by half to reduce traffic in the hospital and increased distancing between surgical patients from February 22, 2020 to March 31, 2020.

Approximately 30% to 40% of patients who tested positive for SARS-CoV-2 by quantitative RT-PCR were asymptomatic [10, 11]. Therefore, to prevent asymptomatic carrier transmission, we screened all surgical patients for SARS-CoV-2. Sputum or nasopharyngeal swab samples were collected, but sputum samples were preferred if available [12].

The reported sensitivity of SARS-CoV-2 quantitative RT-PCR is approximately 70% to 90% [13]. Furthermore, approximately 3% to 12% of infected patients do not show any suspected symptoms and are reported to be negative. Therefore, we conservatively enrolled COVID-19–related patients and classified them according to contact history and COVID-19–associated symptoms.

SARS-CoV-2 is transmitted through respiratory droplets, contact, fomites, and fecal-oral routes [14, 15]. The viral load in the upper respiratory tract is high, and the virus is likely to shed and spread under asymptomatic conditions [16, 17]. In addition, SARS-CoV-2 can be transmitted via aerosols [18]. Therefore, we preferred regional anesthesia techniques to minimize aerosol production in the operating theater. In particular, we performed cesarean sections under regional anesthesia in 36 out of 44 cases. We also installed HEPA filters between the anesthetic machine and the patient to decrease the risk of environmental contamination during general anesthesia.

To prevent aerosol transmission, we avoided aerosol-producing interventions such as face mask ventilation and open airway suctioning as much as possible in all anesthesia cases [4, 18]. We adopted a rapid sequence intubation technique to prevent aerosol generation during mask ventilation. Intubation and extubation can also generate aerosols. Tracheal extubation produces 15 times more aerosols than intubation [19]. However, aerosol generation during extubation is still less than that of a single cough, and most aerosols generated during extubation may be produced by coughing after extubation [19]. Therefore, these procedures are not included in high-risk aerosol-producing procedures, and cough prevention during induction of anesthesia and after extubation is essential to prevent aerosol generation [20].

PAPR offers full face and respiratory protection. It does not require a fit test for loose fitting [21]. It also provides a cool and

Table 2. Types of surgeries during COVID-19 outbreak

<table>
<thead>
<tr>
<th>Name of surgery</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section</td>
<td>44</td>
</tr>
<tr>
<td>Laparoscopic exploration</td>
<td>22</td>
</tr>
<tr>
<td>Laparoscopic appendectomy</td>
<td>10</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>9</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>7</td>
</tr>
<tr>
<td>Gynecologic surgery</td>
<td>6</td>
</tr>
<tr>
<td>Urologic surgery</td>
<td>6</td>
</tr>
<tr>
<td>Laparoscopic cholecystectomy</td>
<td>3</td>
</tr>
<tr>
<td>Incision and drainage</td>
<td>3</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>3</td>
</tr>
<tr>
<td>Otolaryngologic surgery</td>
<td>2</td>
</tr>
<tr>
<td>McDonald operation</td>
<td>2</td>
</tr>
<tr>
<td>Wound repair</td>
<td>1</td>
</tr>
</tbody>
</table>

comfortable environment for the operator, decreases fatigue, and allows the operator to focus on the procedure. However, there is no strong evidence that it reduces viral transmission more than N95 respirators [22]. In addition, the supply of PAPRs was limited during the early outbreak, and this equipment requires a considerable amount of time to be cleaned and recharged after use. Therefore, we only included PAPR in the enhanced PPE.

We converted a positive-pressure OR to a temporary, negative-pressure OR with an adequate pressure gradient. The negative-pressure OR maintained a continuous negative-pressure gradient (−11.3 Pa) by increasing the exhaust air volume. We did not prepare an anteroom because we did not have a connected OR and did not have time to implement structural changes to the OR complex. Therefore, our HCWs wore and removed their PPE in the COVID-19 OR. We used disposable anesthetic and surgical equipment whenever possible to decrease the risk of virus exposure to sterile processing technicians. The disposed PPE and surgical equipment were sealed in zipper bags.

This study had some limitations. First, we performed only three surgeries in SARS-CoV-2-infected patients who were actively shedding virus because procedures in SARS-CoV-2-infected patients (such as tracheostomy and venoarterial extracorporeal membrane oxygenation cannulae insertion and removal) were typically performed in the ICU. Since there were few surgeries for confirmed patients, there is a limit to establishing the effectiveness of our infection prevention measures. Second, the negative-pressure OR was used mainly for abdominal surgeries. We did not perform neurosurgical or cardiovascular emergency procedures in COVID-19-related patients during this period. However, we believe that this fact does not diminish our infection prevention measures. Third, during PPE shortages, our infection prevention protocols should be conservatively applied. Ten additional SARS-CoV-2-positive patients were confirmed in the hospital during this period, including private caregivers and shop employees. Nevertheless, there were no verified nosocomial transmissions due to the strict adherence to the protocols and guidelines of our conservative infection prevention protocols.

COVID-19 infections and transmission in the hospital setting can lead to breakdown of medical systems. To prevent nosocomial transmission during surgical procedures, we converted a positive-pressure OR to a negative-pressure OR and implemented a perioperative protocol to prevent COVID-19 transmission to HCWs. With strict adherence to these protocols and guidelines, there was no transmission of COVID-19 to other persons within the OR. We hope that this report will help other hospitals prepare for COVID-19 outbreaks in limited situations.

Notes

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

Funding
None.

Author contributions
Conceptualization: JY, KHK, KTK; Data curation: JKK; Investigation: JKK; Visualization: JKK, JY; Writing - original draft: JKK, JY; Writing - review & editing: JKK, KTK, JY.

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Assessment of normal anal sphincter anatomy using transanal ultrasonography in healthy Korean volunteers: a retrospective observational study

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**Background:** To date, there have been no studies on the normal anatomic values of the anal sphincter in healthy Koreans. Therefore, this study aimed to determine the normal anatomic values of transanal ultrasonography (TAUS).

**Methods:** The thickness of the external anal sphincter (EAS) and internal anal sphincter (IAS) was measured by TAUS from healthy Korean volunteers between September 2019 and August 2021.

**Results:** Thirty-six volunteers with a median age of 37 years (range, 20–77 years) and a median body mass index (BMI) of 23.5 kg/m² (range, 17.2–31.2 kg/m²) were examined. The median thickness of the EAS at 4 cm and 2 cm from the anal verge was 7.4 mm (range, 5.8–8.8 mm) and 6.5 mm (range, 5.6–8.0 mm), respectively. The median thickness of the IAS at 2 cm from the anal verge was 1.8 mm (range, 0.8–4.3 mm). There were no differences in sphincter muscle thickness between the sexes. However, the EAS tended to thicken as the BMI increased (EAS at 2 cm and 4 cm from the anal verge, Spearman rho = 0.433, 0.363; p = 0.008 and p = 0.029, respectively).

**Conclusion:** In healthy Korean, the median thickness of the IAS at 2 cm from the anal verge was 1.8 mm and the median thickness of the EAS at 2 cm and 4 cm from the anal verge was 6.5 mm and 7.4 mm respectively. There were no differences in anal sphincter thickness between sexes, but BMI was related to EAS thickness.

**Keywords:** Anal canal; Anal sphincter; Anus; Ultrasonography

**Introduction**

According to data from the Korean Statistical Information Service, 183,908 patients underwent hemorrhoidectomy in Korea in 2019, ranking it the third most frequent surgery [1]. As such, a representative and essential test for diagnosing anal disease, which is one of the most frequent diseases, is transanal ultrasonography (TAUS). TAUS is a useful test for examining the anatomical structure of the anus [2,3]. The advantage of TAUS is that it has no risk of radiation exposure and is less expensive than magnetic resonance imaging (MRI). In addition, TAUS can be easily performed in outpatient clinics.

Anatomical deterioration, such as anal fistulas, abscesses, and sphincter defects, can be easily detected on TAUS by ultrasound-skilled clinicians [4]. In contrast, most diseases, such as fecal incontinence, constipation, or simple hemorrhoids, show no anatomical deterioration on TAUS. However, the absence of anatomical deterioration on TAUS does not indicate a normal finding. This is because the thickness of the sphincter and the degree of ultrasound shadowing may appear differently depending on the pa-
tient’s age, sex, past history, or degree of symptoms.

Indeed, according to previous studies conducted in Western countries, the thickness of the internal sphincter is measured differently according to age, and there is a difference in the length of the anal canal and thickness of the external sphincter according to sex [4-6]. In addition, the results may vary depending on the observer [5-7].

However, until now, there have been no studies on the normal anatomic value of the anal sphincter on TAUS in Koreans with no anal disease or symptoms. Therefore, research is needed to establish normal anatomic values for TAUS in healthy Koreans. The purpose of this study was to determine those normal values.

Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2019-09-062-008) and all the subjects included in this study provided written informed consent.

This prospective study was conducted in a tertiary medical center and local colorectal clinic in Daegu, Korea between September 2019 and August 2021.

Healthy Korean adult volunteers who had no anal disease and symptoms were recruited through research subject recruitment notices on bulletin boards in hospitals, subways, and buses. The inclusion criteria were as follows: (1) age of ≥ 20 years, (2) no ano-rectal symptoms, (3) Wexner score of ≤ 2, and (4) no anorectal surgical history. The applicant’s participation in the study was finally decided through an interview and physical examination with the researcher. If asymptomatic anatomical deterioration was found during TAUS, the subject was excluded from the study.

TAUS was performed using an endorectal probe (ALBIT ultrasound scanner, anorectal rotating 360, RS10; ECHO-SON, Ltd., Pulawy, Poland) at a frequency of 7.5 and 12 MHz by an experienced colorectal surgeon (DS) (Fig. 1). An enema or bowel preparation drug was not administered prior to TAUS. The subject lay in the left lateral position, and serial radial images were acquired throughout the anal canal. The thickness of the internal anal sphincter (IAS) was measured in the direction of 12 o’clock (anterior), 3 o’clock (left lateral), 6 o’clock (posterior), and 9 o’clock (right lateral) at 2 cm from the anal verge (Fig. 2A). The thickness of the external anal sphincter (EAS) was measured in the direction of 3 o’clock (left lateral), 6 o’clock (posterior), and 9 o’clock (right lateral) at 2 cm and 4 cm from the anal verge (Fig. 2B).

Non-normally distributed data, presented as median (range),
were analyzed using the Mann-Whitney U-test. Correlations between variables were analyzed using Spearman rank correlation test. Statistical significance was set at p-value of < 0.05. Statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

**Results**

Thirty-six volunteers were examined for anal anatomy using TAUS. The median age of the subjects was 37 years (range, 20–77 years) and the median body mass index (BMI) was 23.5 kg/m$^2$ (range, 17.2–31.2 kg/m$^2$). Nineteen patients (52.8%) were male. The age distribution was 21 to 30 years (7 individuals, 19.4%), 31 to 40 years (14 individuals, 38.9%), 41 to 50 years (5 individuals, 13.9%), 51 to 60 years (5 individuals, 13.9%), 61 to 70 years (4 individuals, 11.1%), and 71 to 80 years (1 individual, 2.8%). The demographic characteristics of the study participants are presented in Table 1.

The median thickness of the EAS at 4 cm and 2 cm from the anal verge was 7.4 mm (range, 5.8–8.8 mm) and 6.5 mm (range, 5.6–8.0 mm), respectively. The median thickness of the IAS at 2 cm from the anal verge was 1.8 mm (range, 0.8–4.3 mm).

There were no differences in sphincter muscle thicknesses between male and female patients (Table 2, Fig. 3). However, the EAS tended to thicken as the BMI increased (EAS at 2 cm and 4 cm from the anal verge, Spearman rho = 0.433 and 0.363; p = 0.008 and 0.029, respectively) (Fig. 4).

**Discussion**

In this study, we report a normal value of anal sphincter thickness in healthy Koreans as measured by TAUS. TAUS is the most frequently used examination for detecting anorectal anatomical variants because it can easily be performed in outpatient clinics without radiation exposure. Only a few studies have described the normal value of anal sphincter thickness in healthy adults [5,6,8,9]. However, all these studies were conducted in Western countries, and there have been no studies on healthy Asian or Korean volunteers.

In our study, the median IAS thickness at 2 cm from the anal verge was 1.8 mm. This is consistent with the results of previous studies conducted in Western countries (2 mm; range, 1–3 mm) [9]. Although the median value in our study was thinner than that in the cited study, this difference was not considered meaningful because of the measurement error and range.

The median EAS thickness in our study was 6.5 mm (range,
Fig. 3. Distribution plot by sex. (A) Internal anal sphincter (IAS) 2 cm from anal verge. (B) External anal sphincter (EAS) 2 cm from anal verge. (C) EAS 4 cm from anal verge.

Fig. 4. Scatter plots by body mass index (BMI). (A) Internal anal sphincter (IAS) 2 cm from anal verge. (B) External anal sphincter (EAS) 2 cm from anal verge. (C) EAS 4 cm from anal verge.

5.9–8.0 mm) at 2 cm from the anal verge. This is also consistent with the results of a previous study (6 mm; range, 5–8 mm) [9]. Unlike in the cited study, we also described the thickness of the EAS at the upper part of the anal canal (4 cm from the anal verge). The median EAS thickness of the upper anal canal was greater than that of the mid-anal cannula, although the difference was not statistically significant.

In the present study, no relationship was found between sex and sphincter thickness. This result is also consistent with that of a previous study [5]. However, interestingly, BMI correlated with EAS thickness in our study. The higher the BMI, the thicker the EAS was; however, IAS thickness was not correlated with BMI. A previous report revealed that BMI was not correlated with IAS thickness on MRI [10]. However, the investigators did not examine EAS thickness in that study. Another study revealed that BMI was correlated with IAS and EAS thickness [11]. However, the BMI correlation differed according to the measuring level of the anal canal. Interestingly, the investigators revealed that BMI was negatively correlated with EAS thickness, which was the opposite of our result. However, as the previous study was conducted with only females and our study was conducted with a small sample size, further studies are needed to clarify the correlation between BMI and anal sphincter thickness.

Our study has some limitations. First, the sample size was small. More than 80 participants were recruited at the beginning of the study. However, it was challenging to recruit healthy volunteers due to the outbreak of coronavirus disease 2019 at the beginning of the study. Therefore, the final sample size for this study was smaller than originally intended. Second, due to the small number of samples, we could not investigate the relationship between age and sphincter thickness. Third, we did not describe sphincter tone, which is possibly related to the thickness of the anal sphincter muscle. However, previous studies have reported no correlation between sphincter tone and anal canal pressure [7]. Fourth, we could not measure the length of the anal sphincter muscle because of the limitations of the two-dimensional scope. Nevertheless, we...
believe that this study is meaningful as the first study to elucidate normal TAUS values in healthy Koreans.

In this study, in healthy Korean volunteers, the median thickness of the IAS 2 cm from the anal verge was 1.8 mm, and the median thickness of the EAS at 2 cm and 4 cm from the anal verge was 6.5 mm and 7.4 mm, respectively, as measured by TAUS. There were no differences in anal sphincter thickness between sexes, but BMI was related to anal sphincter thickness. Further large-scale studies are required to confirm the results.

Notes

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

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Author contributions
Conceptualization, Investigation, Data curation, Formal analysis, Funding acquisition, Methodology, Visualization, Supervision: all authors; Project administration, Resources, Software: SIK; Writing-original draft: DS, SIK; Writing-review & editing: all authors.

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References

Preemptive pyloroplasty for iatrogenic vagus nerve injury in intrahepatic cholangiocarcinoma patients undergoing extensive left-sided lymph node dissection: a retrospective observational study

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Division of Hepatobiliary Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: Intrahepatic cholangiocarcinoma (ICC) of the left liver often shows left-sided lymph node (LN) metastasis. If gastric lesser curvature is extensively dissected, it can induce an iatrogenic injury to the extragastric vagus nerve branches that control motility of the pyloric sphincter and lead to gastric stasis. To cope with such LN dissection-associated gastric stasis, we performed pyloroplasty preemptively. The objective of this study was to analyze our 20-year experience of preemptive pyloroplasty performed in 10 patients.

Methods: We investigated clinical sequences of 10 patients with ICC who underwent preemptive pyloroplasty following left hepatectomy and extended left-sided LN dissection. Incidence of gastric stasis and oncological survival outcomes were analyzed.

Results: All 10 patients were classified as stage IIIB due to T1-3N1M0 stage according to the 8th edition of American Joint Committee on Cancer staging system. The overall patient survival rate was 51.9% at 1 year, 25.9% at 2 years, and 0% at 3 years. Seven patients showed uneventful postoperative recovery after surgery. Two patients suffered from gastric stasis, which was successfully managed with supportive care. One patient suffered from overt gastric paresis, which was successfully managed with azithromycin administration for 1 month.

Conclusion: We believe that preemptive pyloroplasty is an effective surgical option to prevent gastric stasis in patients undergoing extensive left-sided LN dissection. Azithromycin appears to be a potent prokinetic agent in gastroparesis.

Keywords: Gastric emptying; Gastroparesis; Pylorus; Vagus nerve

Introduction
Frequent sites of lymph node (LN) metastasis in patients with left-sided intrahepatic cholangiocarcinoma (ICC) include the common hepatic artery, celiac axis, and even the lesser curvature of the stomach, thus named as left-sided LN metastasis [1,2]. If metastatic LNs are located at the lesser curvature of the stomach, the connective tissues over the gastric serosa at the lesser curvature should be dissected to ensure complete LN dissection. Such surgical procedure inevitably results in iatrogenic vagus nerve injury because the running course of this nerve toward the pylorus and antrum is interrupted by extensive LN dissection, by which vagotomy-associated gastric stasis can occur. We have previously reported that preemptive pyloroplasty is effective in preventing such LN dissection-associated gastric stasis [3]. The objective of the present study was to analyze the effect of preemptive pyloro-
plasty in 10 patients who underwent preemptive pyloroplasty during left hepatectomy combined with extensive LN dissection for left-sided ICC.

**Methods**

**Ethical statements:** The study protocol was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No: 2021-1347). The requirement for informed consent from patients was waived due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

1. **Patient selection**
   The liver cancer database of our institution was searched to identify patients who underwent left hepatectomy or left lateral sectionectomy combined with extensive LN dissection for left-sided ICC. During the 20-year study period from January 2001 to June 2021, 10 patients underwent preemptive Heineke-Mikulicz pyloroplasty to prevent iatrogenic vagus nerve injury-associated gastric stasis. These 10 patients were selected as the study group in the present study.

   The study patients were followed until August 2021 through institutional medical record review and assistance of National Health Insurance Service.

2. **Decision on whether to perform preemptive Heineke-Mikulicz pyloroplasty**
   After completion of left-sided hepatectomy and extensive LN dissection for left-sided LN metastasis (Fig. 1), we decided whether to perform preemptive pyloroplasty after careful inspection of the gastric serosa at the lesser curvature. If the gastric serosa was fully

![Fig. 1. Preoperative abdominal computed tomography of patients with left-sided intrahepatic cholangiocarcinoma. (A, B) Regional lymph node metastasis is identified around the lesser curvature of the stomach (arrows) in a 59-year-old male patient and (C, D) a 57-year-old female patient.](https://doi.org/10.12701/yujm.2021.01550)
exposed with clearing of the overlying connective tissues and feeding vessels, the vagus nerve branch toward the pylorus and antrum was determined to be transected. The denervated extent by the vagus nerve transection was comparable to that of selective vagotomy (Fig. 2). Thus, such condition was reasonably indicated for preemptive pyloroplasty [3]. We performed the classical hand-sewing pyloroplasty of Heinke-Mikulicz type. The wall of the distal antrum and the duodenal first portion was longitudinally incised with electrocautery and then transversely repaired with inner continuous sutures using 4-0 absorbable monofilament and outer continuous sutures using 5-0 nonabsorbable monofilament or interrupted sutures with 3-0 or 4-0 black silk (Fig. 3).

2. Postoperative assessment for gastric stasis
A nasogastric tube (NGT) was routinely kept under natural drainage for 3 days after surgery in all patients who had undergone preemptive pyloroplasty. If gastric stasis of any degree was suspected, the NGT was kept and frequently aspirated until recovery of gastrointestinal motility. The NGT was removed if the amount of daily drainage was less than 300 mL/day with absence of air-fluid level at the stomach on simple abdominal X-ray. During fasting, all patients received total parenteral nutrition until intake of soft diet. Prokinetics were administered with temporary clamping of the NGT with an expectation to facilitate recovery of bowel motility [4,5].

3. Postoperative treatment and surveillance
All patients underwent adjuvant chemotherapy with or without concurrent chemoradiation therapy. General principles of treatment for stage IIIB ICC according to the 8th edition of American Joint Committee on Cancer (AJCC) staging system were applied. Detailed follow-up protocol was presented previously [6].

4. Statistical analysis
Numerical data are reported as mean with standard deviation. Survival curve was estimated with the Kaplan-Meier method. All statistical analyses were performed using IBM SPSS ver. 22 (IBM Corp., Armonk, NY, USA).

Results

1. Patient demographics and survival outcomes
All 10 patients were classified as stage IIIB according to the 8th edition of AJCC staging system because of T1-3N1M0 stage. Their clinicopathological profiles are summarized in Table 1. The overall patient survival rate was 51.9% at 1 year, 25.9% at 2 years, and 0% at 3 years (Fig. 4).

2. Incidence of gastric stasis
For eight patients, the NGT was kept for the first 3 days after surgery. For the remaining two patients, it was kept for 4 days after surgery. One day after NGT removal, sips of water were initiated. Thereafter, intake of liquid diet was started after careful physical examination and daily simple abdominal X-ray follow-up.

Seven patients showed no evidence of gastric stasis. Thus, diet intake was started at 5 days after surgery. No gastrointestinal motility disorder occurred until hospital discharge.
In contrast, the remaining three patients manifested clinical findings suggesting gastric stasis or paresis. Three patients showed gaseous distension of the stomach and air-fluid level in simple abdominal X-ray in the next few days after removal of the NGT. Thus, the early postoperative incidence of gastric motility disorder after preemptive pyloroplasty was 30%.

3. Clinical sequences of two patients showing gastric stasis

A 61-year-old male patient who showed gastric stasis and paralytic ileus was well tolerated with fasting for 7 days after removal of the NGT without reinsertion of an NGT. Gastric distension and paralytic ileus slowly resolved. Diet intake was initiated 11 days after surgery and continued uneventfully until hospital discharge.

A 67-year-old male patient showed prolonged gastric distension and paralytic ileus after removal of the NGT, thus a new NGT tube was reinserted at 8 days after surgery and two prokinetic agents (gasmotin and ganakhan) were orally administered for 7 days until daily drainage of less than 200 mL/day with resolution of paralytic ileus pattern on simple abdominal X-ray follow-up. Diet intake was initiated 15 days after surgery and continued uneventfully until hospital discharge.

4. Clinical sequences of one patient showing gastric paresis

A 57-year-old female patient underwent left hepatectomy, choledochal cyst excision, and Roux-en-Y hepaticojejunostomy due to choledochal cyst-associated ICC (Fig. 1B, Fig. 5). The patient showed marked gaseous distension of the stomach with air-fluid level on simple abdominal X-ray (Fig. 6A, 6B) since removal of the NGT at 4 days after surgery. Two prokinetic agents (gasmotin and ganakhan) were orally administered, but they were ineffective. An NGT tube was reinserted at 9 days after surgery, but the amount...
of daily drainage was less than 200 mL/day despite overt gaseous distension of the stomach and persistence of air-fluid level at the stomach. Thus, the NGT was repeatedly aspirated every 4 hours, which resulted in daily drainage of more than 1,000 mL/day. For 10 days of NGT drainage, gastric distension did not resolve at all. Oral administration of bethanechol was ineffective. On the postoperative 20th day, upper gastrointestinal series with gastrografin showed delayed gastric emptying (Fig. 6C, 6D), indicating gastric paresis rather than gastric outlet obstruction. We presumed that the cause of such overt gastric paresis was denervation of the vagus nerve.

On the postoperative 21st day, azithromycin 500 mg was administered intravenously once a day. On the next day, the patient felt the loss of epigastric discomfort and NGT tube drainage decreased markedly. After intravenous administration of azithromycin for 3 days, the NGT tube was removed. Endoscopic gastroduodenoscopy showed a slight narrowing of the duodenum probably due to extrinsic compression, thus balloon dilatation was performed. Diet intake was initiated with oral administration of azithromycin and two prokinetics, and oral intake was progressed uneventfully. The patient was discharged after azithromycin administration for 8 days on the postoperative 29th day with uneventful oral intake (Fig. 7A, 7B). One prokinetic agent was stopped 1 week after discharge due to diarrhea and another agent was also discontinued 1 week later. Diarrhea disappeared after discontinuation of prokinetics (Fig. 7C, 7D). Azithromycin was discontinued after overall 4 weeks of use.

Table 1. Clinicopathological features of patients with intrahepatic cholangiocarcinoma and left-sided lymph node metastasis

<table>
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<td>ICG-R15 (%)</td>
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</tr>
<tr>
<td>T4</td>
<td>0</td>
</tr>
<tr>
<td>Incidence of gastric motility disorder</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number only.

ICG-R15, indocyanine green retention test at 15 minutes; AJCC, American Joint Committee on Cancer.
Thereafter, bowel motility was well maintained without any medication. The patient has undergone the scheduled adjuvant chemotherapy for 6 months without delay.

**Discussion**

ICC is the second most common primary malignancy of the liver. Its diagnosis has been gradually rising in the general population. ICC comprises approximately 15% of primary liver malignancies in patients undergoing surgical resection in our institution [6]. LN metastasis is known to be the most potent prognostic factor in patients undergoing surgical resection for ICC [6-8]. We have previously presented that LN metastasis and perineural invasion are independent risk factors for ICC [6]. LN metastasis alone makes the tumor stage IV in the 7th AJCC staging system and tumor stage IIIIB in the 8th AJCC staging system for ICC. Presence of LN metastasis is associated with very poor outcomes. The clinical benefit of aggressive LN dissection has not been clearly defined yet, but it has been regarded as an essential part of resectional surgery for ICC [8-11].

If left-sided LN metastasis is identified, the usual extent of LN dissection may include the hepatoduodenal ligament, common hepatic artery, celiac axis, left gastric artery, and lesser curvature of the stomach. If an LN is located close to the lesser curvature of the stomach, its dissection procedure may include clearing of the gastric lesser curvature and ligation of the left gastric artery. This surgi-

Fig. 6. Postoperative simple abdominal X-ray images follow-up. (A, B) Images taken on the postoperative 8th day show marked gaseous distension of the stomach with air-fluid level. (C, D) Images taken on the postoperative 20th day show stagnated gastrograffin within the stomach at (C) 1 hour and (D) 6 hours after oral intake.
cal procedure can induce an iatrogenic injury to the vagus nerve branches which control motility of the pyloric sphincter, by which intractable gastric stasis can occur. Denervation of the controlling vagus nerve branches to the antrum and pylorus can manifest delay of gastric emptying, which persists up to 2 months, as presented in our previous study [3].

Not to mention LN dissection, left hepatectomy per se is known to be associated with disorders of gastric motility. After living-donor left hepatectomy, the stomach adheres to the liver cut surface, which can cause unwanted gastric stasis [12-14]. The underlying mechanisms of gastric stasis after left hepatectomy are different from those of the usual laparotomy-associated adhesive ileus possibly due to rightward dislocation of the stomach after left hepatectomy and adhesion of the stomach to the cut surface of the remnant right liver [14].

The majority of patients who underwent extensive left-sided LN dissection were destined to receive adjuvant chemotherapy at 4 to 6 weeks after surgery. Thus, recovery of oral intake is essential to endure cytotoxic adjuvant chemotherapy. Postoperative delayed gastric emptying can deteriorate patients’ quality of life because they have to restrict oral intake for a few weeks after surgery or keep an NGT until recovery of gastric motility [3]. Such gastric motility disorder also has a negative effect as it can significantly delay the start of adjuvant chemotherapy. Considering the poor prognosis of ICC patients with LN metastasis, gastric stasis and its associated degradation of quality of life can be considered as serious surgical complications.

To prevent left-sided LN dissection-associated gastric stasis, we

Fig. 7. Postoperative simple abdominal X-ray follow-up images after azithromycin administration. The images taken at (A, B) hospital discharge and (C, D) 2 weeks later show no significant abnormal finding.
have performed pyloroplasty as a preemptive procedure during resection of ICC with left-sided LN metastasis [3]. Prolonged gastric stasis universally happened in patients who had undergone extensive dissection of the gastric lesser curvature in our previous case series [3]. In contrast, gastric stasis occurred in 30% after preemptive application of pyloroplasty in the present study. Considering that temporary gastric stasis can occur in 10% to 20% of patients who have undergone simple left hepatectomy without LN dissection [12-14], the actual incidence of gastric stasis after preemptive pyloroplasty was around 20% in the present study.

Two patients with gastric stasis were successfully treated with supportive care. However, one patient showed serious gastric paresis, which might be associated with vagotomy. The occurrence of chronic symptomatic gastric paresis has been reported to be 3% to 5% in patients following vagotomy and antrectomy [15]. Intravenous administration of erythromycin can improve the initial phase of meal gastric emptying in such patients [15]. However, erythromycin has not been available for a long time in our institution. Thus, we searched for alternative agents. Although metoclopramide and bethanechol were reported to increase gastric motor activity in the patients with diabetic and post-vagotomy gastroparesis [16], they were ineffective in our patient. Azithromycin is a macrolide like erythromycin. These two drugs can accelerate the gastric emptying of adult patients with gastroparesis. Azithromycin has advantages of longer duration of action and better side-effect profile while lacking P450 interaction, over erythromycin [17]. We followed the azithromycin administration protocol used in an old woman with diabetic gastroparesis [18], in which gastrointestinal symptoms were significantly improved after 3 days of treatment. Surprisingly, our patient showed noticeable improvement after only one session of azithromycin injection, as like triggering the start of gastric motility. A literature review study has concluded that azithromycin might be an alternative prokinetic agent in gastroparesis [19].

Performance of conventional Heinke-Mikulicz type pyloroplasty is a simple procedure that takes only 10 minutes because the pylorus-antrum area is usually normal in the majority of patients with ICC. Preemptive pyloroplasty has been proven to be effective to prevent gastric stasis. Thus, we think that there is no reason to hesitate whether to perform pyloroplasty or not if vagus nerve injury-associated gastric stasis is anticipated.

This study has some limitations. First, this study was a small case series from a single center, thus high-volume multicenter studies are necessary. Second, this study was a retrospective study, thus a prospective clinical trial is needed to validate the effect of preemptive pyloroplasty.

In conclusion, we believe that preemptive pyloroplasty is an effective surgical option to prevent gastric stasis in patients undergoing extensive left-sided LN dissection. Azithromycin appears to be a potent prokinetic agent in gastroparesis.

Notes

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

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Author contributions
Conceptualization, Data curation, Visualization: SH; Methodology: EKJ, DHJ, YK; Writing-original draft: SH; Writing-review & editing: all authors.

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References

Effect of nonsurgical periodontal therapy and smoking status on hematological variables related to anemia of chronic disease in chronic periodontitis patient: a case-control study

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Background: Chronic infectious, inflammatory, or neoplastic disorders are associated with anemia of chronic disease. Chronic inflammatory diseases such as periodontitis may contribute to masked anemia, especially in smokers. This study was aimed at verifying and comparing the efficacy of nonsurgical periodontal therapy (NSPT) for improving anemia among chronic periodontitis patients with and without the habit of smoking.

Methods: Thirty systemically healthy individuals with chronic periodontitis were divided into two groups of 15 each, smokers (group A) and nonsmokers (group B). The groups were compared based on hematological parameters such as serum erythropoietin (SE) and serum ferritin (SF) levels at baseline and 3 months after NSPT for anemia evaluation.

Results: The baseline SE levels in groups A and B were 11.84 and 15.19 mIU/mL ($p=0.031$), respectively; the corresponding levels at 3 months after NSPT were 13.00 and 17.74 mIU/mL ($p=0.022$). The baseline SF levels in groups A and B were 95.49 and 44.86 ng/mL ($p=0.018$), respectively; the corresponding levels at 3 months after NSPT were 77.06 and 39.05 ng/mL ($p=0.009$). Group B showed a significant increase and decrease in the SE and SF levels, respectively, at 3 months after NSPT ($p=0.035$ and $p=0.039$, respectively), whereas group A showed insignificant changes ($p=0.253$ and $p=0.618$, respectively).

Conclusion: NSPT led to an improvement in anemia among chronic periodontitis patients. However, the improvement is less in smokers compared to that in nonsmokers. Furthermore, SF and SE levels might serve as effective biomarkers for assessing anemia in smokers and nonsmokers with chronic periodontitis.

Keywords: Anemia; Chronic periodontitis; Erythropoietin; Ferritin; Smoking
Introduction

Chronic infectious, inflammatory, or neoplastic disorders are associated with anemia of chronic disease (ACD) [1]. Pathophysiological factors such as limited iron availability to erythroid progenitor cells, a blunted response to erythropoietin, erythropagocytosis, diminished erythropoiesis, and microbial/tumor cell infiltration of bone marrow contribute to the development of ACDs. Patients with ACD demonstrate diminished levels of serum iron, normal to elevated serum ferritin (SF) levels, and normocytic to microcytic anemia [2]. Periodontitis is a chronic inflammatory disease characterized by increased production of inflammatory cytokines that can contribute to the prevalence of anemia by directly inhibiting erythropoiesis and inducing changes in iron absorption and release [3].

Patients with chronic periodontitis (CP) who are regular smokers show lower gingival redness and bleeding on probing due to potential vasoconstriction caused by the nicotine content in tobacco. This may lead to an inaccurate assessment of periodontal status and failure to diagnose the underlying pathogenic state [4]. In addition, smoking causes an increase in hemoglobin (Hb) concentration mediated by carbon monoxide, which bonds with Hb and forms inactive carboxyhemoglobin (COHb) with a reduced ability to deliver oxygen to the tissues. Therefore, as a compensatory mechanism, smokers maintain a higher Hb level than nonsmokers, which is referred to as secondary polycythemia [5,6]. Despite the higher Hb levels found in smokers, this hypoxic state triggers erythropoietin production, thereby increasing erythropoiesis. Erythropoietin is a large glycoprotein hormone produced by the peritubular cells lining the kidneys and hepatocytes; it is the principal regulator of the erythrocyte lineage [7]. This clearly implies that the underlying anemic state in smokers is masked by high Hb values, which may lead to an underestimation of the prevalence of anemia among smokers [8]. In such a scenario, an estimation of serum erythropoietin (SE) levels may aid in assessing the anemia status of smokers.

In chronic inflammatory conditions such as CP, proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor-α, and transforming growth factor-β not only increase hemolysis and impair erythropoiesis via direct bone marrow suppressive effects but also release reactive oxygen species that inhibit erythropoietin gene expression [9]. Singh et al. [10] and Hutter et al. [11] found lower erythropoietin levels in patients with CP, thereby strengthening the hypothesis that CP may lead to ACD.

Acute-phase proteins are biomarkers that show changes in plasma concentration that increase (positive acute-phase proteins), such as ferritin, or decrease (negative acute-phase proteins) by at least 25% during inflammatory disorders, due to their altered production by hepatocytes [12]. Ferritin serves as the main iron storage protein in the body and contains 20% iron by weight. The serum iron concentration is directly proportional to its storage in the body, which increases under inflammatory conditions and iron overload. Chakraborty et al. [13] observed that SF levels were higher in patients with CP than in healthy controls, and a reduction was noted with remission of chronic inflammation following nonsurgical periodontal therapy (NSPT). Considering the prevalence of periodontal disease in the community at large, its deleterious effects on the systemic health of affected individuals, the increased use of tobacco in the form of cigarette smoking, and the resultant masking of anemia status, therapeutic measures such as scaling and root planning (both NSPTs) might significantly improve anemia status in such individuals.

The available literature suggests that NSPTs were not tested while evaluating erythropoietin levels in smokers and nonsmokers with CP. To date, only a few studies have evaluated NSPTs with a single hematological parameter to assess ACD in CP cases. Hence, multiple hematological parameters, such as SF and SE levels, collectively might serve as a better means to assess the anemia status of smokers with CP instead of any single parameter. The aim of the present study was to verify and compare the efficacy of NSPT in improving anemia status among patients with CP who do or do not smoke.

Methods

**Ethical statements:** This study was carried out following CONSORT (Consolidated Standards of Reporting Trials) guidelines and written informed consent was obtained from all participants who fulfilled the inclusion criteria and agreed to participate voluntarily. Details about the nature, risk, and benefits of the hematological investigations as well as the associated procedures were explained to all participants. The experimental protocol and consent form were approved by the Institutional Ethical Committee and Institutional Review Board (IRB) of Dr. R. Ahmed Dental College and Hospital (IRB No: DCH/07/18-19).

**1. Study design**

This clinico-biochemical study included 30 systemically healthy patients diagnosed with CP stage I/II (probing pocket depth of ≥ 4 mm but < 6 mm) requiring NSPT who were selected from the outpatient Department of Periodontics [14]. CP was confirmed clinically and radiographically according to the guidelines of the

https://doi.org/10.12701/jyms.2022.00045
2017 Periodontology Consensus Report [14]. Subjects were divided into two groups (n = 15 per group) based on their smoking history. Group A included current smokers (i.e., individuals with a history of smoking ≥ 100 cigarettes in their lifetime and currently smoking) and group B included never smokers (i.e., individuals who never smoked/history of smoking < 100 cigarettes in their lifetime) [15]. Pregnant and lactating mothers, former smokers, and those with any history of systemic illness, history of iron supplements or blood loss, any periodontal surgery in the last 6 months, and pocket depth ≥ 6 mm were excluded from the study.

After careful periodontal examination and diagnosis, venous blood samples were obtained in the early morning to avoid diurnal variations in SE levels. Peripheral venous blood (4 mL) was obtained by venipuncture (Mokshy Surgical Ltd., Mumbai, India) in the antecubital fossa from each participant selected for hematological tests. The blood was transferred to non-vacuum clot activator (coated with micronized silica) blood collection tubes. The collected blood samples were kept at room temperature for approximately 2 hours to allow the blood to clot, and serum was obtained after centrifugation for 10 minutes at 2,500 revolutions per minute (Remi Elektrotechnik Ltd., Thane, India). The serum was then assayed for baseline periodontal and hematological parameters (SF and SE). The selected subjects in both groups then received NSPT, including ultrasonic scaling, root planing, and polishing, as required. Thorough oral hygiene instructions and demonstration of proper brushing technique were provided. The patients were asked to return at 1- and 3-month intervals for follow-up, and additional oral prophylaxis was administered at those times if required. All periodontal interventions were performed by an expert periodontist who was unaware of the specific grouping of the subjects.

The final hematological data were recorded at the 3-month follow-up, and statistical analysis of the data was carried out. Oral hygiene was maintained at an optimal level during the study period.

SF levels were measured using an Access Immunoassay System and analyzed using an automated analyzer (Beckman Coulter Immunoassay System, Brea, CA, USA). SE levels were assessed using an enzyme-linked immunosorbent assay (ELISA) kit for erythropoietin and an Adonis ELISA plate reader system (Triveni Traders & Diagnostic Private Ltd., Thane, India).

2. Statistical analysis
The Shapiro-Wilk test was performed to assess the assumption of normality of the data. Data are presented as mean ± standard error of mean (SEM). An unpaired Student t-test was performed to compare the parameters of the two groups that showed normal distributions. Normally distributed paired data of each group were compared using a paired Student t-test. Non-normally distributed unpaired data were evaluated using the Mann-Whitney U-test, and paired data were evaluated using the Wilcoxon matched-pairs signed-rank test. Correlations between two normally distributed parameters were evaluated using the Pearson correlation test. Sex distribution between the two groups was evaluated using Fisher exact test. The correlation between two non-normally distributed parameters was evaluated using Spearman nonparametric correlation. Direct and inverse correlations were indicated by positive and negative correlation coefficient (r) values, respectively. An absolute value of r of 1.0 to 0.5, 0.5 to 0.3, 0.3 to 0.1, and < 0.1 was considered strong, moderate, weak, and no correlation, respectively. Differences were considered statistically significant at p < 0.05. Statistical analysis was performed using Graph Pad Prism ver. 5, 2007 (Graph Pad Software Inc., San Diego, CA, USA).

Results
The Shapiro-Wilk test and visual inspection of the histograms and quantile-quantile plots suggested that the collected data were normally distributed. In the present study, the ages (mean ± SEM) of the participants in groups A and B were 47.73 ± 2.33 years and 41.93 ± 2.79 years, respectively. An unpaired Student t-test showed that the mean age of the participants was not statistically different between the groups (p = 0.122) (Table 1). Regarding sex distribution between the groups, group A had nine male patients and six female patients, and group B had seven male patients and eight female patients. A chi-square test showed that there was no statistically significant difference in the sex distribution (p = 0.457).

Hence, confounding variables, such as age and sex, did not affect the study results (Table 1). Group B showed higher SE levels than group A both at baseline (group A, 11.84 ± 1.24 mIU/mL and group B, 15.19 ± 0.79 mIU/mL; p = 0.031) as well as after 3 months of periodontal intervention (group A, 13.00 ± 1.40 mIU/mL and group B, 17.74 ± 1.36 mIU/mL; p = 0.022) (Table 2, Fig. 1). No significant alteration in the SE level was observed in group A compared to baseline. No correlation between age, history of smoking, and SE was observed in any of the groups.

Table 1. Demographic details of the different study groups

<table>
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<th>Demographic variable</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47.73 ± 2.33</td>
<td>41.93 ± 2.79</td>
<td>0.122&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Sex, male:female</td>
<td>9 (60.0):6 (40.0)</td>
<td>7 (46.7):8 (53.3)</td>
<td>0.457&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard error of mean, or number (%). Group A, smokers; group B, nonsmokers.
<sup>a</sup>Analysed by independent samples t-test; <sup>b</sup>analysed by chi-square test. p < 0.05, statistically significant.
after 3 months of periodontal therapy (Table 2). However, the SE level in group B increased significantly \((p = 0.035)\) after 3 months compared to the baseline level (Table 2, Fig. 1).

Considering the SF level data, group A showed statistically significant higher values of SF than group B at baseline (group A, \(95.49 \pm 21.53\) ng/mL and group B, \(44.86 \pm 4.69\) ng/mL; \(p = 0.018\)). Whereas group B showed statistically lower (group A, \(77.06 \pm 14.06\) ng/mL and group B, \(39.05 \pm 5.46\) ng/mL; \(p = 0.009\)) SF level compared to group A after 3 months of NSPT (Table 3, Fig. 2). However, no significant alteration \((p = 0.618)\) in SF level was observed in group A after 3 months of treatment compared to the baseline level. However, the SF level in group B decreased significantly \((p = 0.039)\) after 3 months of NSPT compared with the corresponding baseline level (Table 3, Fig. 2).

### Discussion

The underlying anemia status in smokers may be masked by relatively higher Hb values, which are usually tested to assess anemia. This may lead to an underestimation of the prevalence of anemia among smokers. The available literature suggests that only a few studies have analyzed the efficacy of periodontal interventions, such as NSPT, on the anemia status of such patients by assessing SE or SF.

In the present study, the baseline mean SE levels were significantly lower \((p = 0.031)\) in smokers with CP than in nonsmokers with CP. In addition, SE levels were negatively correlated with smoking at baseline. These findings are consistent with those of Tanabe et al. [16] and Eisenga et al. [17]. During daytime smoking, higher SE levels lead to erythrocytosis, which in turn inhibits
further erythropoietin production through a negative feedback loop. Endogenous circulating erythropoietin with a half-life of 6 to 8 hours would result in low SE in the morning hours when blood samples are usually drawn [17]. This phenomenon is supported by the circadian rhythm of SE levels described by Miller et al. [18]. An alternative explanation may be derived from the study by Weinberg et al. [19] who observed the JAK2 V617F mutation in cigarette smokers and suggested that the erythrocytosis observed in smokers occurs via an erythroid cell-intrinsic erythropoietin-independent mechanism. They also stated that this may be an unidentified direct effect of smoking on erythropoiesis. Chronic smoking initially induces an increase in erythrocyte volume, plasma volume, and erythropoietin concentration, the latter of which is reduced when the erythrocyte volume increases. Hence, erythropoietin production represents a balance between stimulation by hypoxia and negative feedback by increasing erythrocyte volume [14]. The release of proinflammatory cytokines from peripheral neutrophils and various parameters of inflammation in plasma seem to be affected more by cigarette smoking than periodontal disease, which might contribute to the downregulation of erythropoietin production. Elevation of these inflammatory mediators leads to inhibition of the hormone erythropoietin and erythropoiesis, leading to the development of anemia [20].

In the present study, 3 months following the NSPT intervention, SE levels increased from baseline values in group A, although they were not statistically significant (p = 0.253). In contrast, the group B patients showed a statistically significant (p = 0.035) improvement in SE levels following periodontal intervention. This is in agreement with the results of Miller et al. [21], who failed to detect differences in SE levels when the COHb concentration changed following smoking cessation. As a possible explanation, they mentioned that small changes in COHb were not sufficient to trigger an erythropoietin response in persons with normal lung function. In the present study, the mean SF levels at baseline were significantly higher (p = 0.018) in group A than in group B. Ghio et al. [22] supported this finding of increased SF levels among smokers compared with those among nonsmokers. They correlated this finding with the systemic accumulation of iron after cigarette smoke exposure and concluded that cigarette smoke alters iron homeostasis both in the lung and systemically. However, that study did not include patients with CP. Contradictory findings were obtained in a study by Erdemir et al. [23], who noted similar SF levels among smokers and nonsmokers. These findings were in agreement with those of patients with ACD, who had normal to elevated SF levels. However, the possible cause of the similar SF values in both groups was not explained in that report. A cross-sectional study conducted by Prakash et al. [24] assessed the anemia status of nonsmoking patients with CP by evaluating various hematological parameters. No significant changes in SF levels were observed between the study groups. In the present study, the mean SF levels in group B were significantly lower (p = 0.0397) at 3 months after NSPT than at baseline. This is in agreement with the study of Chakraborty et al. [13], who detected relatively higher SF levels in smokers with CP than in nonsmokers with CP, and these levels were restored to normal following NSPT intervention. The mean SF levels in the present study at 3 months after NSPT were reduced in group A compared to baseline; however, the difference was not statistically significant (p = 0.618). The available literature does not include any comparable studies.

One limitation of the present study is its relatively small sample size. Further studies involving larger sample sizes and other parameters may be conducted in the future if required.

Overall, NSPT leads to a relative increase in SE levels and a relative decrease in SF levels, thereby indicating an improvement in the anemia status of both smokers and nonsmokers. However, the magnitude of the changes was less in smokers. Hematological parameters such as SF and SE might serve as effective biomarkers for assessing anemia status in nonsmokers with CP. For smokers with CP, further studies with larger sample sizes may clearly demonstrate the effect of NSPT on SE and SF levels among these individuals.

**Notes**

**Conflicts of interest**

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

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**Author contributions**

Conceptualization: all authors; Investigation: SS, KST; Resources: AKD, PCP, KST; Software: AKD, KST; Supervision, Validation: SB; Data curation: AKD, RB, KST; Formal analysis: SB, RB, PCP; Methodology: SB, RB, PP, KST; Project administration: SS, AKD, PCP, KST; Visualization: AKD, PCP; Writing - original draft: SS, AKD, PP; Writing - review & editing: SS, PCP.

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Pedunculated mucinous cystic neoplasm of the liver: a case report

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In 2010, the World Health Organization classified mucin-producing bile duct tumors of the liver into two distinct entities: mucinous cystic neoplasm of the liver (MCN-L) and intraductal papillary mucinous neoplasm of the bile duct. We present the case of a patient with MCN-L having a uniquely pedunculated shape. A 32-year-old woman was referred to our institution with a diagnosis of biliary cystic neoplasm. She had undergone left salpingo-oophorectomy for ovarian cancer 15 years ago. Imaging studies showed an 8 cm-sized well defined, multiloculated cystic lesion suggesting a mucinous cystic neoplasm. The cystic mass was pedunculated at the liver capsule and pathologically diagnosed as MCN-L. The mass was resected with partial hepatectomy. The patient recovered uneventfully. She was discharged 7 days postoperatively. The patient has been doing well for 6 months after the operation. The patient will be followed up annually because of the favorable postresection prognosis of MCN-L.

Keywords: Cystic neoplasm; Intraductal papillary neoplasm; Mucins; Ovarian-like stroma; WHO classification

Introduction

In 2010, the World Health Organization (WHO) classified mucin-producing bile duct tumors of the liver into two distinct entities: mucinous cystic neoplasm of the liver (MCN-L) and intraductal papillary mucinous neoplasm of the bile duct (IPMN-B) [1,2]. MCN-L is a rare disease that accounts for less than 5% of all cystic liver lesions [2-6]. This disease predominantly occurs in women [1,4,7]. Histologically, it is defined as a cyst-forming epithelial neoplasm composed of mucin-producing epithelium associated with ovarian-like stroma (OLS) [2]. MCN-L is graded as low-, intermediate-, and high-grade intraepithelial dysplasia, carcinoma in situ, or associated invasive carcinoma [1,2,8].

MCN-L has previously been known as biliary cystadenoma and seven cases of biliary cystadenocarcinoma [9], for which the definition of MCN-L according to the WHO 2010 classification was not adopted because these study patients had undergone surgical resection between 2007 and 2013.

We present the case of a patient who underwent hepatic resection for MCN-L with a uniquely pedunculated shape.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No: 2021-0839), and informed consent was obtained from the patient.
A 32-year-old woman was referred to our institution with a diagnosis of biliary cystic neoplasm. The patient underwent computed tomography (CT) at a local hospital because of a sudden onset of upper abdominal pain persisting for 1 day. The abdominal CT showed an 8 cm-sized multiseptated cystic mass with some high attenuation fluid in the right lobe of the liver, suggesting a biliary cystic neoplasm. She had undergone left salpingo-oophorectomy for ovarian cancer 15 years ago.

A repeat abdominal CT scan showed an 8 cm-sized well-defined, multiloculated cystic lesion, suggesting a mucinous cystic neoplasm (Fig. 1). A high attenuation portion was observed within the cystic lesion, indicating hemorrhage rather than a thickened septum. There was no attenuation change in the surrounding liver tissue or bile duct dilatation. Diffuse fatty liver and splenomegaly were present. Fluorodeoxyglucose positron emission tomography-CT showed an 8 cm-sized metabolic defect in the right liver (Fig. 2). In the right ovary, a cystic lesion with mild hypermetabolic uptake was observed. Pelvic ultrasonography performed at the Department of Obstetrics and Gynecology showed a 3.5 cm-sized cystic lesion in the right adnexa, which was an indication for further follow-up. There was no evidence of ovarian cancer recurrence or liver metastasis.

Because the patient had undergone surgery for ovarian cancer, she wanted to receive an upfront surgery for liver mass resection.

**Fig. 1.** Preoperative computed tomography showing an 8 cm-sized well-defined, multiloculated cystic lesion. There is some high attenuation portion within the cystic lesion indicating hemorrhage (arrows) in (A, C) the arterial phase and (B, D) portal phase images. Diffuse fatty liver is present.
Fluorodeoxyglucose positron emission tomography showing an 8 cm-sized metabolic defect in the right liver (arrow).

We planned to perform a partial hepatectomy to remove the cystic mass. After laparotomy, the gallbladder was resected because of previous surgery-associated adhesions. There were noticeable adhesions around the cystic mass in the right dome of the liver. After meticulous dissection of the liver dome, we unexpectedly identified that the cystic mass was uniquely pedunculated in the liver capsule (Fig. 3). The cystic mass compressed the liver parenchyma; thus, the corresponding portion was depressed to hold it. We presumed that hemorrhagic expansion of the cystic mass was associated with the sudden onset of upper abdominal pain. The mass was delivered after partial hepatectomy in the pedunculated neck portion. The right ovarian cyst was assessed intraoperatively by obstetricians and regarded as a functional ovarian cyst.

The pathology report revealed that the cystic lesion was multiloculated and filled with mucinous fluid (Fig. 4). The diagnosis was a low-grade MCN-L of 8 × 6 × 4 cm that was attached to the Glisson capsule. There was no finding of a usual discolored hematoma in the lumen of the cystic lesion. Focal luminal thickening, which was well matched with the preoperative CT findings, appeared to be suggestive of a resolved hematoma. The cyst was lined by tall columnar tumor cells possessing supranuclear cytoplasmic mucin with elongated nuclei and mild cytologic atypia. Subepithelial OLS cells with elongated nuclei were diffusely positive for estrogen receptors (Fig. 5). Focal positivity was also observed in the OLS cells.

The patient recovered uneventfully (Fig. 6). She was discharged 7 days postoperatively. The patient has been doing well for 6 months after the operation. The patient will be followed up every 6 to 12 months because of MCN-L and ovarian cyst.

Discussion

MCN-L shows multilocular cysts with septation. It is often located in the left liver. Considering these usual findings of MCN-L, our patient showed a unique feature of pedunculated MCN-L. The cystic mass occupied the space at the liver dome, leaving a counterpart cast-like depression in the liver parenchyma. Such intraoperative findings suggested that the cystic tumor had grown very slowly over a long period. We presumed that hemorrhagic expansion of the cystic mass was associated with preoperative upper abdominal pain, which occurred suddenly and persisted for a day.

MCN-L should be differentiated from IPMN-B, which is recognized as a biliary counterpart to the papillary intraductual mucinous neoplasm of the pancreas. The characteristics of IPMN-B include multicystic appearance, bile duct dilation, the presence of intraluminal masses, and intraductal nodules [1,5,7,10,11]. IPMN-B has the typical characteristics of an absence of OLS. It is histologically described as a mucinous and papillary neoplasm, with a clear origin in the biliary epithelium and solitary or diffuse intraductal growth [10]. However, there are some case reports of MCN-L showing the presence of a prolapsed tumor mass in the left hepatic duct and common bile duct that can cause ductal dilation [10,12]. These findings suggest that ductal dilation and communication with the bile duct might not be typical signs of IPMN-B because they can be identified in MCN-L.

It is difficult to differentiate between MCN-L and IPMN-B preoperatively. MCN-L usually shows the absence of communication with the bile duct, absence of bile duct dilation, and multilocular shape, but these findings might not always be decisive when defining the diagnosis of MCN-L. The presence of OLS in the histopathological section was established by the WHO 2010 classification as a diagnostic criterion for MCN-L. In contrast, immunohistochemical profiling of mucin core proteins (MUC1, MUC2, and MUC5AC) and cytokeratin (CK7 and CK20) is used to classify IPMN-B into four types; pancreaticobiliary, intestinal, gastric, and oncocytic types [13,14].

There are some common characteristics between MCN-L and IPMN-B, such as mucin production rare incidence. However, some clinicopathological features are more typical of each neoplasm. MCN-L predominantly occurs in females but not IPMN-B [1,7,12,15]. It is also difficult to differentiate MCN-L from simple liver cysts.
Fig. 3. Intraoperative findings. (A) There are noticeable adhesions around the cystic mass in the right liver dome. (B) The cystic mass is pedunculated at the liver capsule. (C) The mass is delivered after partial hepatectomy at the pedunculated neck portion. (D) A cast-like depression is left at the liver parenchyma.

Fig. 4. Gross photographs of the resected specimen. (A) External shape and (B) internal morphology of the cystic mass are visible. The cystic lesion of 8 × 6 × 4 cm is multiloculated and filled with mucinous fluid. Arrow indicates the resected liver parenchyma attached to the neck portion. Arrowhead indicates the focal luminal thickening suggestive of resolved hematoma.
Fig. 5. Microscopic findings. (A) The cyst is lined by tall columnar tumor cells having intracytoplasmic mucin and elongated nuclei with mild cytologic atypia (hematoxylin and eosin stain, ×200). (B) The subepithelial ovarian-type stromal cells are diffusely positive for estrogen receptor (immunohistochemical stain, ×200).

Fig. 6. Computed tomography at 5 days after the operation showing usual postoperative findings. (A) Fluid collection is identified at the site of mass. (B) Multiple metal clips indicate the site of pedunculated neck portion.

A large cyst at the initial presentation, an increase in size during follow-up, and the manifestation of symptoms are general indications for surgical resection [3,11]. A 5-year survival rate of 100% has been reported in patients with MCN-L [1,4]. Considering such favorable postresection outcomes, follow-up protocols for the patient in the present case include the first imaging study at 6 months after resection and subsequent follow-up studies every 12 months for more than 5 years.

Notes

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

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Primary hepatic sarcoidosis presenting with cholestatic liver disease and mimicking primary biliary cholangitis: a case report

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Sarcoidosis often involves the liver. However, primary hepatic sarcoidosis confined to the liver without evidence of systemic involvement is rare. We report the case of a 37-year-old man with hepatic sarcoidosis who initially presented with elevated liver enzymes and suspicious cirrhotic nodules on computed tomography. The patient had cirrhosis but did not have portal hypertension. Based on the initial histopathologic finding of chronic granulomatous inflammation and the common clinical characteristics of sarcoidosis, he was initially diagnosed with primary biliary cholangitis, and his daily dosage of ursodeoxycholic acid was increased to 900 mg. After 14 months of treatment, his total serum bilirubin concentration was 10.9 mg/dL (upper normal limit, 1.2 mg/dL). Additionally, a transjugular liver biopsy revealed multiple noncaseating granulomas. He was diagnosed with primary hepatic sarcoidosis involving the lungs, heart, spleen, kidneys, and skin. Treatment with methylprednisolone was initiated. Two weeks later, he was started on azathioprine, and the dose of steroid was simultaneously reduced. These findings indicate the importance of including hepatic sarcoidosis as a possible diagnosis in patients with elevated liver enzymes or cryptogenic cirrhosis.

Keywords: Biliary tract; Cholestasis; Liver cirrhosis; Sarcoidosis

Introduction

Sarcoidosis is a multisystem disease characterized by the formation of noncaseating granulomas in affected organs. Sarcoidosis can affect almost all organs, with more than 90% of patients showing involvement of the lungs and hilar lymph nodes. The liver is the third most commonly affected organ [1]. Most patients with hepatic involvement are asymptomatic, but 5% to 30% of these patients present with abdominal pain in the right upper quadrant, nausea, vomiting, and/or hepatomegaly [2-4]. A small number of patients with hepatic sarcoidosis present with chronic cholestasis, cirrhosis, portal hypertension, and Budd-Chiari syndrome [5,6]. Cirrhosis occurs in less than 1% of patients with sarcoidosis [5]. This study reports the case of a patient who presented with elevated liver enzymes and abnormal hepatic morphology as the first clinical signs of systemic sarcoidosis and was ultimately diagnosed with systemic sarcoidosis.
Case

Ethical statements: This retrospective study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No: 2106-033-104), and the requirement for informed consent from the patient was waived by the IRB.

A 37-year-old man visited our outpatient clinic with elevated liver enzymes and computed tomography (CT) findings indicative of liver cirrhosis. The patient reported that his liver enzymes had been elevated during the previous 4 to 5 years, but he was not further tested. He had not been diagnosed with any disease and had not taken any medications or had traveled. At presentation, the patient was asymptomatic; his liver and spleen were not palpable, and there were no signs of chronic liver disease, such as palmar erythema, spider nevi, gynecomastia, and ascites, and no unusual skin lesions. The patient was 187 cm tall and weighed 104 kg (body mass index, 29.7 kg/m²), drank alcohol 2 to 3 times per month, and was a current smoker with a history of seven pack-years. His maternal grandfather had hepatocellular carcinoma.

Laboratory examination showed elevated concentrations of liver enzymes, including aspartate aminotransferase (AST, 133 IU/L; upper normal limit [UNL], 40 IU/L), alanine aminotransferase (ALT, 158 IU/L; UNL, 40 IU/L), alkaline phosphatase (ALP, 378 IU/L; UNL, 129 IU/L), and gamma-glutamyl transferase (GGT, 2,162 IU/L; UNL, 73 IU/L). However, serum bilirubin (0.71 mg/dL) and albumin (5.0 g/dL) concentrations were not elevated and the prothrombin time was not prolonged (11.8 seconds). Abdominal CT showed cirrhotic nodules in both lobes of the liver (Fig. 1A), but a chest X-ray showed no evidence of hilar lymphadenopathy (Fig. 1B).

The elevated liver enzymes and abdominal CT findings, showing multiple cirrhotic nodules in both lobes, led to further laboratory evaluations to determine the cause of liver cirrhosis. Serological tests for hepatitis A, B, and C viruses were all negative, and levels of antimitochondrial antibody (AMA), anti-smooth muscle antibody, anti-liver kidney microsome type 1, antineutrophil cytoplasmic antibody, alpha-1-antitrypsin, ceruloplasmin, fluorescent antinuclear antibody, and quantitative copper were all within normal ranges. Serum concentrations of immunoglobulins (Igs), including IgG (1,440 mg/dL), IgA (289 mg/dL), and IgM (120 mg/dL), were not elevated.

Because treatment with the usual dose of ursodeoxycholic acid (UDCA, 600 mg/day) for 5 months had no effect on liver enzyme levels and all serologic markers were negative, a transjugular liver biopsy was performed. Histopathologic evaluation of the specimen indicated chronic granulomatous inflammation (Fig. 2), with no staining for fungi or acid-fast bacilli, and a polymerase chain reaction test negative for *Mycobacterium tuberculosis*. Based on the biopsy results and the clinical characteristics of sarcoidosis, he was initially diagnosed with primary biliary cholangitis (PBC), and his daily dosage of UDCA was increased to 900 mg. After 6 months of

Fig. 1. Initial abdominal computed tomography (CT) and chest X-ray of the patient. (A) Enhanced CT image of the abdomen in the portal-venous phase, showing underlying liver cirrhosis with multiple cirrhotic nodules in both lobes of the liver. (B) The first chest X-ray shows no evidence of hilar lymphadenopathy.
treatment, however, his liver enzyme levels did not decrease significantly, and a follow-up chest X-ray showed no abnormal findings.

Routine laboratory testing after the patient had taken 900 mg/day UDCA for 14 months showed a total bilirubin concentration of 10.9 mg/dL (UNL, 1.2 mg/dL), and the patient was hospitalized. Abdominal CT showed innumerable and scattered low-attenuation lesions in the liver parenchyma, spleen, and kidneys, as well as multiple small lymph nodes at the lower paraesophageal, perigastric, portocaval, retrocaval, paraaortic, retroperitoneal, liver hilum, hepatoduodenal ligament, common hepatic artery, and celiac axis areas. After admission, erythematous plaques were observed on the right elbow and left knee (Fig. 3A). Biopsy specimens from these areas indicated the presence of epithelioid cell granulomas (Fig. 3B). Based on the results of the skin biopsy, he was diagnosed with sarcoidosis, a diagnosis confirmed by his serum angiotensin-converting enzyme (ACE) levels elevated to 92.2 U/L (UNL, 47 U/L) and the results of chest and abdominal CT. The patient underwent transthoracic echocardiography and fundus examination to identify the extent of sarcoidosis. Examination of a second transjugular liver biopsy sample showed multiple confluent noncaseating granulomas in the hepatic capsule, portal and focal periporal inflammation, mild lobular activity, and portal fibrosis (Fig. 4). These results confirmed the diagnosis of hepatic sarcoidosis, accompanied by involvement of the lungs, heart, spleen, kidneys, and skin (Supplementary Fig. 1).

After confirmation of sarcoidosis, the patient was administered intravenous methylprednisolone (40 mg/day for 3 days) followed by oral prednisolone (80 mg/day for 3 days and then tapered down to 40 mg/day). The patient was started on azathioprine (25 mg/day) 2 weeks after initiation of prednisolone, and the dose of steroid was simultaneously reduced by 5 mg/day every 3 days. After 3 weeks of steroid treatment, his liver enzyme concentrations had markedly decreased (AST, 95 IU/L; ALT, 62 IU/L; ALP, 379 IU/L; total bilirubin, 2.32 mg/dL) and the patient was discharged from the hospital. At follow-up 49 months after the initiation of steroid treatment, the patient was taking prednisolone (10 mg/
day) and azathioprine (100 mg/day), and blood chemistry indicated continued improvements in liver enzymes (AST, 46 IU/L; ALT, 45 IU/L; ALP, 174 IU/L; total bilirubin, 0.98 mg/dL; GGT, 790 IU/L) (Supplementary Fig. 2).

Discussion

The present report describes the procedures used to diagnose sarcoidosis involving the liver, lungs, heart, spleen, kidneys, and skin in a patient who initially presented with elevated liver enzymes and abnormal hepatic morphology. The characteristics of this patient were unusual in that an elevation in liver enzymes was the first and only clinical finding of systemic sarcoidosis, and there was no initial involvement of the lungs or skin. Although hepatic involvement has been observed in 5% to 30% of patients with sarcoidosis, isolated liver involvement without lung disease is rare and observed in only 13% of patients with sarcoidosis.

On initial examination, abdominal CT of the patient revealed cirrhotic hepatic nodules, whereas laboratory tests showed elevated liver enzymes, findings suggestive of cirrhosis. A liver biopsy, however, showed mild hepatocellular cholestasis and portal fibrosis, providing no pathological evidence of cirrhosis. In addition, the CT scan provided no evidence of portal hypertension, such as dilatation of the portal and/or mesenteric vein, contrast enhancement of the paraumbilical vein, collateral vessels or varices, splenomegaly, or ascites. Sarcoidosis and granulomatous liver disease have been classified into four broad categories, with the present patient having group III sarcoidosis, which is characterized by clinical and laboratory evidence of hepatocellular disease with or without portal hypertension. The prevalence of liver cirrhosis at the time of diagnosis of hepatic sarcoidosis has been reported to range from 6% to 24%, with signs of liver cirrhosis and portal hypertension observed in up to 18% of patients with hepatic sarcoidosis.

Although the initial liver biopsy confirmed hepatic granulomas, the final diagnosis of sarcoidosis was delayed. This patient was negative for AMA, had normal IgM levels, and bile duct inflammation was unclear in the liver biopsy sample. These findings suggested an initial diagnosis of PBC, because less than 10% of patients with sarcoidosis have isolated extrapulmonary sarcoidosis, and because cirrhosis is not common in patients with hepatic sarcoidosis.

Hepatic sarcoidosis can manifest as intra- or extrahepatic cholestasis. Intrahepatic cholestasis in patients with hepatic sarcoidosis is characterized histologically by numerous well-formed granulomas located mainly in the peribiliary area. In comparison, PBC manifests as poorly demarcated granulomas located in portal tracts along damaged bile ducts, whereas primary sclerosing cholangitis is characterized by prominent concentric periductal fibrosis. Extrahepatic cholestasis in patients with hepatic sarcoidosis has been associated with the occurrence of extrahepatic obstruction due to narrowing of the common hepatic duct by granulomas located in the biliary tract.

During the differential diagnosis of an unexplained increase in liver enzymes, it is important to consider sarcoidosis as a possible cause. Because of the relatively asymptomatic nature of hepatic sarcoidosis and liver enzyme elevation, imaging methods have a deci-

Fig. 4. Histopathology of the second transjugular liver biopsy. (A, B) The liver shows multiple noncaseating granulomas in the hepatic capsule and portal tracts (hematoxylin and eosin stain; [A] x200, [B] x400).
sive role in the diagnosis of hepatic sarcoidosis [9]. The most common liver enzyme abnormalities in sarcoidosis are elevations in ALP and GGT to more than three times their UNLs. AST and ALT elevations are less common, usually less than twice the UNLs, and less severe than ALP and GGT elevations [6,9]. Hyperbilirubinemia is uncommon in patients with sarcoidosis, with all patients presenting with preserved liver synthetic function [9]. The epithelioid cells of sarcoid granulomas may be responsible for the elevation of serum ACE [18], but elevated serum ACE has a sensitivity of only 57% and a specificity of 90% for the diagnosis of sarcoidosis [19].

Guidelines to date have not specified the initial treatment (drug of choice, dose, and duration) of patients with hepatic sarcoidosis [17]. Glucocorticoids are generally administered as first-line therapy [9], but large controlled studies performed to date do not provide supporting evidence for the efficacy and long-term benefits of glucocorticoids and other immunosuppressive agents [15,20]. Although steroid treatment can reduce clinical symptoms, liver enzyme levels, and hepatomegaly [3], it does not prevent the progression of hepatic sarcoidosis [2].

The diagnosis of sarcoidosis in our patient was difficult because the initial clinical findings included only elevated liver enzymes, abnormal hepatic morphology, and no evidence of systemic involvement. To our knowledge, this report describes the first patient to date diagnosed with hepatic sarcoidosis who had elevated hepatic enzyme levels and suspicious cirrhotic nodules on CT and had cirrhosis without portal hypertension. These findings indicate the importance of considering hepatic sarcoidosis as a possible diagnosis in patients with unexplained elevations in liver enzymes or cryptogenic cirrhosis.

**Supplementary materials**

Supplementary Figs. 1 and 2 can be found via https://doi.org/10.12701/yujm.2021.01151.

**Notes**

**Conflicts of interest**

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**Author contributions**

Conceptualization: JH; Funding acquisition: JH; Data curation: MBK, JA; Writing-original draft: YJP, HYW; Writing-review & editing: YJP, HYW, MBK, JA, JH.

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**References**

Introduction

Mondor disease (MD) is a palpable, painful, subcutaneous induration caused by superficial venous thrombosis [1,2]. In 1939, the first report involved a female patient with symptoms in the thoracoepigastric region. Penile MD was first reported in 1958 [2,3]. MD is rare and its etiology remains to be established. However, a relationship with Virchow's triad is strongly suspected [1,3]. Moreover, rare cases of MD related to oral contraceptives have been reported [4]. Sildenafil, also known as Viagra, is currently used for the management of male erectile dysfunction and has been approved for the treatment of pulmonary hypertension [5]. We report a case of penile MD that was suspected to be related to prolonged oral sildenafil use.

Case

A 46-year-old man visited the emergency department (ED) with sustained penile pain and swelling that began 7 hours after sexual intercourse. He had a history of hypertension, gastroesophageal reflux disease, and posttraumatic stress disorder. He had used oral sildenafil intermittently for 11 years for erectile dysfunction, and...
the night prior to arrival at the ED, he had engaged in sexual intercourse after taking sildenafil. No clinical signs of intercourse-related trauma to the genital area were observed. The following morning, he noted a sustained, painful penile erection with swelling. Using a visual analogue scale, the patient’s pain intensity was scored at approximately 2 points. His initial vital signs were as follows: blood pressure, 100/60 mmHg; heart rate, 110 beats/min; respiratory rate, 20 breaths/min; and body temperature, normal. He reported no urinary symptoms and declined biochemical laboratory tests. On physical examination, the penis was swollen, with no increase in skin temperature. He complained of tenderness over the dorsal penile vein area and a mild protrusion was noted (Fig. 1). The differential diagnosis included suspected unidentified priapism, soft tissue infection, or penile fracture, and an ED ultrasound examina-
tion was performed. No abnormal disruption of the tunica albuginea was noted in the penile shaft. However, a dilated vein with hyperechoic thrombosis was observed in the right superficial dorsal vein of the penis with soft tissue swelling. Moreover, the absence of flow signal in the thrombotic lesion was identified on the color Doppler ultrasound image (Fig. 2). Following ED-administered pain management, he was advised to avoid sexual intercourse and was discharged from the ED with a prescription for nonsteroidal anti-inflammatory medication. A follow-up appointment at the Department of Urology in outpatient clinic was made to determine whether surgical thrombectomy would be required. During the next 2 weeks of outpatient follow-up, the patient’s symptoms improved.

Discussion

MD is a rare, painful, superficial venous thrombosis that has been reported to predominantly occur in the chest wall or penis [2]. Penile MD comprises venous thrombosis of the dorsal superficial penile vein and is typically benign and self-limiting. However, its pathophysiology remains unclear [1]. Virchow’s triad, involving vascular wall injury, venous stasis, and hypercoagulation, has been reported to cause venous thrombosis [1]. The most likely cause of penile MD is vascular wall injury, which is one factor in Virchow’s triad, due to lengthening or splitting of the vessel from prolonged vigorous sexual activity, typically within 24 to 48 hours [3]. Hypercoagulation due to protein S, protein C, and antithrombin III deficiency has also been reported to cause penile thrombosis [6]. Di-

Fig. 1. Photo of the penis. Arrows indicate a slight protrusion of the superficial dorsal vein with mild swelling of the penis. No erythema is present.

Fig. 2. Penile ultrasonography and color Doppler ultrasound imaging. (A) Ultrasonography shows thrombosis (arrows) in the penile superficial dorsal vein. (B) Color Doppler ultrasound indicates the absence of a flow signal (blue or red signal) in the thrombotic lesion (arrow). Imaging results support the diagnosis of penile Mondor disease.
Platelet aggregation activation

Right side weakness

Superior sagittal sinus

Supposed mechanism

Left middle cerebral artery

Jugular vein

Platelet aggregation activation

Vascular insufficiency and stasis

Bilateral blurred vision

Bilateral blurred vision

Right transverse and sigmoid sinus

Sildenafil-induced transient arrhythmic cardiac embolism

Site of thrombus

Symptom

Table 1. Previous reports of sildenafil-associated vascular thrombosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom</th>
<th>Site of thrombus</th>
<th>Supposed mechanism</th>
</tr>
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<tbody>
<tr>
<td>Rufa et al. [5]</td>
<td>Bilateral blurred vision</td>
<td>Superior sagittal sinus</td>
<td>Vascular insufficiency and stasis</td>
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<td>Right transverse and sigmoid sinus</td>
<td>Platelet aggregation activation</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>Right side weakness</td>
<td>Left middle cerebral artery</td>
<td>Sildenafil-induced transient arrhythmic cardiac embolism</td>
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<tr>
<td>Karti et al. [9]</td>
<td>Bilateral blurred vision</td>
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agnosia is possible through a detailed history, physical examination, and color Doppler ultrasound [1]. Penile MD is most frequently treated conservatively, and patients are advised to avoid sexual activity and to take nonsteroidal anti-inflammatory medication. However, in rare cases, thrombectomy can be proposed in chronic forms of penile MD or in forms resistant to treatment (persistence of the symptomatology and absence of permeabilization of the vein at 6 weeks) [1,7]. Antibiotics are prescribed if there is evidence of infection, such as superficial cellulitis or a sexually transmitted disease [3].

Sildenafil acts by blocking phosphodiesterase-5, an enzyme that promotes the breakdown of cyclic guanosine monophosphate (cGMP), causing relaxation of the corpora cavernosa and penile arteriolar smooth muscle. Owing to the localized vasodilatory effect of the nitric oxide–guanosine monophosphate pathway, the U.S. Food and Drug Administration has approved its use in the treatment of pulmonary hypertension [5]. However, sildenafil has been reported to have various adverse effects, including venous thrombosis. Table 1 shows previous reports on the association between venous thrombosis and oral sildenafil [5,8,9].

According to previous reports, the mechanisms of vascular thrombosis may be due to vascular stasis and/or platelet aggregation resulting from long-term sildenafil use. cGMP can inhibit platelet aggregation. Initially, cGMP causes platelets to clump to seal a wound and later reverses this action to stop an excessive build-up of cells that might then block a blood vessel. Sildenafil-enhanced intracellular cGMP activates cGMP-dependent protein kinase (PKG) [10]. PKG promotes von Willebrand factor-induced activation of human platelets [11]. Rufa et al. [5] suggested that the chronic use of sildenafil causes high cGMP levels, which might interfere with normal endothelial function. Moreover, sildenafil lowers systolic blood pressure by 8 to 10 mmHg owing to its vascular relaxation effect, which could be the cause of vascular insufficiency [12]. Decreased blood flow owing to blood vessel relaxation may be an additional cause of thrombus formation.

Penile MD is not life-threatening, but it can negatively affect a patient’s quality of life. Considering the adverse effects of sildenafil, prolonged oral administration could cause abnormal venous thrombosis of the superficial dorsal penile vein. It is also reasonable to consider that sildenafil can cause penile MD in men with other risk factors, such as penile vascular wall injury due to vigorous sexual activity. We believe that long-term use of sildenafil causes genital vascular thrombosis, and further studies are needed to support the development of optimal guidelines for long-term use.

Notes

Conflicts of interest

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

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Author contributions

Conceptualization, Data curation, Formal analysis and Investigation: YHM, HSC; Writing-original draft: YHM; Writing-review & editing: YHM, HSC.

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5. Rufa A, Cerase A, Monti L, Dotti MT, Giorgio A, Sicurelli F, et


We present the case of a 21-year-old previously healthy varsity rugby athlete with left common fibular nerve (CFN) injury following knee dislocation. She presented to a local hospital with a traumatic knee injury following blunt anterior impact causing posterior dislocation. Immediately, she noted anesthesia of the lateral leg and dorsal foot, and dorsiflexion paralysis. Computed tomography revealed a tibial plateau fracture with 2 mm impaction. Magnetic resonance identified torn anterior and posterior cruciate ligaments, a torn lateral collateral ligament, and a grade one medial collateral ligamentous sprain. The fibular nerve was not commented on. Electromyography (EMG) studies confirmed a CFN mononeuropathy. She underwent orthopedic surgery for ligament repair 2 weeks post-injury followed by consultation with a peripheral nerve surgeon.

The patient was seen in our musculoskeletal medicine clinic for preoperative ultrasonographic assessment. She had regained partial sensation of the left distal extremity, however, remained unable to dorsiflex and evert the foot. Ultrasonographic analysis (Samsung RS80A machine, linear L4-18B probe; Samsung, Seoul, Korea) identified a tortuous fibular nerve extending 5 cm proximal to its passage over the fibular neck (Fig. 1, Supplementary Video 1). Loss of fascicular pattern began prior to division from the sciatic nerve and extended 7 cm distally, with maximal edema at 9 cm proximal to the fibular neck measuring 1 cm in diameter, with no nerve discontinuity. Common and superficial fibular nerves were unremarkable distal to the fibular neck. Upon surgical exploration, the CFN distal to its branching off the sciatic nerve was scarred and hardened. The neuroma in continuity was excised followed by grafting using cable grafts from the sural nerve. Pathology results confirmed a traumatic neuroma. At the 1-year follow-up, there was slight improvement on clinical and EMG exam in the fibular muscles (Medical Research Council Scale for Muscle Strength score 2/5), but no improvement in the muscles of the anterior compartment of the leg (tibialis anterior, extensor digitorum longus, extensor hallucis longus: strength 0/5).

Like seven of the eight patients described by Coraci et al. [1], we did not observe CFN neurotmesis. In our

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Fig. 1. Ultrasonography of the left common fibular nerve shows intraneural swelling and loss of fascicular pattern without discontinuity after a knee posterior dislocation, in transverse axis (A) without and (B) with color doppler imaging, (C) with area (75 mm²) and diameter (9.9 mm) measurements, and (D) in longitudinal axis.
patient, we additionally described distinct features of a neuroma which was tortuous at the popliteal fossa. Ultrasonographic analysis changed the course of treatment and the surgical approach. Numerous studies have shown the incidence of CFN palsy post-knee dislocation ranges from 10% to 40% [2]. Imaging findings include perineural edema, nerve discontinuity, and neuroma formation. Morris et al. [3] described a case of fibular nerve looping at the site of injury, which they termed the “lariat sign.” What we have described here is a redundant nerve in the absence of rupture, raising the question as to whether the anomaly is that of severe nerve stretching without rupture or rather nerve entrapment within disorganized fibrous scar tissue leading to its tortuous nature.

Supplementary material

Supplementary Video 1 can be found via https://doi.org/10.12701/yujm.2021.01389.

Notes

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Instructions to authors

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**Research ethics**

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Categories of publications

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, RFS (clinical vignette, teaching images), and imagery. Editorials are invited perspectives on an area of medical science, dealing with very active fields of research, current medical interests, fresh insights and debates. Review articles provide a concise review of a subject of importance to medical researchers written by an invited expert in medical science. Original articles are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers. Case reports deal with clinical cases of medical interest or innovation. Image vignettes present state-of-the-art imaging that can be used in the evaluation of unusual clinical cases. Communications are interesting and instructive information for readers. RFS - Clinical vignette is interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees. RFS - Teaching images are previously unpublished Magnetic Resonance Images, Computed Tomography Scans, Ultrasound Images, X-rays, Patient Photographs/Videos, or other pictorial/videographic material. Imagery is drawings, illustrations, or photographs of artistic and imaginative qualities of the readers.

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Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Methods, Results, Discussion, References (up to 40 references), and tables and/or illustrations.

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The title page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list (first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

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This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

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Image vignette should be organized in the following sequence: a summary of the presentation, imaging features and discussion. No abstract is required for this manuscript. There should be no more than five references and no more than two figures. Total length should be no longer than 500 words (excluding figure legends, ethical statements, conflicts of interest, author contributions, ORCID, and references).

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Interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees. Cases may focus on either diagnosis or management. Vignettes should progress logically and be divided into the following sections:
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- Differential diagnosis or potential approaches to management. Include discussion regarding reasons for selected differential or potential management approaches.
- Diagnostic results including lab results/imaging (if relevant).
- Diagnosis and discussion of management and outcomes. Include a discussion of the relevant literature related to the vignette.
Clinical vignette should be maximum of 1,500 words, 1–2 tables or figures and maximum of 10 references.

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ther the education of the trainee audience. The title of the article should be brief and include the patient’s age and sex, accompanied by a succinct 5–10 word description of the patient’s presentation. Up to two labeled images or figures should be provided with a short description and/or legend. The case description should be written in 300 words or less and directly address the image provided while detailing the clinical significance of the presented findings and correlation with the patient’s symptoms. Intended for trainees, teaching images should progress through a patient’s history and physical exam while focusing on differential diagnoses, the clinical reasoning for selecting the particular diagnostic study, and the appropriate interpretation, subsequent treatment strategies, and achieved outcome. Finally, 2–3 bulleted learning points should accompany the submission to advance trainee knowledge (will not count toward word limit).

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I am informed and aware of photographs, videotapes and other images (imaging records) taken by Dr. ________________ or his designee(s) of myself or any parts of my body regarding surgical procedures carried out by Dr. ________________. I understand and consent that such imaging records may and will be used by Dr. ________________ as reference in diagnosing and treating other patients in the future. I further consent to the release and transfer of copyright ownership by Dr. to *Journal of Yeungnam Medical Science* of such imaging records.

I understand that by consenting on release of my imaging records, these may and will be used in upcoming issue or issues of the journal, as well as on the journal website, or any other print or electronic media for the purpose of informing medical professionals or other readers about surgical methods. I understand that when these imaging records are included in any articles, medical information regarding sex, age, operative date and treatment results may and will be included together. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identification impossible.) I understand that whether I consent on this form or not, it bears no consequences whatsoever on any future actions, and that there will be no effect on the medical treatment I receive from Dr. ________________ or any subordinates.

I grant this consent as a voluntary contribution in the interest of public education, and certify that I have read the above Consent, Authorization and Release form and fully understand its terms. I understand that, if I do not revoke this authorization, it will expire 10 years from the date written below.

I hereby transfer in above-mentioned terms, the copyright of my imaging records to

Dr. ________________________________ .

Name: ________________________________ Signature: ________________________________

Hospital: ________________________________ Department: ________________________________

Designated Doctor: __________________________ Signature: ________________________________

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