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Aims and scope

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The KMJ aims to communicate new medical information to medical personnel, and to facilitate the development of medicine, medical science, medical ethics, medical policy, and medical education, as well as the propagation of medical knowledge by publishing high-quality, evidence-based articles.

The KMJ publishes editorials, review articles, original articles, and case reports. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of medical diseases and the communication of valuable information about all fields of medicine, medical science, medical ethics, medical policy, and medical education.

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Contents

KMJ
KOSIN MEDICAL JOURNAL

Vol. 39, No. 2, June 2024

Editorial

81 Coronavirus disease 2019 infection in pediatric patients in Korea: insights and implications
Yu Jin Jung

Review articles

83 Bone-modifying agents for bone metastasis in patients with breast cancer
Lee Chun Park, Eun Mi Lee

89 Treatment of pediatric obstructive sleep apnea
Tae Kyung Koh, Jooyeon Kim

94 Surgical management of recurrent laryngeal nerve invasion by papillary thyroid carcinoma
Jae Hong Park, Hyoung Shin Lee

Original articles

99 Clinical features of coronavirus disease 2019 in Korean pediatric patients: a single-center retrospective study
Ji Eun Jeong, Hai Lee Chung, Young Hwan Kim, Nawon Lee, Younghyun Kim, Yoon Young Jang

112 Statins as a possible factor affecting fluoroquinolone resistance of coagulase-negative *Staphylococcus* in the conjunctiva: a case-control study
Yoo Rha Hong, Chi Eun Oh, Sang Joon Lee

120 Orbital complications of acute rhinosinusitis in adults: a 21-year experience
Yung Jin Jeon, Woohyen Jin, Yeon-Hee Joo, Hyun-Jin Cho, Sang-Wook Kim

Case reports

127 Cardiovascular collapse during transcatheter aortic valve replacement in monitored anesthesia care using an end-tidal carbon dioxide monitor: a case report
Wonjin Lee, Jaewoo Suh

132 Interpedicular approach in percutaneous sacroplasty for treating pain due to direct invasion of rectal cancer into the S3 body: a case report
Jinseok Yeo, Saeyoung Kim, Chang Sub Lee

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Contents

KMJ
KOSIN MEDICAL JOURNAL

Vol. 39, No. 2, June 2024

138 **Disseminated herpes zoster with vagus nerve involvement in a kidney transplant recipient: a case report**

Dong Eon Kim, Da Woon Kim, Hyo Jin Kim, Harin Rhee, Sang Heon Song, Eun Young Seong

144 **Total intravenous anesthesia using remimazolam for patients with heart failure with reduced ejection fraction: a case series**

Jimin Lee, Ji-Uk Yoon, Gyeong-Jo Byeon, Hong-Sik Shon, Ahhyeon Yi, Hee Young Kim

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Editorial

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Coronavirus disease 2019 infection in pediatric patients in Korea: insights and implications

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See "Clinical features of coronavirus disease 2019 in Korean pediatric patients: a single-center retrospective study" by Ji Eun Jeong, Hai Lee Chung, Young Hwan Kim, Nawon Lee, Younghyun Kim, Yoon Young Jang

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), remains a topic of considerable concern and interest worldwide [1,2]. With over 500,000 reported deaths attributed to COVID-19 infections [3], it is crucial to understand the pandemic's impact on children to address concerns associated with the infection [4]. Therefore, understanding the unique signs and effects of the COVID-19 virus in the pediatric population is of the utmost importance.

In the current issue of the *Kosin Medical Journal*, Jeong et al. [5] present an analysis of clinical characteristics and outcomes of COVID-19 in pediatric patients based on cases from a single institution in Korea. The study found that out of 311 pediatric patients diagnosed with COVID-19, the majority were aged 6–11 years [5]. Fever was the most common symptom, and its prevalence decreased with age. When comparing clinical characteristics of patients aged 6 and older in the asthma and non-asthma groups, no significant differences were observed in symptoms such as cough, runny nose, nasal stuffiness, and dyspnea. Adolescents were categorized into two groups: those who had completed the basic two-dose vaccination regimen and those who had not. There was no difference in the average time from COVID-19 diagnosis to clinic visit between the vaccinated and unvaccinated groups. However, the incidence and peak values of fever were significantly lower in the vaccinated group. The study underscores the importance of vigilance in pediatric patients with underlying conditions like allergic rhinitis and precocious puberty, even though children generally exhibit milder symptoms than adults [5]. Precocious puberty, marked by the early onset of puberty, may suggest an underlying endocrine or metabolic imbalance that could affect the immune response to infections [6]. Children with such conditions may need closer monitoring during a COVID-19 infection due to their potentially altered physiological state, which could make them more susceptible to severe outcomes. The study also noted a significantly higher incidence of post-acute COVID-19 syndrome, such as a cough persisting for more than 4 weeks, in the asthma group. Long COVID-19 syndrome, characterized by prolonged symptoms like persistent cough and fatigue, can impact children's daily activities and overall well-being. Additionally, although not covered in this study, it is crucial to be aware that some pediatric COVID-19 patients may develop multisystem inflammatory syndrome in children (MIS-C) [7,8]. MIS-C is a serious condition that can emerge

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weeks after infection, involving inflammation across multiple organ systems and necessitating immediate medical attention. Therefore, it is important to monitor and promptly address potential complications.

This study highlights the necessity for ongoing research to fully understand the complex and varied clinical manifestations of COVID-19 in children. Additionally, the observation that 90% of the families or cohabitants of pediatric patients also contracted the infection has profound implications for infection control and public health policy [5]. By clarifying the clinical spectrum of COVID-19 in pediatric patients, healthcare providers can more effectively customize diagnostic and treatment strategies, ensuring timely interventions and optimal outcomes [9]. Moreover, these findings highlight the critical importance of pediatric-specific preventive measures, including vaccination and infection control strategies, in safeguarding the health and well-being of children [1].

While this study has limitations due to its single-institution scope and limited duration, it offers valuable data on the clinical characteristics of COVID-19 in Korean pediatric patients. The insights derived from this research can help reduce anxiety about COVID-19 infections in children. However, further large-scale domestic studies are necessary to validate these findings.

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Review article

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KMJ
KOSIN MEDICAL JOURNAL

Bone-modifying agents for bone metastasis in patients with breast cancer

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The bone is the most common location of breast cancer metastasis. Bone metastasis causes pain and skeletal-related events (SREs), and affects the quality of life and survival of breast cancer patients. Bone-modifying agents, including bisphosphonates and denosumab, reduce the risk of SREs in these patients. Among bisphosphonates, zoledronic acid is preferred due to its higher efficacy. Denosumab is marginally more effective than zoledronic acid in reducing the frequency of SREs. Patients with renal impairment should receive zoledronic acid with caution due to nephrotoxicity, and denosumab is an alternative option in these patients. Osteonecrosis of the jaw is a rare but severe complication of both zoledronic acid and denosumab, and all patients should undergo dental examinations before and during treatment. Although these drugs can reduce the risk of SREs in bone metastasis, no significant improvement in survival has been noted. This study reviews the effects and adverse events of bone-modifying agents for the treatment of bone metastasis from breast cancer.

Keywords: Bone neoplasm; Breast neoplasm; Diphosphonate; Denosumab

Introduction

Worldwide, breast cancer is the most common diagnosed cancer and the leading cause of cancer in women [1]. The bone is the most typical metastatic location in breast cancer, with bone metastasis developing in up to 75% of metastatic breast cancer patients [2]. Bone metastases are a major cause of a variety of morbidities and cause skeletal-related events (SREs) such as pain, pathologic fracture, spinal cord compression, and hypocalcemia [3]. The prognosis is poor once SREs develop in patients with bone metastasis. In a population-based cohort study, the 5-year survival rate of metastatic breast cancer patients was 8.3%, whereas that of patients with bone metastasis who developed SREs was 2.5% [4].

The management of patients with bone metastases aims to control symptoms, minimize the risk of SREs, stabilize the bone, and preserve and restore function [5]. Bone-modifying agents, bisphosphonates and denosumab, significantly reduce the risk of and delay SREs in patients with bone metastases from various cancer types, including breast cancer [6]. We here review the effects and adverse events of bone-modifying agents for the treatment of bone metastatasis from breast cancer.

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Mechanism of bone metastasis from breast cancer

Normal bones are continually remodeled, with osteoclasts responsible for bone resorption and osteoblasts responsible for the deposition of new bone. Osteolytic and osteoblastic bone metastases are typically classified on the basis of the radiologic findings, primarily bone destruction or new bone deposition. Approximately 80% of bone metastasis from breast cancer presents as osteolytic lesions, and osteoclasts are mainly responsible for bone resorption of osteolytic metastases. Numerous substances produced by breast cancer cells can directly or indirectly cause the production of osteoclasts, and growth factors that are released from the bone matrix during osteoclast-mediated bone resorption promote tumor growth and bone destruction. Several factors, including parathyroid hormone-related peptide, receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL), osteoprotegerin, transforming growth factor beta, and many other transcription factors, are implicated in this process. The RANKL/RANK system plays a particularly critical role in breast cancer development, both during initial tumorigenesis and secondary tumor formation [7-9].

Bone-modifying agents

Bisphosphonates

Bisphosphonates inhibit osteoclast activity and reduce bone resorption by inducing apoptosis in osteoclasts, which promotes mineralization. There are two types of bisphosphonates: non-nitrogen-containing and nitrogen-containing. Late-generation bisphosphonates (nitrogen-containing bisphosphonates including ibandronate, pamidronate, and zoledronic acid) exhibit a more potent osteoclast inhibitory effect than early-generation bisphosphonates (non-nitrogen-containing bisphosphonates including clodronate, and etidronate) [10,11].

Bisphosphonates prevent SRE, delay the time to SREs, relieve bone pain, and improve patients' quality of life (QOL). In a 2017 Cochrane review that analyzed the effects of bone-modifying agents for breast cancer treatment, bisphosphonates significantly reduced the absolute risk of SREs by 14% (risk ratios [RR], 0.86; 95% confidence interval [CI], 0.78–0.95) in breast cancer patients with bone metastasis, compared with placebo/no bisphosphonate. Furthermore, bisphosphonates significantly delayed the median time to SRE and improved bone pain and QOL compared with placebo or no bisphosphonate; however, there was no significant effect in terms of overall survival [12].

Compared with other bisphosphonates, zoledronic acid is preferred owing to better efficacy, compared with other bisphosphonates [13]. The ZICE trial, which directly compared between ibandronate and zoledronic acid, found that zoledronic acid was more effective at preventing SRE in metastatic breast cancer patients [14]. Although pamidronate and zoledronic acid resulted in equivalent efficacy in preventing SREs in a phase 3 trial, long-term follow-up data indicated that zoledronic acid was more beneficial for breast cancer patients with bone metastasis [15,16].

Denosumab

Denosumab, a fully human monoclonal anti-RANKL antibody, is another effective bone-modifying agent. The RANKL is a crucial component in the pathway for osteoclast formation and activation, and denosumab suppresses the RANKL/RANKL signaling-mediated bone resorption, decreasing bone turnover and leading to prevention of SREs in breast cancer [17,18]. Several randomized phase 3 clinical trials demonstrated denosumab was more effective than zoledronic acid in SRE prevention and pain reduction [19-22]. In a 2017 Cochrane review, denosumab reduced the risk of SRE compared with bisphosphonates by 22% (RR, 0.78; 95% CI, 0.72–0.85; p<0.001; three studies) in breast cancer patients with bone metastasis [12]. Patients receiving denosumab demonstrated greater clinical improvement in health-related QOL than those receiving bisphosphonates [23]. However, no significant difference was noted in terms of overall survival between patients receiving denosumab and bisphosphonate [12].

Dose interval

The approved dose and schedule of administration for zoledronic acid and denosumab are 4 mg every 3 or 4 weeks and 120 mg every 4 weeks, respectively. Recently, there is increasing interest in the de-escalation of bone-modifying agents (every 12-week schedule) for bone metastasis treatment.

The Zoom and the Optimize 2 trials compared the effica-

cy and safety of every 4-week versus every 12-week schedules of zoledronic acid after 10–15 months of previous bisphosphonate treatment in breast cancer patients with bone metastasis and showed that every 12-week schedule was not inferior to every 4-week schedule in preventing SREs [24,25]. Moreover, in a randomized phase 3 trial, Himelstein et al. [26] reported that compared with every 4-week schedule, the use of zoledronic acid every 12-week schedule for patients with bone metastasis with on previous zoledronic acid did not increase the risk of SREs. A recent meta-analysis, which compared every 4-week and every 12-week dosing intervals of bone-modifying agents in patients with breast cancer, confirmed that the de-escalation of zoledronate is a reasonable option for breast cancer patients with bone metastases [27]

Conversely, data supporting the de-escalation of denosumab are limited [27]. Currently, the REDISE trial of denosumab 120 mg every 4 weeks versus 12 weeks for the treatment of bone metastasis from breast and prostate cancer is ongoing, and the results of this study will inform the benefit of the de-escalation of denosumab.

Duration of treatment

There is no randomized clinical data on whether all patients with bone metastases should receive bone-modifying agents as soon as bone metastases are identified. A population-based cohort study in Denmark reported that breast cancer patients with bone metastases had a high incidence rate of SREs, especially in the first year after a diagnosis of bone metastases (38.5% at 1 year and 51.7% at 5 years) [28]. Additionally, other studies showed that the risk of symptomatic SREs was high in the first year after diagnosis of bone metastasis [19,29]. Therefore, the European Society for Medical Oncology (ESMO) 2020 guidelines recommend starting zoledronate or denosumab in all breast cancer patients with bone metastasis, whether they are symptomatic or not, at diagnosis of bone metastasis [30]. For patients starting bone-modifying agents, there is also no data on the optimal duration of treatment. According to a systemic review on the risk-benefit of bone-modifying agents for long-term duration in breast and prostate cancer, the risk of symptomatic SREs decreased with longer follow-up, while the risk of cumulative toxicities increased [6]. The ESMO 2020 guideline recommends that bone-modifying agents should be considered throughout the course of the disease in absence of excessive toxicity [30].

Adverse events of bone-modifying agents

Bone-modifying agents, bisphosphonate and denosumab, are associated with several adverse events including acute-phase reactions, hypocalcemia, nephrotoxicity, and osteonecrosis of the jaw (ONJ).

Acute-phase reactions are characterized by flu-like symptoms, including fever, chills, bone pain, headache, nausea, myalgias, and arthralgias [31]. In 15%–30% of patients who have not previously received bisphosphonates, intravenous (IV) administration of zoledronic acid and pamidronate can cause these reactions [19,21,31]. These symptoms generally occur in the first 3 days of treatment, resolve after a few days, and frequently do not recur with subsequent treatment. Acetaminophen or nonsteroidal anti-inflammatory drugs are effective in controlling symptoms [31].

Hypocalcemia is a common electrolyte abnormality associated with the use of bisphosphonates and denosumab. This is because these drugs inhibit the action of osteoclasts, which resorb bone and release calcium. In a combined analysis of randomized trials comparing denosumab and zoledronic acid, denosumab was associated with a higher incidence of hypocalcemia than zoledronic acid (16.0% vs. 7.2%), and serious hypocalcemia also occurred more frequently with denosumab (3% vs. 1%) [32]. Clinical features include lethargy, fatigue, general weakness, or tetany. Before initiating treatment, it is necessary to address preexisting hypocalcemia and potential vitamin D deficiency, and calcium and vitamin D supplementation is recommended for all patients unless there is a contraindication. Furthermore, serum calcium level monitoring is needed during treatment.

Nephrotoxicity is a well-known adverse event of IV bisphosphonates. Pamidronate and zoledronic acid are associated with renal insufficiency, and acute kidney injury has been reported more frequently with zoledronic acid [16,33]. Patterns of renal injury due to zoledronic acid and pamidronate include toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis, respectively [34]. Renal insufficiency is dependent on dose and infusion time and is mostly reversible following drug discontinuation but may be irreversible. In contrast, in a comparative trial, de-

nosumab showed a much lower nephrotoxicity than zoledronic acid; therefore, it may be beneficial for patients with preexisting renal insufficiency [19]. Renal function must be checked before initiating treatment of bisphosphonate, and close monitoring of renal function during treatment is needed. Bisphosphonate should be reduced or discontinued if creatinine level increases. For patients with underlying renal insufficiency, denosumab could be indicated.

ONJ is a relatively rare but potentially serious adverse effect of treatment with bisphosphonates or denosumab and pain, infection, and necrotic bone in the mandible or maxilla are usual symptoms of ONJ [31]. Although the pathogenesis of bone-modifying agent associated with ONJ remains not well understood, bone remodeling suppression, compromised angiogenesis, and infection are believed to be involved [35]. Denosumab has a slightly higher incidence of ONJ than bisphosphonates; however, a meta-analysis of several randomized trials comparing the safety and efficacy of denosumab and bisphosphonate showed that there was no difference in incidence of ONJ between the two groups [23]. The risk of ONJ increases with longer exposure duration, with a cumulative incidence of 0.7%–1.4% during the first year of treatment and increases to 2%–3.4% with continued treatment beyond 1 year [36]. Invasive dental procedures and poor oral hygiene are well-known risk factors for ONJ [31]. As this event is difficult to treat, strategies for preventing of ONJ is significant. All patients should undergo dental examination and complete any required invasive dental procedures before starting bone-modifying agents. A careful evaluation of patient's oral health is required during treatment of bone-modifying agent, and patients should maintain proper oral hygiene and avoid invasive dental procedures wherever possible.

Conclusion

Bone-modifying agents, bisphosphonate and denosumab, are effective in reducing SREs in breast cancer patients with bone metastasis; however, survival benefit are controversial. These agents are associated with several adverse events, some of which could be irreversible (renal insufficiency) or could cause serious outcomes (ONJ); therefore, caution is required before and during treatment. Moreover, to reduce adverse events and to improve survival and SREs using these drugs, further studies are needed.

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Treatment of pediatric obstructive sleep apnea

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In the majority of cases, pediatric obstructive sleep apnea (OSA) is associated with adenotonsillar hypertrophy. Therefore, adenotonsillectomy is typically considered as the first line of treatment. However, the severity of pediatric OSA is not always directly correlated with the size of the adenoids and tonsils. Other factors, such as upper airway anatomy or obesity, may interact in a multifactorial manner to contribute to its occurrence. For these reasons, sleep apnea in obese children may resemble the condition in adults. Furthermore, in these cases, if adenotonsillar hypertrophy is present, adenotonsillectomy is likely to be prioritized. Reevaluation should be conducted 6 to 8 weeks post-surgery, and additional treatment for residual sleep apnea should be performed thereafter when necessary.

Keywords: Adenoids; Palatine tonsil; Sleep apnea

Introduction

Sleep-related respiratory disorders in pediatric populations encompass a spectrum of conditions, ranging from neonatal apnea to pediatric sleep-related breathing disorders, encompassing all of the manifestations that occur during sleep. Therefore, understanding pediatric sleep-related breathing disorders requires knowledge not only of the anatomical characteristics of the pediatric respiratory system, but also of the physiology of sleep. Specifically, obstructive sleep apnea (OSA) occurs when the physiological balance is disrupted, resulting from a complex interplay of anatomical and physiological factors. The primary anatomical factor of OSA is hypertrophy of the tonsils and adenoids. Particularly in pre-school-aged children, anatomically narrow airways and relatively large tonsils and adenoids are the predominant contributors to this disorder. Moreover, the upper airway contains numerous proprioceptors that regulate muscle tone, the loss of which leads to reduced muscle tone during the onset of sleep, resulting in increased upper airway resistance. Consequently, individuals with neuromuscular disorders are at an increased risk of developing OSA due to decreased muscle tone (Table 1) [1,2].

In 2012, the American Academy of Pediatrics published guidelines for the treatment of pediatric OSA [3]. These guidelines primarily focus on the regulation of hypertrophic lymphoid tissues and positive airway pressure (PAP) therapy. Key treatments outlined include adenotonsillectomy, PAP therapy, weight loss, and pharmacotherapy [1]. However, various other treatments, including orthodontic treatment, high-flow nasal cannula treatment, myofunctional therapy, and upper airway surgeries, are also currently being employed for the clinical management of pediatric OSA [4].

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Table 1. Representative disorders or conditions predisposing to obstructive sleep apnea in childhood

A. Adenotonsillar hypertrophy or allergic rhinitis
B. Obesity
C. Special craniofacial characteristics or profound craniofacial anomalies
Small mandible with/without mandibular malpositioning
Narrow nasomaxillary complex with/without high and narrow hard palate
Marked nasomaxillary (midface) deficiency (e.g., Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, repaired cleft palate)
Marked mandibular hypoplasia (e.g., Pierre Robin sequence, severe juvenile rheumatoid arthritis, Treacher Collins syndrome, Nager syndrome, Stickler syndrome)
D. Abnormal neuromotor tone or control of breathing
Cerebral palsy
Duchenne muscular dystrophy
E. Combinations of the above disorders or conditions
Down syndrome
Achondroplasia
Prader-Willi syndrome
Mucopolysaccharidoses

Tonsillectomy and adenoidectomy

Tonsillectomy and adenoidectomy are widely recognized as the most effective primary treatment for OSA [5]. The success rate of this surgery in children with OSA is approximately 79%, significantly higher than the 46% success rate observed in individuals managed by observation alone (i.e. without surgery). However, in high-risk groups with severe obesity, craniofacial anomalies, or neuromuscular disorders, there is a higher likelihood of persistent symptoms or recurrence of OSA even after successful surgery. Additionally, surgical interventions carry inherent risks. Therefore, in high-risk cases, the benefits of surgery must be carefully weighed, and continuous postoperative monitoring for recurrence is crucial.

With the exception of postoperative pain, complications following surgery for OSA are rare and typically minor. However, serious complications, such as excessive bleeding from the surgical site, pulmonary edema, and airway obstruction, can occur, with an incidence of 1 in 16,000 to 35,000 cases resulting in postoperative complications. The criteria for high-risk groups of surgical complications include an age of less than 3 years, craniofacial anomalies affecting the upper airway, growth disorders, muscle tone abnormalities, obesity, neuromusculoskeletal disorders, cardiovascular complications of OSA (right ventricular hypertrophy and pulmonary hypertension), a history of upper airway trauma, concomitant tonsillectomy and adenoidectomy with craniofacial surgery, and respiratory infections. According to polysomnography criteria, individuals with severe OSA (apnea hypopnea index ≥10 or minimum arterial oxygen saturation <80%, or both) are considered to be at high-risk for complications after tonsillectomy and adenoidectomy [6].

In efforts to reduce postoperative complications, various surgical techniques employing different instruments, including radiofrequency, microdebrider, coblator, and harmonic scalpel, have been introduced. Partial intracapsular tonsillectomy and adenoidectomy (PITA), which entails less bleeding and pain, is also a treatment option. However, it is noted that PITA may lead to tonsillar tissue regrowth and the potential for the recurrence of OSA [7].

PAP therapy

Following tonsillectomy and adenoidectomy, residual OSA persists in 13% to 29% of low-risk pediatric patients. In high-risk pediatric populations, such as those with obesity, neuromuscular disorders, or conditions like Down syndrome (trisomy 21), over 70% may continue to exhibit OSA even after surgery. Additionally, children who refuse surgery or have contraindications to general anesthesia cannot undergo tonsillectomy and adenoidectomy. In these cases, the most effective treatment option is PAP therapy [8].

Although PAP therapy has in use for over 30 years, in recent years its usage has increased over 3-fold compared to previous rates of intervention. At present, various types of PAP devices are available in children, including auto-titrating PAP, continuous PAP (CPAP), and bilevel PAP (BiPAP). However, CPAP or BiPAP are predominantly used. The selection of the PAP device based on an individual patient's needs can enhance compliance. The types and indications of PAP therapy for pediatric OSA treatment are as follows (Table 2). To determine the appropriate pressure for CPAP therapy, a sleep study needs to be conducted. Unlike in adults, split-night polysomnography is not typically performed in children to determine optimal pressure, as the sudden application of a mask during the study can negatively affect compliance. Thus, gradual adaptation to

Table 2. PAP devices used in pediatric patients

Mode	Primary indication and clinical utility
CPAP: Fixed-pressure CPAP	OSA
Auto-CPAP: Auto-titrating CPAP mode	1. OSA 2. Positional or REM-related OSA 3. PAP therapy acclimatization prior to PSG 4. CPAP patients with sudden changes in OSA severity due to surgery or rapid weight change
BiPAP-S: Spontaneous BiPAP mode	Patients with OSA who are intolerant to CPAP at high pressures due to discomfort exhaling, not mitigated by comfort features
Auto-BiPAP: Auto-titrating BiPAP mode	1. Positional or REM-related OSA where patient is intolerant to high Auto-PAP pressures 2. BiPAP therapy acclimatization prior to PSG
BiPAP-ST: Spontaneous-timed BiPAP mode	Children with OSA who present with mixed apnea, CPAP emergent central apnea, or persistent hypoventilation following resolution of OSA with CPAP
VAPS: VAPS BiPAP mode	Obesity hypoventilation syndrome Congenital central hypoventilation syndrome

PAP, positive airway pressure; CPAP, continuous PAP; OSA, obstructive sleep apnea; REM, rapid eye movement; PSG, polysomnography; BiPAP, bilevel PAP; VAPS, volume-assured pressure support.

wearing the mask followed by titration polysomnography for pressure adjustment is recommended [9].

A significant challenge of PAP therapy in children is lower compliance compared to adults. Children in their growth phase require periodic mask replacement due to facial skeletal growth. Furthermore, pressure caused by the mask may adversely affect facial bone development. Moreover, parental involvement is essential, necessitating education for parents and caregivers. Recent advances in interfaces have somewhat improved comfort with PAP therapy, making it effectively implementable even in infants and adolescents [10].

Weight loss

While there is a substantial amount of evidence indicating that surgical or nonsurgical weight loss improves OSA in adults, literature regarding the effects of weight loss on pediatric OSA improvement is somewhat limited. That being said, overall, studies recommend weight loss for obese patients with pediatric OSA [11,12]. In cases of severely obese patients with pediatric OSA where weight loss is unsuccessful, bariatric surgery may be considered, although this option should be evaluated carefully before proceeding [13,14].

Medical treatment

In the treatment of OSA, pharmacotherapy aims to reduce the size of the tonsils and adenoids. An increase in the expression of leukotriene receptor 1, 2, and leukotriene C4 synthase has been reported in the tonsillar tissue of patients with pediatric OSA compared to that in healthy children. Several clinical studies have reported on the efficacy of the leukotriene receptor antagonist montelukast in pediatric OSA [15]. Nasal corticosteroids have also been reported to be effective in the treatment of pediatric OSA, as their anti-inflammatory action is known to reduce the size of the tonsils and adenoids [16]. Although some studies have reported on the effects of combined therapy with these two drugs, further research is needed to fully ascertain the benefits of combination therapy. Therefore, montelukast or nasal corticosteroid therapy may be considered as an alternative treatment for pediatric OSA in cases where surgery is not feasible, as well as in mild cases.

Other treatment methods

Orthodontic interventions targeting malocclusion and maxillofacial anomalies are also associated with the treatment of OSA. Dental orthodontic treatments applied to pediatric OSA include rapid maxillary expansion, intraoral appliances, midface distraction osteogenesis, and mandibular osteotomies [17,18]. Various studies have reported on the effectiveness of orthodontic treatment in increasing airway volume and improving OSA. Among these, intraoral appliances and rapid maxillary expansion are commonly

employed methods. In particular, rapid maxillary expansion may be considered as a primary treatment method for patients with pediatric OSA with midface hypoplasia in the central one-third of the face, narrow and high palates, and submerged maxillary arches with associated malocclusion, provided there is no obesity or adenotonsillar hypertrophy (grade 1) [19]. In children, rapid maxillary expansion is typically performed without surgery using dental orthodontic appliances, applying force directly to the teeth and maxilla using expanders with multiple arms. Surgical intervention may be necessary after midpalatal suture fusion [19]. In cases of persistent OSA, an evaluation for multilevel obstruction should be conducted following adenotonsillectomy and orthodontic treatment. Depending on the case, additional interventions, such as uvulopalatal flap, lingual tonsillectomy, or nasal surgery, may need to be performed.

Intraoral appliances are suitable for mild to moderate OSA and are usually applied after any permanent dentition has erupted. Upper airway myofunctional therapy strengthens upper airway muscles through exercises involving the tongue, soft palate, facial muscles, and mandible to alleviate OSA. Recently, passive upper airway myofunctional therapy using intraoral appliances for mandibular advancement has been introduced as a treatment option for OSA [20]. While upper airway myofunctional therapy is effective for patients with mild OSA, compliance remains a limitation of this approach [21,22]. High-flow nasal cannula therapy delivers humidified air to the upper airway through a nasal cannula and can be considered as an alternative therapy for infants or children with maxillofacial developmental anomalies who cannot tolerate mask-based therapies, such as CPAP [23].

In cases of severe respiratory distress due to upper airway obstruction that poses a life-threatening situation, in addition to being unresponsive to other methods, such as CPAP, a tracheostomy may be warranted [24].

Conclusions

Adenotonsillar hypertrophy and obesity represent the predominant predisposing factors for OSA syndrome in pediatric populations, often accompanied by significant morbidity. Common treatment modalities include adenoidectomy alone or in combination with tonsillectomy, intranasal corticosteroids, oral appliances, and nasal CPAP. In cases of severe upper airway obstruction where other interventions prove ineffective in establishing airway patency, tracheostomy remains a crucial and urgent intervention.

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Surgical management of recurrent laryngeal nerve invasion by papillary thyroid carcinoma

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Preservation of the recurrent laryngeal nerve (RLN) is a priority for surgeons during thyroidectomy in patients with papillary thyroid carcinoma (PTC). RLN invasion by PTC in a patient presenting with preoperative vocal fold paralysis may require resection of the nerve with the tumor. However, the decision should be made regarding whether to preserve or sacrifice a functioning RLN invaded by PTC. Under certain conditions, preservation of the nerve with incomplete tumor resection could be considered. An RLN that has been resected due to PTC invasion may be managed by various reinnervation techniques to improve vocal outcomes. This article reviews clinical considerations and rationales for surgical decisions related to patients with PTC invasion of the RLN.

Keywords: Neuromuscular monitoring; Recurrent laryngeal nerve; Thyroid neoplasms; Thyroidectomy

Introduction

Recurrent laryngeal nerve (RLN) invasion by papillary thyroid carcinoma (PTC) can occur either from the primary tumor or the lymph node metastasis. Invasion of the RLN may be identified in 33% to 61% of patients with local invasion of PTC into surrounding organs [1-3]. Since the RLN may be difficult to identify on preoperative imaging studies, the anatomy of the RLN should be considered when the primary PTC or metastatic lymph node is located along the tracheoesophageal groove. The right RLN comes from the vagus nerve looping more laterally at the subclavian artery. Hence, a tumor located in the right posterior lower lobe could also have invasion of the RLN [4].

Up to 68% of patients with RLN invasion might have normal vocal fold movement [4,5]. Therefore, clinical suspicion based on preoperative imaging studies and preparation for possible RLN injury/resection and patient counseling is mandatory if nerve invasion is predicted. A surgical strategy on whether to preserve or sacrifice a functioning RLN invaded by PTC needs to be established before the surgery. The decision may be controversial because previous studies have reported that invasion of the RLN showed no independent impact on survival outcomes in patients with PTC [1]. In addition, there have been controversial outcomes regarding the survival benefit of RLN resection in patients with locally invasive PTC [6-8]. Moreover, the feasibility and oncologic safety of incomplete tumor removal (R2 resection) to preserve the RLN with local invasion has been reported [9,10].

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Therefore, patients with PTC invasion of the RLN require a thorough preoperative evaluation and preparation followed by an appropriate intraoperative decision for both oncologic safety and functional outcomes. In this article, clinical considerations and rationales for surgical decisions related to patients with PTC invasion to the RLN will be reviewed.

Preoperative laryngeal evaluation

Preoperative laryngoscopy to examine the vocal function is recommended to identify any vocal fold paresis or paralysis [2,11]. It has been reported that 70% of patients with preoperative vocal fold paralysis (VFP) undergoing thyroidectomy were diagnosed with invasive thyroid cancer [12]. On the other hand, almost one-third of patients with VFP after thyroidectomy showed normal vocal function, thereby showing the necessity of a laryngoscope exam to detect neural dysfunction [13,14]. Moreover, Newman et al. [4] reported that almost one-third of patients had normal vocal fold mobility despite gross invasion of the RLN. Thus, laryngeal examination may be mandatory to check preoperative vocal fold function. Ultrasonography could be considered as an alternative method to examine the vocal function [15].

Preoperative imaging study

Ultrasound image presenting a tumor with protrusion into the tracheoesophageal groove was reported to have a diagnostic accuracy of 96.3% to predict RLN invasion by thyroid cancer [16]. Loss of normal thyroid tissue between cancer and the tracheoesophageal groove may also be an ultrasonographic finding of thyroid cancer with RLN invasion (Fig. 1). Seo et al. [17] reported that computerized tomography (CT) showed a sensitivity, specificity, and accuracy of 78.2%, 89.8%, and 85.5%, respectively, for invasion of the RLN. The kappa value presenting the interobserver variability was 0.7546, showing a substantial agreement. The CT findings suggesting RLN invasion were completely effaced fatty tissue in the tracheoesophageal groove, greater than 25% of the circumference of the tumor abutting the capsule at the posterior portions of the thyroid [18]. Magnetic resonance imaging could also suggest findings for suspected invasion to the RLN [19]. However, another study found that imaging studies may predict extension of thyroid cancer to the RLN in only one-quarter (26.7%) of patients [4].

Patient education and informed consent

Meticulous preoperative evaluation and imaging may suggest possible invasion of the RLN by thyroid cancer. Potential risk of RLN invasion should be explained to the patient with possible temporary/permanent VFP from traction injury or permanent VFP due to resection of the nerve invaded by the tumor [2,11]. Possibility of bilateral VFP (with tracheostomy) and staging the surgery to prevent such complication should be included in the informed consent. In the case of RLN resection, the reinnervation procedure, postoperative rehabilitation and expected outcomes need to be explained. In the case of a patient with a functioning RLN potentially invaded by cancer, preservation of the nerve even with microscopic or macroscopic residual tumor could be discussed with the patient considering the age, occupation, and personal preference of the patient [10,11].

Intraoperative decision (preservation versus resection of RLN)

In patients presenting preoperative VFP due to gross invasion of thyroid cancer, resection of the nerve with removal

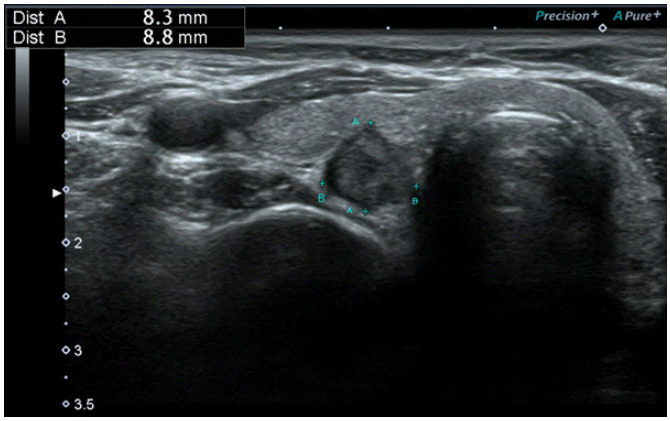

Fig. 1. Ultrasound image of a patient with suspected invasion of the recurrent laryngeal nerve by a papillary thyroid carcinoma. Protrusion of the tumor into the right tracheoesophageal groove and partial loss of normal thyroid tissue between cancer and the tracheoesophageal groove can be seen. The photograph was provided by the author, Hyoung Shin Lee.

of the tumor should be considered [2,11]. However, the decision to preserve or sacrifice a functioning RLN invaded by PTC is controversial. This may be due to the lesser impact of RLN invasion on oncologic outcome compared to invasion of other organs categorized as T4a. Some authors have even suggested that it may be more appropriate to consider RLN invasion as the T3b category [11]. Invasion of RLN does lead to higher risk of recurrence, but to a lesser degree than tracheal or esophageal invasion [20]. In addition, RLN invasion showed no significant impact on survival of patients with PTC [1]. Moreover, resection of a RLN invaded by PTC had no advantage to improve recurrence-free survival [5,6,9], disease-specific survival [21], and overall survival [22].

Accordingly, the consensus of the American Head and Neck Society (AHNS) states that PTC may be shaved off to preserve a functioning RLN if all gross tumors are removed [2]. Macroscopic completeness of tumor resection may be achieved if tumor involvement of the nerve is confined to the epineurium [11]. However, preservation of the RLN may be impossible if the tumor involves the perineurium and endoneurium. Wu et al. [11] proposed that there may be factors to consider in favor of preserving the RLN even if the tumor undergoes incomplete resection with small remnant followed by adjuvant therapy: (1) young patients and voice professionals or those with preference to preserve their vocal function; (2) elderly patients and those with reduced pulmonary function leading to higher risk of aspiration pneumonia; (3) patients with contralateral VFP at risk of bilateral VFP; (4) active distant metastasis; and (5) generally iodine-avid patients when efficiency of adjuvant treatment is judged to be good.

Lee et al. [10] recently reported that shaving the tumor with gross residual tumor (incomplete tumor resection) smaller than 1 cm in length and 4 mm in thickness followed by high-dose radioactive iodine ablation (RAI) led to acceptable oncologic and functional outcomes. All the patients underwent more than one RAI treatment (>100 mCi), and 61.7% underwent two RAI treatments. Among the 47 patients with isolated invasion of the RLN (excluding patients with invasion of the trachea or esophagus), 10.6% showed recurrence with lymph node metastasis with no death or distant metastasis. The nerve was resected only in one case (2.1%) due to progression of the residual tumor. There were no patients with permanent VFP, with six cases (12.8%) of temporary VFP. The final non-stimulated serum thyroglobulin was 0.7±1.8 ng/mL. On the other hand, partial resection of the RLN has been suggested by Kihara et al. [23]. They applied this technique to patients with the thickness of the preserved RLN less than half of its original size. Among 18 patients, 83% of the patients had functioning vocal folds 1 year after surgery presenting nearly normal phonation. Based on these studies and alternate adjuvant treatments such as RAI, T3 suppression, radiotherapy, and tyrosine kinase inhibitors, attempts to spare a functioning RLN invaded by PTC could be considered, and its oncologic safety should be confirmed in further studies [11].

Role of intraoperative neuromonitoring

The AHNS recommended intraoperative neuromonitoring (IONM) in all cases of invasive differentiated thyroid carcinoma [2]. IONM is helpful for identification and preservation the RLN during thyroidectomy [24]. It may predict postoperative vocal fold function, prevent bilateral VFP or predict the necessity for tracheostomy [11]. The International Neural Monitoring Study Group [11] introduced a management algorithm in patients with ipsilateral preoperative VFP. They suggested performing contralateral RLN dissection first and proceeding to the invaded side if the nerve is well preserved (no loss of signal). The proximal electromyogram data could be considered for decisions on preservation or sacrifice of the RLN in patients with preoperative VFP. Since one-third of patients with abnormal laryngoscope findings may maintain stimulability with IONM, resecting an RLN with proximal stimulability may lead to deterioration of dysphonia and dysphagia [11].

Reinnervation of the RLN

In patients with anticipated resection of the RLN, reinnervation should be prepared before surgery [2]. Reinnervation of the RLN also should be considered for patients with preoperative VFP due to PTC invasion since it led to improved vocal outcomes and spared the need for laryngeal framework surgery [25]. Methods of reinnervation include direct anastomosis, free nerve grafting, ansa cervicalis to RLN anastomosis, and vagus to RLN anastomosis [2,25-27]. Reinnervation can restore the muscle tone of the paralyzed vocal fold and thereby improve vocal outcomes [25-27].

The reinnervated vocal fold is fixed at the median, but may restore its tension and recover from atrophy, leading to reduced vocal gap and enhanced tension between vocal folds [26].

Conclusion

Preoperative imaging and laryngoscopy should be reviewed thoroughly to identify possible RLN invasion by PTC. Informed consent should be obtained for possible resection/reinnervation of the RLN or preservation of the nerve with microscopic/macroscopic residual tumor and necessity of adjuvant treatment. IONM may be helpful to preserve the nerve during tumor dissection and aid in intraoperative decisions regarding surgical extent. The limited impact of isolated RLN invasion by PTC on oncologic outcomes and the uncertain benefit of resecting the RLN due to tumor invasion should be considered by clinicians when facing the decision of whether to preserve or sacrifice the nerve.

Article information

Conflicts of interest

Hyoung Shin Lee is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Clinical features of coronavirus disease 2019 in Korean pediatric patients: a single-center retrospective study

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Background: To address the public's fear of coronavirus disease 2019 (COVID-19), understanding the clinical features of the disease is essential. However, research on the clinical features of COVID-19, including illness duration and post-acute COVID-19, in Korean pediatric patients has been limited. Therefore, this study investigated the clinical features of COVID-19 based on the medical records of pediatric patients with a history of COVID-19 who visited a single center.

Methods: In total, 311 patients were included in this study. The presence and duration of 19 symptoms were examined. Additionally, clinical features were investigated by dividing the patients into different age ranges. Patients aged 6 and above were further categorized according to the presence of asthma, while adolescent patients were divided into vaccinated and unvaccinated groups.

Results: Fever and cough were the most common symptoms. The mean illness duration was 2–4 days. Only 3.5% of the patients were asymptomatic. Post-acute COVID-19 was observed in 13.2% of the patients. The incidence of most symptoms tended to increase with age. Post-acute COVID-19 was observed more frequently in patients with asthma than in those without asthma. Vaccinated patients experienced less fever, vomiting, and fatigue than unvaccinated patients.

Conclusions: Our data suggest that most patients had mild disease lasting less than a week, and the clinical course may differ depending on the presence of asthma. The findings also indicate that vaccination may alleviate the symptoms of COVID-19 in breakthrough infections.

Keywords: Adolescent; Child; COVID-19; Korea; Signs and symptoms

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization declared COVID-19 pandemic on March 11, 2020 [1]. In Korea, the number of daily confirmed cases reached a maximum of 621,035 in mid-March 2022 and gradually decreased afterwards; however, it saw a resurgence beginning in the summer of 2023, coinciding with the relaxation of the mask mandate. According to the Korea Disease Control and Prevention Agency (KDCA), as of August 31, 2023, the cumulative number of confirmed cases stood at 34,571,873. Among them, 3,270,242 involved children aged 0–9 years, and 4,246,913 involved children aged 10–19 years, accounting for 19% of the total cumulative cases [2].

Pediatric patients with COVID-19 experience a milder course of the disease than that in adults [3,4]. However, anxiety surrounding COVID-19 has become widespread due to disruptions in daily routines. A study on anxiety among

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Korean adolescents during the COVID-19 pandemic found that the fear of infection was one of the factors related to anxiety [5]. One of the contributing factors to this fear of COVID-19 is ignorance about the disease. To overcome this fear, the public and physicians must possess sufficient knowledge about COVID-19 [6].

Hence, this study aimed to provide a trigger point for research on the general course of COVID-19 in children and adolescents in Korea by investigating the clinical features of patients with a history of COVID-19 who visited a single healthcare center.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Daegu Catholic University Medical Center (IRB No: CR-22-135). The requirement for patient consent was waived because this study was a retrospective chart review study in which there are minimal risks to subjects.

1. Patients and study design

Among patients who visited the outpatient clinic of the Department of Pediatrics at Daegu Catholic University Medical Center from March 1 to May 31, 2022, we screened 317 patients under the age of 20 who reported having previously been diagnosed with COVID-19 using SARS-CoV-2 rapid antigen kit for professional use or polymerase chain reaction. We excluded four patients within 7 days of the COVID-19 diagnosis because the follow-up period was too short and could provide inaccurate information about the presence or duration of symptoms. Two patients suspected of having other superimposed infections within 1 week before and after the COVID-19 diagnosis were also excluded. Finally, 311 medical records were analyzed retrospectively. The following demographic data and clinical symptoms were obtained from the electronic medical records: sex, age, history of vaccination against COVID-19, fever, cough, runny or stuffy nose, dyspnea, chest discomfort, chest pain, myalgia, headache, dizziness, sore eyes, sore throat, nausea, vomiting, abdominal pain, diarrhea, loss of smell, loss of taste, fatigue, COVID-19-associated hospitalization, and underlying diseases. Loss of smell and taste included both partial and complete loss. Clinical symptoms that rely on verbal expression capability were evaluated for individuals aged 3 years and older. Underlying diseases were evaluated based on medical records; however, only patients who reported being diagnosed with asthma and whose bronchial hyperresponsiveness was confirmed through a methacholine provocation test were classified into the asthma group. Bronchial hyperresponsiveness was defined as a provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 second (PC20) ≤16 mg/mL [7]. Patients with no history of asthma in their medical records were classified into the non-asthma group. Post-acute COVID-19 was defined as the persistence of one or more clinical symptoms for over 4 weeks [8].

Patients were divided into infant and toddler (aged 0–2), preschooler (aged 3–5), middle childhood (aged 6–11), and adolescent (aged 12 years and older) groups to compare the symptoms of COVID-19 by age. In addition, children aged 6 years and older were divided into an asthma group and a non-asthma group, while adolescents were divided into a vaccinated group that had completed two primary doses and an unvaccinated group that had not. The clinical features of the two groups were compared.

2. Statistical analysis

The chi-square test was used to compare categorical variables. The Fisher exact test was performed if more than 20% of the cells had an expected frequency of less than five. When comparing continuous data from the two groups, the independent samples *t*-test was performed if the distribution of the variable was normal, and the Mann-Whitney *U* test was used if the distribution was not normal. The one-way analysis of variance was performed to compare normally distributed continuous variables between three or more groups, and the Kruskal-Wallis test was used to compare non-normally distributed continuous data. Post-hoc analysis was performed to compare three or more groups. Variables with fewer than 20 available data points in any group were not analyzed to achieve alpha levels of 0.05 and 80% power when comparing the groups. The Cochran-Armitage trend test was used to analyze trends between age categories.

When comparing the asthma and non-asthma groups, age and sex were adjusted for using 1:1 propensity score matching.

When comparing the vaccinated and unvaccinated groups, propensity score matching could not be performed

because the number of unvaccinated participants was smaller than the number of vaccinated participants. Therefore, to adjust for age and sex in the clinical features that showed differences in the univariate analysis, age, sex, and vaccination history were added as covariates, and multivariate regression analysis was performed.

Statistical analyses were performed using IBM SPSS Statistics version 25.0 software (IBM Co.) and R version 4.2.0 software package (R Project for Statistical Computing). A *p*-value less than 0.05 was considered statistically significant. When post-hoc analysis was performed, the Bonferroni correction was applied to adjust for type I errors. A *p*-value <0.008 in the comparison of the four groups and a *p*-value <0.017 in the comparison of the three groups were considered statistically significant.

Results

1. Characteristics of the study population

Table 1 presents the demographic characteristics of the 311 patients included in this study. The median age was 8 years. Considering age categories, those aged 6–11 was the majority (48.9%), followed by those aged 12 and older, those aged 3–5 years, and those aged 0–2 years. One hundred and sixty-seven participants (52.7%) were male. The median duration from COVID-19 diagnosis to the clinic visit was 30 days (interquartile range [IQR], 20–44 days).

According to reports from patients or caregivers, the most common sources of infection were educational institutions or childcare centers (43.4%) and family or relatives (37.3%). Six infections occurred in public places: two in restaurants, three in hospitals, and one in a swimming pool. Concurrent COVID-19 illness in families or cohabitators occurred in 90% of patients.

South Korea has approved the use of SARS-CoV-2 vaccine for children aged 12 years and older since Oct 2021 [9]. Of 73 patients eligible for vaccination, 42 patients (58%) had been vaccinated. Most of those vaccinated patients had completed two primary vaccinations, and three had received booster doses.

The most frequently reported underlying disease was allergic rhinitis (39.2%), followed by precocious puberty (14.8%). All children with immunodeficiency exhibited selective IgG3 deficiency. Genetic comorbidities were Marfan syndrome in one patient, Prader–Willi syndrome in one patient,

Table 1. Demographic characteristics

Characteristic	Value (n=311)
Age at diagnosis (yr)	8 (5–11)
Age category	
0–2 yr	34 (10.9)
3–5 yr	52 (16.7)
6–11 yr	152 (48.9)
≥12 yr	73 (23.4)
Male sex	164 (52.7)
Duration from diagnosis of COVID-19 to clinic visit (day)	30 (20–44)
Probable source of infection	
Education or childcare system	135 (43.4)
Family or relatives	116 (37.3)
Public spaces	6 (1.9)
Unknown	54 (17.4)
Family or cohabitor's history of concurrent COVID-19	
Yes	280 (90.0)
No	25 (8.0)
Unknown	6 (1.9)
Vaccination (n=73)[a]	
Yes	42 (57.5)
No. of vaccinations among those vaccinated	
1	1 (2.4)
2	38 (90.5)
3	3 (7.1)
No	30 (41.1)
Unknown	1 (1.4)
Underlying disease	
Preterm	43 (13.8)
Bronchial asthma	53 (17.0)
Allergic rhinitis	122 (39.2)
Atopic dermatitis	47 (15.1)
Chronic urticaria	5 (1.6)
Postinfectious bronchiolitis obliterans	27 (8.7)
Immunodeficiency	5 (1.6)
Precocious puberty	46 (14.8)
Other endocrine diseases[b]	43 (13.8)
Primary amenorrhea	1 (0.3)
Diseases of the digestive system[c]	3 (1.0)
Epilepsy	5 (1.6)
Muscular dystrophy	1 (0.3)
Hypertension	1 (0.3)
Orthostatic proteinuria	1 (0.3)
Developmental delay	17 (5.5)
Genetic disease	6 (1.9)

Values are presented as median (interquartile range) or number (%).
COVID-19, coronavirus disease 2019.
[a]Considering South Korea's vaccination approval requirements, only those aged 12 or older were analyzed.
[b]This category included 20 patients with growth hormone deficiency, 17 patients with thyroid diseases, three patients with diabetes mellitus, two patients with congenital adrenal hyperplasia, and one patient with hereditary hypertriglyceridemia.
[c]This category included two patients with fatty liver and one patient with Crohn's disease.

Wolf–Hirschhorn syndrome in one patient, Lamb–Shaffer syndrome in one patient, and 3p deletion syndrome in one patient. Thirty-eight patients had no underlying disease.

2. Clinical manifestations

The most common clinical symptom was fever, observed in 263 patients (84.6%), followed by cough (76.2%) and sore throat (56.7%). Rhinorrhea and nasal stuffiness occurred in 44.7% and 46.3% of the patients, respectively. Symptoms lasted for 2–4 days and improved within 7 days. Eleven patients (3.5%) remained asymptomatic. Forty-one patients (13.2%) developed post-acute COVID-19 (Table 2). Hospitalization occurred in four cases, with stays lasting 7 days in two cases, 6 days in one case, and 4 days in one case. Among the 311 patients, 18 were diagnosed with overlapping clinical syndromes. Overlapping syndrome included croup and bronchitis in five patients each, asthma exacerbation in four patients, acute pharyngitis in one patient, and acute gastroenteritis in one patient.

When evaluating patients with post-acute COVID-19, the most prevalent symptom reported was persistent coughing, observed in 26 out of 41 cases (63%). This was followed by fatigue in eight patients (20%), nasal stuffiness in six patients (15%), and headache and rhinorrhea in four patients (10%). Other symptoms included loss of taste, chest discomfort, nausea, sore throat, dyspnea, loss of smell, diarrhea, abdominal pain, dizziness, and myalgia. In addition, one patient reported only a feeling of sputum production lasting more than 4 weeks without any other symptoms (Fig. 1).

3. Clinical features by age category

The symptoms were compared by dividing the patients into four age groups. Fever was significantly less frequent at 12 years of age and older than at 3–5 years of age (p<0.008) and showed a tendency to decrease as age increased (p=0.013). The incidences of cough, nasal stuffiness, chest discomfort, myalgia, headache, dizziness, sore eyes, sore throat, nausea, loss of smell, and loss of taste increased with age. There was no trend in rhinorrhea according to age category, but the 6- to 11-year-old group showed a significantly lower incidence rate than the other groups (p<0.008). The incidence rates of dyspnea, chest pain, vomiting, abdominal pain, diarrhea, and asymptomatic presentation did not differ between the age categories, and there was no trend. The frequency of post-acute COVID-19 tended to increase with age; however, there was no significant

Table 2. Clinical manifestations of the analyzed patients

Variable	No. of patients with data available	No. (%) or median (IQR)
Fever	311	263 (84.6)
Peak value	258	39.0 (38.5–39.8)
Duration (day)	256	2.0 (2.0–3.0)
Cough	311	237 (76.2)
Duration (day)	195	4.0 (2.0–7.0)
Rhinorrhea	311	139 (44.7)
Duration (day)	127	4.0 (3.0–7.0)
Nasal stuffiness	311	144 (46.3)
Duration (day)	133	3.0 (2.5–6.0)
Dyspnea	310	20 (6.5)
Duration (day)	18	3.0 (2.0–5.5)
Chest discomfort[a)]	277	22 (7.9)
Duration (day)	18	3.0 (2.8–7.0)
Chest pain[a)]	277	16 (5.8)
Duration (day)	15	3.0 (2.0–7.0)
Myalgia[a)]	277	69 (24.9)
Duration (day)	64	3.0 (2.0–3.0)
Headache[a)]	277	101 (36.5)
Duration (day)	92	3.0 (2.0–3.0)
Dizziness[a)]	277	61 (22.0)
Duration (day)	58	3.0 (2.0–3.0)
Sore eyes[a)]	277	12 (4.3)
Duration (day)	12	2.5 (1.3–5.0)
Sore throat[a)]	277	157 (56.7)
Duration (day)	150	3.0 (3.0–5.0)
Nausea[a)]	277	32 (11.6)
Duration (day)	30	2.0 (2.0–3.0)
Vomiting	311	31 (10.0)
Duration (day)	30	1.5 (1.0–2.3)
Abdominal paina)	277	29 (10.5)
Duration (day)	27	2.0 (2.0–3.0)
Diarrhea	311	44 (14.1)
Duration (day)	43	2.0 (2.0–4.0)
Loss of smell[a)]	276	17 (6.1)
Duration (day)	15	4.0 (2.0–8.0)
Loss of taste[a)]	277	33 (11.9)
Duration (day)	27	4.0 (2.0–7.0)
Fatigue[a)]	277	88 (31.8)
Duration (day)	77	4.0 (3.0–7.0)
Asymptomatic	311	11 (3.5)
Post-acute COVID-19	311	41 (13.2)
Hospitalization	311	4 (1.3)
Overlapping clinical syndromes	311	18 (5.8)

IQR, interquartile range; COVID-19, coronavirus disease 2019.
[a)]Only 3 years or older.

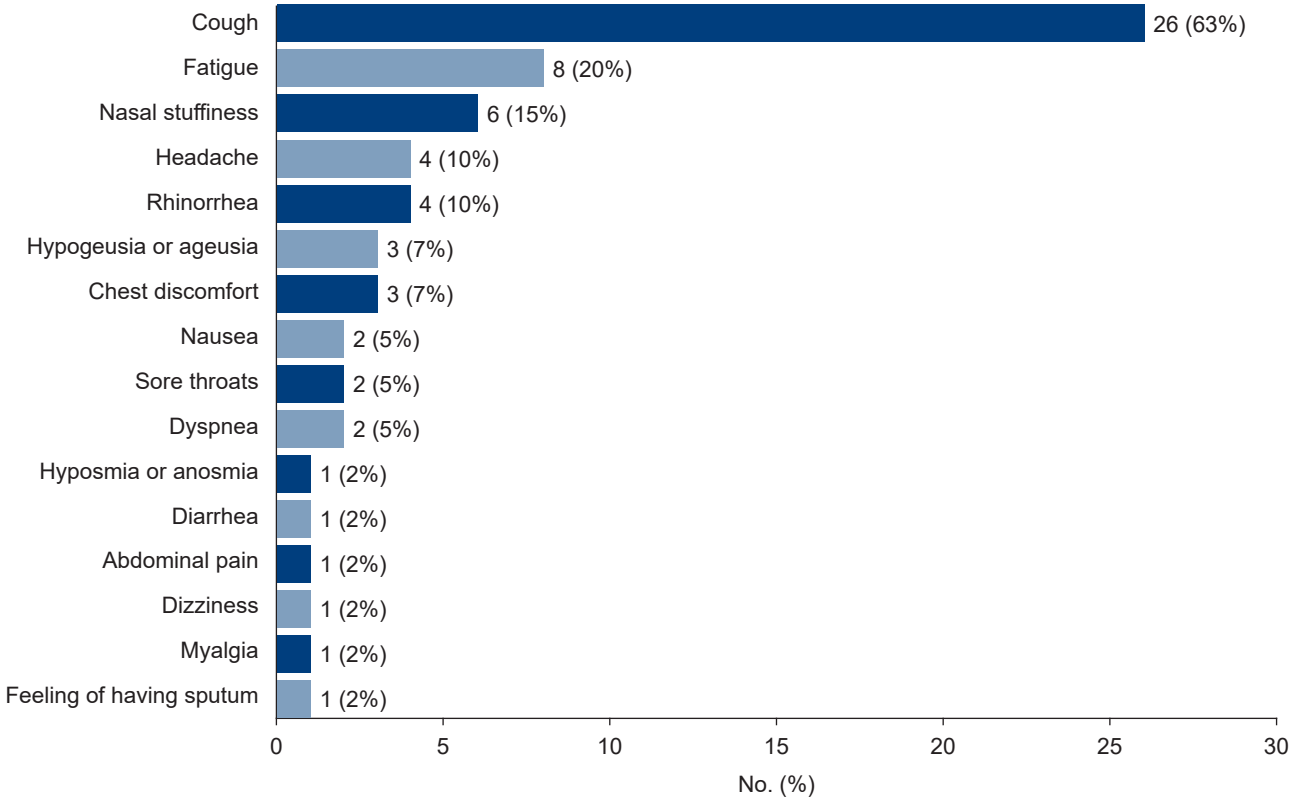

Fig. 1. Proportion of patients with post-acute coronavirus disease 2019 symptoms. If a patient had multiple symptoms, multiple variables corresponding to the symptoms were selected.

difference between the groups (Fig. 2).

4. Clinical features of asthma

There were no significant differences between the two groups regarding the duration from the diagnosis of COVID-19 to the clinic visit, age at diagnosis, sex, or vaccination history (p=0.128, p=0.698, p=1.000, respectively). Allergic rhinitis and atopic dermatitis were more frequently observed in the asthma group than that in the non-asthma group. When comparing clinical features, no significant differences were observed between the two groups for all symptoms, including cough, rhinorrhea, nasal stuffiness, and dyspnea. However, the post-acute COVID-19 rate was significantly higher in the asthma group (22.6%) than in the non-asthma group (3.8%) (p=0.004) (Table 3).

Among the 12 patients with asthma and post-acute COVID-19, six reported only a cough lasting more than 4 weeks, and two reported rhinorrhea and cough lasting more than 4 weeks. The remaining four patients each reported that cough and fatigue, rhinorrhea and chest discomfort, loss of taste, and the feeling of having sputum persisted for more than 4 weeks.

5. Clinical features of vaccination

There was no difference in mean duration from diagnosis of COVID-19 to clinic visit between the vaccinated and unvaccinated groups (p=0.110). The median age of the vaccinated group was 15 years (IQR, 14.0–16.3 years), significantly older than that of the unvaccinated group (13 years old: IQR, 12.0–14.0 years; p=0.001); there was no difference in sex between the groups (Table 4). In the vaccinated group, fever occurred in 24 patients (63.2%) with a peak value of 38.5 °C (IQR, 38.0–39.0 °C), significantly lower than that observed in the 27 unvaccinated patients (87.1%), with a peak value of 39 °C (IQR, 38.1–39.5 °C) (p=0.024, p=0.047, respectively). The frequencies of cough, rhinorrhea, nasal stuffiness, dyspnea, chest discomfort, chest pain, myalgia, headache, dizziness, sore eyes, and sore throat did not differ between

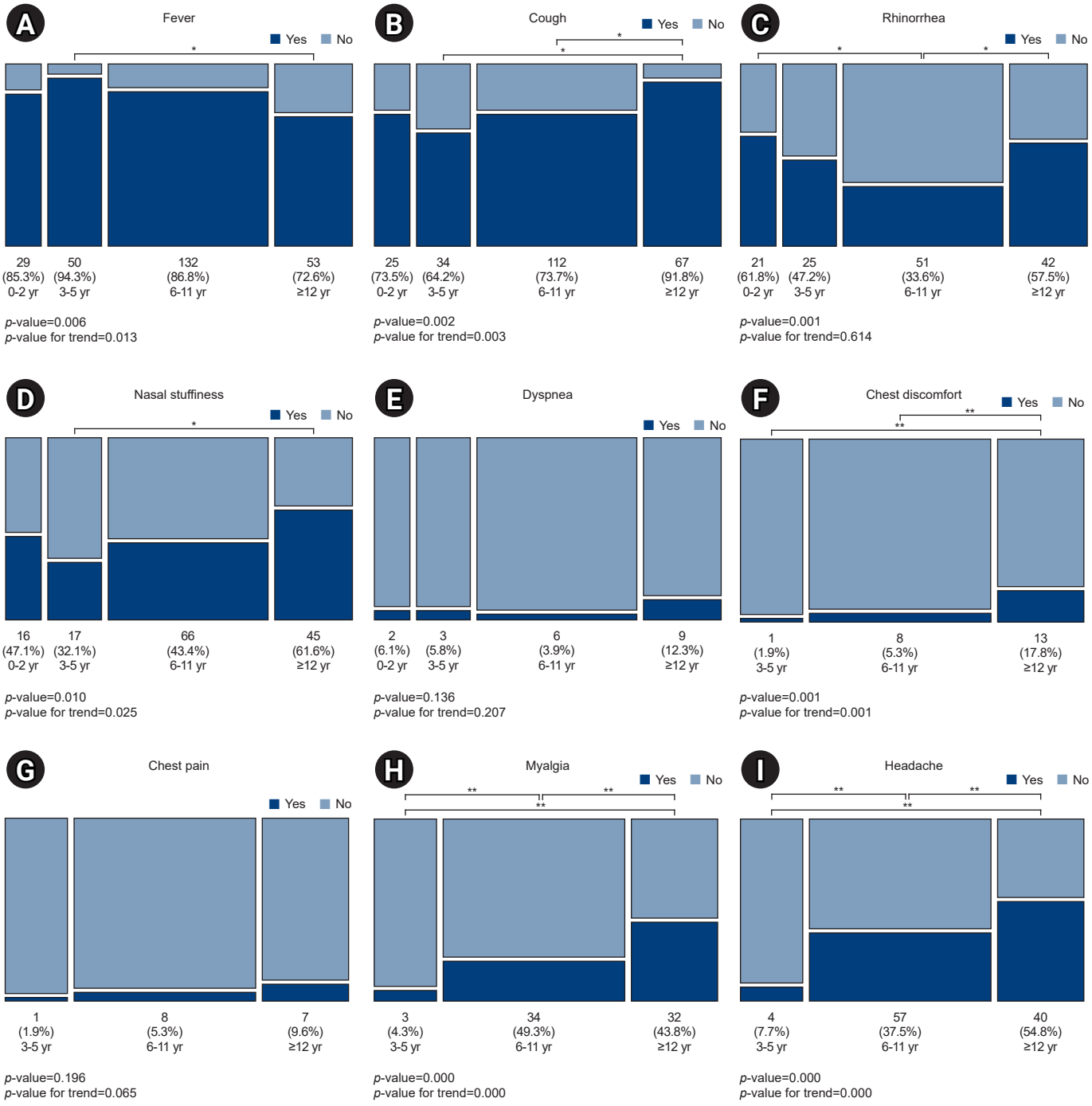

Fig. 2. Clinical features by age category: (A) fever, (B) cough, (C) rhinorrhea, (D) nasal stuffiness, (E) dyspnea, (F) chest discomfort, (G) chest pain, (H) myalgia, (I) headache, (J) dizziness, (K) sore eyes, (L) sore throat, (M) nausea, (N) vomiting, (O) abdominal pain, (P) diarrhea, (Q) loss of smell, (R) loss of taste, (S) fatigue, (T) asymptomatic, and (U) post-acute coronavirus disease 2019 (COVID-19). *p<0.008; **p<0.017. (Continued)

the two groups. Among the gastrointestinal symptoms, the frequency of nausea, abdominal pain, and diarrhea did not differ between the two groups; however, the frequency of vomiting differed significantly between the two groups: one patient (2.6%) in the vaccinated group and seven patients (22.6%) in the unvaccinated group (p=0.019). The frequen-

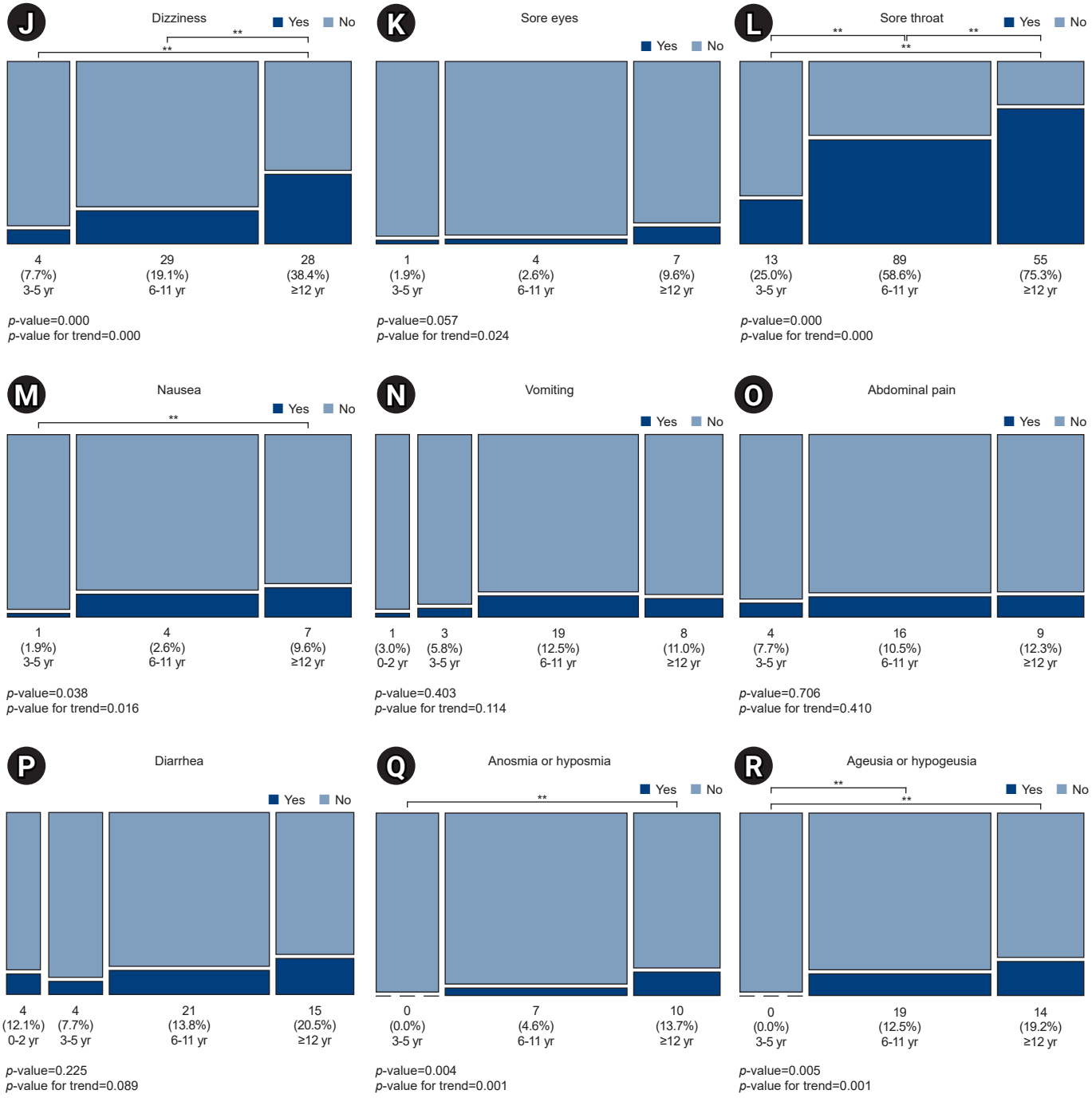

Fig. 2. (Continued from the previous page)

cies of alterations in smell and taste did not differ between the two groups. The frequency of fatigue was significantly lower in the vaccinated group: 15 patients (39.5%) in the vaccinated group and 20 patients (64.5%) in the non-vaccinated group (p=0.038). The incidence rates of asymptomatic and post-acute COVID-19 did not differ between the two groups.

Age and sex adjustments were made to investigate the effects of vaccination on fever, vomiting, and fatigue. In the vaccination group, the independent decrease in the risk of

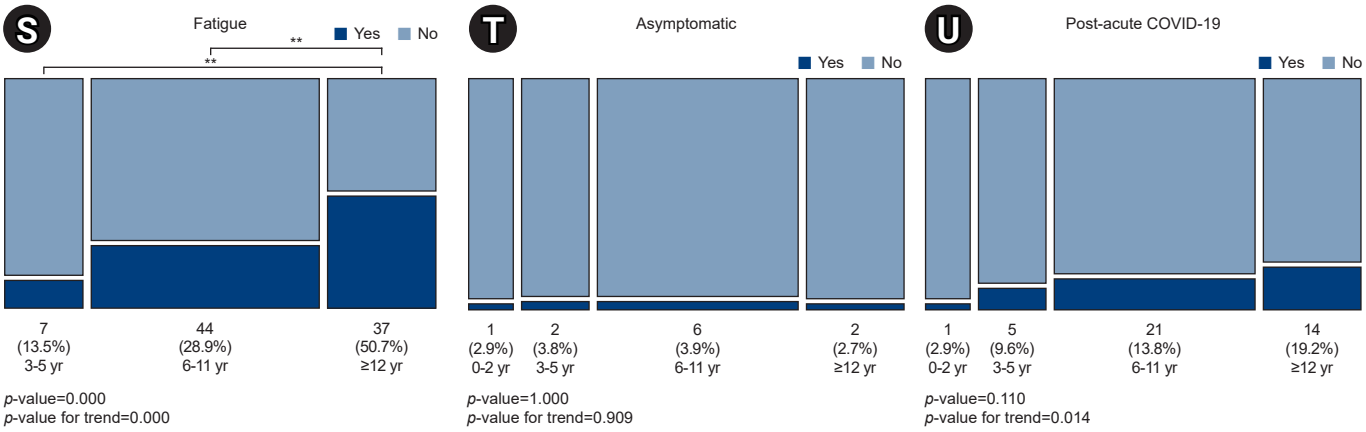

Fig. 2. (Continued from the previous page)

Table 3. Clinical features according to the presence of asthma

Variable	Asthma (n=53)		Non-asthma (n=53)		*p*-value
	No. of patients with data available	No. (%) or median (IQR)	No. of patients with data available	No. (%) or median (IQR)	
Age at diagnosis (yr)	53	9.0 (7.0–12.5)	53	10.0 (7.0–13.0)	0.698
Male sex	53	38 (71.7)	53	38 (71.7)	1.000
Allergic rhinitis	53	45 (84.9)	53	7 (13.2)	0.000
Atopic dermatitis	53	12 (22.6)	53	4 (7.5)	0.030
Vaccination	51	9 (17.6)	53	12 (22.6)	0.526
Fever	53	42 (79.2)	53	42 (79.2)	1.000
Peak value (°C)	42	39.0 (38.3–40.0)	41	39.0 (38.8–39.6)	0.820
Cough	53	44 (83.0)	53	40 (75.5)	0.338
Rhinorrhea	53	26 (49.1)	53	23 (43.4)	0.559
Nasal stuffiness	53	29 (54.7)	53	24 (45.3)	0.331
Dyspnea	53	4 (7.5)	53	1 (1.9)	0.169
Chest discomfort	53	6 (11.3)	53	4 (7.5)	0.506
Chest pain	53	5 (9.4)	53	3 (5.7)	0.462
Myalgia	53	14 (26.4)	53	19 (35.8)	0.294
Headache	53	25 (47.2)	53	22 (41.5)	0.558
Dizziness	53	14 (26.4)	53	15 (28.3)	0.828
Sore eyes	53	1 (1.9)	53	1 (1.9)	1.000
Sore throat	53	33 (62.3)	53	32 (60.4)	0.842
Nausea	53	9 (17.0)	53	3 (5.7)	0.066
Vomiting	53	8 (15.1)	53	5 (9.4)	0.374
Abdominal pain	53	6 (11.3)	53	4 (7.5)	0.506
Diarrhea	53	6 (11.3)	53	6 (11.3)	1.000
Loss of smell	53	1 (1.9)	53	5 (9.4)	0.093
Loss of taste	53	8 (15.1)	53	8 (15.1)	1.000
Fatigue	53	18 (34.0)	53	17 (32.1)	0.836
Asymptomatic	53	2 (3.8)	53	4 (7.5)	0.401
Post-acute COVID-19	53	12 (22.6)	53	2 (3.8)	0.004

IQR, interquartile range; COVID-19, coronavirus disease 2019.

fever was observed regardless of age and sex (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.07–0.88; p=0.030), and the peak value of fever also decreased (β, –0.30; 95% CI, –0.94 to –0.03; p=0.038). The risk of vomiting also decreased inde-

Table 4. Clinical features according to vaccination status

Variables	Vaccinated (n=38)		Unvaccinated (n=31)		*p*-value
	No. of patients with data available	No. (%) or median (IQR)	No. of patients with data available	No. (%) or median (IQR)	
Age at diagnosis (yr)	38	15 (14–16)	31	13 (12–14)	0.001
Male sex	38	16 (42.1)	31	14 (45.2)	0.799
Fever	38	24 (63.2)	31	27 (87.1)	0.024
Peak value (°C)	21	38.5 (38.0–39.0)	27	39 (38.1–39.5)	0.047
Cough	38	35 (92.1)	31	28 (90.3)	1.000
Rhinorrhea	38	24 (63.2)	31	16 (51.6)	0.334
Nasal stuffiness	38	23 (60.5)	31	19 (61.3)	0.948
Dyspnea	38	5 (13.2)	31	3 (9.7)	0.722
Chest discomfort	38	7 (18.4)	31	4 (12.9)	0.743
Chest pain	38	3 (7.9)	31	4 (12.9)	0.692
Myalgia	38	18 (47.4)	31	14 (45.2)	0.855
Headache	38	20 (52.6)	31	19 (61.3)	0.470
Dizziness	38	14 (36.8)	31	14 (45.2)	0.484
Sore eyes	38	3 (7.9)	31	4 (12.9)	0.692
Sore throat	38	30 (78.9)	31	23 (74.2)	0.642
Nausea	38	4 (10.5)	31	7 (22.6)	0.202
Vomiting	38	1 (2.6)	31	7 (22.6)	0.019
Abdominal pain	38	3 (7.9)	31	5 (16.1)	0.452
Diarrhea	38	7 (18.4)	31	8 (25.8)	0.459
Loss of smell	38	5 (13.2)	31	5 (16.1)	0.745
Loss of taste	38	6 (15.8)	31	7 (22.6)	0.473
Fatigue	38	15 (39.5)	31	20 (64.5)	0.038
Asymptomatic	38	1 (2.6)	31	1 (3.2)	1.000
Post-acute COVID-19	38	7 (18.4)	31	5 (16.1)	0.803

IQR, interquartile range; COVID-19, coronavirus disease 2019.

pendent of age and sex in the vaccination group (OR, 0.09; 95% CI, 0.01–0.80; p=0.031). Fatigue was related to both sex (OR, 3.36; 95% CI, 1.19–9.46; p=0.022) and vaccination status (OR, 0.34; 95% CI, 0.12–0.95; p=0.040); the risk of fatigue was lower in females and in patients in the vaccination group.

Discussion

In this study, the median illness duration for all symptoms investigated was 2–4 days. Post-acute COVID-19 was observed in 41 patients (13.2%), and the most common symptom was cough. There were no significant differences in the acute symptoms between the asthma and non-asthma groups; however, the incidence of post-acute COVID-19 was significantly higher in the asthma group. Fever, vomiting, and fatigue were less observed in vaccinated group than that in unvaccinated group.

In general, the most frequently observed symptoms in children and adolescents with COVID-19 were fever (20.6%–80.2%) and cough (33.7%–54.2%) [4,10-12]. Although the frequencies were moderately different, fever (84.6%) and cough (76.2%) were the most common in our study. However, a prospective cohort study in the United Kingdom revealed headache and fatigue as the predominant symptoms (62.2% and 55.0%, respectively) [13]. The mean illness duration was 6 days in foreign studies and 4 days in this study, indicating that the symptoms disappeared within 1 week [4,10,13].

The common cold is a viral illness on the upper respiratory tract such as the nose, sinuses, and throat. In general, the severity of symptoms of cold peaks within 2–3 days, and then the symptoms decrease and disappear [14]. Although it was not compared with a control group consisting of patients with other respiratory viral infections during the same period in this study, based on previous research about the common cold, the duration of illness of COVID-19 in

children and adolescents shown in our study is similar to that of the common cold.

The proportion of asymptomatic patients varied among the studies. Data from hospitalized Korean children showed that 4.9%–48.2% of patients were asymptomatic. KDCA data from February to April 2020 showed that 38.6% of patients under the age of 20 were asymptomatic. Foreign studies reported that 66.4% of patients in an American study and 13% of patients in one meta-analysis were asymptomatic [4,10-12,15]. In our study, asymptomatic patients were similar to the finding in two of three studies on hospitalized Korean patients but lower than that reported in other studies. The lower number of asymptomatic patients in these three studies might stem from enrolling only patients who visited the hospital. Another Korean study with hospitalized children reported that 48.2% of patients were asymptomatic. Because the study was conducted on patients when all patients were transferred to community treatment centers or hospitals according to the guidelines of the Korean quarantine authorities, the rate may have been higher than other Korean studies with patients who visited hospital. Therefore, the real number of asymptomatic patients is expected to be higher than reported in this study.

There is a lack of consensus on the definition of long-lasting symptoms after acute COVID-19, and the prevalence varies widely [16]. Even when only studies investigating symptoms lasting more than 4 weeks are considered, the results differ between studies. A national cohort study of patients under 18 years of age in Denmark reported that 12%–51% of patients showed post-acute COVID-19 symptoms depending on age [17], and a prospective cohort study of patients aged 5–17 years in the United Kingdom found that 3%–5% experienced post-acute COVID-19 symptoms [13]. In the current study, 13.2% of all patients had post-acute COVID-19 symptoms, and this finding is similar to that of the Danish study. In a meta-analysis of several case-control studies that surveyed persistent symptoms after SARS-CoV-2 infection, symptoms, such as cough, abdominal pain, myalgia, diarrhea, fatigue, and dizziness, did not show statistically significant differences between the patient and control groups. Loss of smell, headache, sore throat, and sore eyes occurred more frequently in the patient group than in the control group. The authors argued that the incidence of persistent symptoms following SARS-CoV-2 infection may be much less than that reported in the literature [18]. The most frequent symptoms of post-acute COVID-19 in our study were cough and fatigue. Some of the cases among the 13.2% of post-acute COVID-19 cases observed in our study may not have been caused by SARS-CoV-2 infection because these variables did not differ between the patient and control groups in a previously mentioned meta-analysis. When analyzing the data of the participants in our study for the significant variables mentioned above, only five patients had post-acute COVID-19, and the frequency decreased to 1.6%. Therefore, the frequency of post-acute COVID-19 cases is expected to significantly reduce in future studies addressing this issue.

The disease course differs significantly between children and adults. It is speculated that this is due to age-related differences in the immune system, the level of expression of the angiotensin-converting enzyme 2 receptor, and the characteristics of the respiratory system [19]. An American study reported results similar to those of our study. Cough, rhinorrhea, dyspnea, myalgia, headache, sore throat, nausea or vomiting, abdominal pain, diarrhea, and loss of smell or taste were more frequently observed in those aged 10 years and older. Only fever was seen more frequently in children younger than 10 years of age [20]. In our study, the frequency of 12 out of 19 symptoms tended to increase with age, and no age-related trend was observed for six symptoms. Only fever tended to decrease with age, as observed in a previous study in the United States. We believe that this phenomenon reflects not only the hypothesis mentioned above but also the fact that symptoms can be expressed better as age increases.

Asthma was initially hypothesized to be a risk factor for severe COVID-19, given the association between asthma exacerbations and common respiratory viral diseases. Fortunately, however, the overall clinical outcomes of COVID-19 patients with asthma are similar to those of patients without asthma [21]. In a case-control study that compared asthma and non-asthma groups in COVID-19 patients aged 6–18 years, there was no statistically significant difference between the two groups in the incidence of cough and dyspnea during the acute period. The incidence of fever, sore throat, chest pain, and gastrointestinal problems were also similar to our results [22]. Unlike the acute phase symptoms, we observed that post-acute COVID-19 occurred more often in the asthma group than in the non-asthma group. One study of 29 children with a mean

age of 13 years showed that the prevalence of asthma was higher in COVID-19 patients who complained of respiratory symptoms for more than 6 weeks than in the general population under 18 years old [23]. In a prospective cohort study of approximately 1,000 adults with COVID-19 in the United States, asthma patients had a 1.54 times higher risk of developing post-acute COVID-19 [24]. This suggests that asthma may affect the development of prolonged symptoms after COVID-19. There is another opinion as well. In a retrospective cohort study with adult patients with COVID-19, 75% of those with asthma and 76.8% of those without asthma continue to complain of symptoms even 90 days after infection, and some researchers have asserted that post-acute COVID-19 does not occur more often in patients with asthma in their review article [21,25].

Even before the COVID-19 pandemic, cough, which was the most common symptom of post-acute COVID-19 in this study, was usually referred to as postinfectious cough if it persisted for more than 3 weeks following viral infection [26]. There are no studies comparing persistent symptoms including cough after viral infection in patients with and without typical asthma. However, there have been studies that analyzed patients who coughed over 3 weeks by dividing them into postinfectious cough and cough variant asthma. One study of 195 patients with prolonged cough in Japan reported that 99 patients (50.8%) were diagnosed with postinfectious cough, and 40 patients (20.5%) were diagnosed with cough variant asthma. Chinese research investigating 104 patients with subacute cough following cold reported that 45 patients (43.2%) were diagnosed with postinfectious cough, and 17 patients (16.3%) were diagnosed with cough variant asthma [27,28]. In both studies, the number of patients with cough variant asthma were smaller than that of postinfectious cough. It suggests that SARS-CoV-2 may have different effects in asthma unlike other respiratory viruses. However, since the previous two studies excluded patients already diagnosed with asthma, it is difficult to simply compare their results with that of our study. In the future, additional well-designed studies are needed to determine whether post-acute COVID-19, especially prolonged cough, is more prevalent in asthma patients than other viral infections.

One study suggested that the reason why post-acute COVID-19 is more observed in asthma is related to immunoglobulin. A prospective cohort study in Switzerland reported that asthma was associated with risk of developing post-acute COVID-19 (OR, 9.74; p=0.003), and IgG3 in asthma patients was significantly lower (p=0.038) than patients without asthma [29]. Authors of the study suggested that IgG3 secreted from B cells contributes to the development of post-acute COVID-19. This is also supported by an Italian cohort study that showed differences in epigenetic and transcriptional signatures in B cells between patients who did and did not develop post-acute COVID-19 [30].

Despite reports that the overall effectiveness of SARS-CoV-2 vaccination in children is 90%–100% and that it is more effective and safer in children than in adults [29,30], breakthrough infections may occur. In our study, 42 of the 73 patients eligible for vaccination (58%) were vaccinated, and 41 of them were infected with SARS-CoV-2 despite being fully vaccinated more than twice. One review article reported that breakthrough infections were milder than infections in the unvaccinated group [31]. Likewise, in our study, vaccinated adolescents had lower incidences of fever, vomiting, and fatigue than those of unvaccinated adolescents. Similar results were obtained after adjusting for age and sex, which are consistent with the results of previous studies. According to the UK Health Security Agency, of eight studies with COVID-19 patients, six showed that vaccinated patients less developed post-acute COVID than unvaccinated patients [32]. Our study did not show a significant difference between the two groups, contrary to previous studies. The results in this study cannot confirm the effectiveness of vaccination in adolescents and cannot refute or support earlier studies showing that vaccination may reduce post-acute COVID-19. Because our study included a small number of patients in the vaccinated and unvaccinated groups (38 and 31, respectively). Therefore, future studies should assess the effectiveness of vaccination, targeting only Korean children and adolescents. Such studies will hopefully counter and refute rumors and conspiracy theories spreading among the public.

This study had several limitations. First, the number of cases in this study was less than 1% of the 23,719 daily average number of cases of COVID-19 among Korean patients under the age of 20 reported in the first half of 2022; this sample size is too small to adequately represent Korean pediatric patients. Second, recall bias existed in our study because it was a retrospective study based on reports from medical records. Additionally, our data included missing

values, which was an obstacle to the statistical analysis. Finally, selection bias could not be excluded because only patients who visited a single tertiary healthcare center were included; thus, many patients with asymptomatic SARS-CoV-2 infection with no underlying diseases may not have been enrolled in this study. However, severely ill patients may have been underrecruited because our hospital was not COVID-19-dedicated.

Nevertheless, our report has the advantage of examining the duration of each symptom and frequency of post-acute COVID-19 in children and adolescents who visited a single center regardless of hospitalization. Additionally, we showed that the rate of post-acute COVID-19 was significantly higher in the asthma group than in the non-asthma group. In the case of vaccination, even if breakthrough infection occurred, they had milder symptoms compared to those who were not vaccinated. Our findings provide information on the clinical manifestations of COVID-19 in Korean children for patients and their caregivers. Our results also highlight the need to observe patients with asthma for more than 4 weeks. In the future, large-scale, long-term studies are required to more accurately identify the clinical features and prognosis of COVID-19 in Korean pediatric patients to reduce public anxiety and unnecessary socioeconomic costs.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: JEJ, HLC, YYJ. Data curation: JEJ, YHK, NL, YK. Formal analysis: YYJ. Investigation: JEJ, YYJ. Methodology: Project administration; Resources; Software; Supervision: YYJ. Validation; Visualization: JEJ, YYJ. Writing - original draft: JEJ, YYJ. Writing - review & editing: YYJ. Approval of final manuscript: all authors.

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Statins as a possible factor affecting fluoroquinolone resistance of coagulase-negative *Staphylococcus* in the conjunctiva: a case-control study

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Background: Conjunctival bacterial flora is a common cause of endophthalmitis after ophthalmic procedures. This study investigated the conjunctival bacterial flora, especially coagulase-negative *Staphylococcus* (CoNS), and their antibiotic sensitivity in patients who underwent ophthalmic procedures. Factors related to fluoroquinolone resistance were also investigated.

Methods: In total, 167 samples were analyzed from 135 patients who underwent cataract surgery or intravitreal injection at Kosin University Gospel Hospital between April 14, 2014, and September 29, 2016. Bacterial identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry or VITEK 2 equipment. Antibiotic sensitivity tests were performed using an AST-P600 card with VITEK 2 equipment. Clinical information was extracted from patients' medical records. Sixty-eight individuals with conjunctival flora containing CoNS were classified into the fluoroquinolone-sensitive and fluoroquinolone-resistant CoNS groups, and their characteristics were compared.

Results: A total of 192 isolates of Gram-positive bacteria were identified, including *Staphylococcus epidermidis* (33.3%), *Corynebacterium* spp. (18.8%), and CoNS other than *S. epidermidis* (9.2%). Of the 106 CoNS isolates, 68.9%, 69.8%, and 58.5% were sensitive to ciprofloxacin, levofloxacin, and norfloxacin, respectively. In patients with CoNS, statin use within 3 months before sample collection was significantly associated with fluoroquinolone resistance (p=0.016). Statin use was a significant risk factor for fluoroquinolone resistance in multivariate logistic regression analysis (odds ratio, 4.86; 95% confidence interval, 1.25–18.91; p=0.022).

Conclusions: CoNS, including *S. epidermidis*, was the most common conjunctival bacterial flora, with a fluoroquinolone sensitivity rate ranging from 58.5% to 69.8% in patients undergoing ophthalmic procedures. Statin use was a significant risk factor for fluoroquinolone resistance.

Keywords: Cataract extraction; Fluoroquinolones; Hydroxymethylglutaryl-CoA reductase inhibitors; Intravitreal injections; Staphylococcus

Introduction

Although endophthalmitis is a rare complication of cataract surgery and intravitreal injection, it is important to understand antimicrobial resistance with regard to the causative bacteria of endophthalmitis, as this serious ophthalmic dis-

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ease can cause vision loss [1,2]. Since many cataract surgeries and intravitreal injections are performed worldwide, the occurrence of endophthalmitis is increasing. Conjunctival bacterial flora comprises 82% of the causative bacteria of endophthalmitis after cataract surgery [3]. Therefore, regular monitoring for changes in conjunctival flora and antimicrobial susceptibility are required to appropriately select antibiotic eye drops that will prevent endophthalmitis and empirical antibacterial agents for its treatment [1,4,5]. However, because this information varies by region and time, a regular regional monitoring system is necessary [4]. Fluoroquinolones were introduced as antibacterial agents in eye drops in 1990. Between 1990 and the early 2000s, fluoroquinolones were the primary antibiotic eye drops used because conjunctival bacteria had low associated resistance. However, resistance to fluoroquinolones is steadily increasing, especially in coagulase-negative *Staphylococcus* (CoNS) species [2,6,7]. The risk factors for fluoroquinolone-resistant (FR) *Staphylococcus* present in the conjunctiva include the use of topical antibiotics (including fluoroquinolones) within 3 months, previous hospitalization and ophthalmic procedures [8]. After intravitreal injection, antimicrobial prophylaxis with fluoroquinolone eye drops may increase resistance due to multi-step mutations that can arise during short-term and repeated exposure [2].

Statins are commonly used medications to treat hyperlipidemia. In addition to their cholesterol-lowering effect, statins also have antibacterial effects against *Streptococcus pneumoniae* and *Staphylococcus aureus*; therefore, their potential as new antibacterial agents has also been assessed [9]. However, their widespread use for cardiovascular protection has instead created selective pressure for resistance. Ironically, it also has the potential to promote antibiotic resistance [10,11].

The present study investigated the conjunctival microbiota and antimicrobial susceptibility of patients who underwent cataract surgery and intravitreal injection. Our aim was to establish a basis for the selection of prophylactic antibiotics for ophthalmic procedure and empirical antibiotics for the treatment of endophthalmitis. We also sought to identify factors related to antimicrobial resistance, including a history of statin use, which has antibacterial effects.

Methods

Ethical statements: This study was approved by the Institutional Review Board of the Kosin University Gospel Hospital (KUGH 2017-11-045-003). This retrospective study utilized data collected as a part of routine clinical care. The Institutional Review Board of the Kosin University Gospel Hospital determined that the study met IRB exemption criteria based on the retrospective nature of the study and participant consent was therefore not required.

1. Subjects

This retrospective study included patients who underwent cataract extraction, posterior intraocular lens implantation, or intravitreal injection at the Department of Ophthalmology at Kosin University Gospel Hospital between April 14, 2014, and September 29, 2016. Among 135 such patients who also underwent conjunctival colonization culture, 167 specimens were collected. We also included samples of one case in which a patient underwent another ophthalmic procedure during the study period. So if the procedure was repeated, samples were collected from a minimum of 1 to a maximum of 3 times. Among them, samples were collected only once in 105 patients (105 specimens), twice in 28 patients (56 specimens), and three times in two patients (6 specimens). Based on the medical records, the following clinical parameters were collected: age at the time of sample collection, sex, type of ophthalmic disease for which the procedure was performed (cataract, diabetic retinopathy, macular dystrophy or macular degeneration, retinal vascular occlusion, glaucoma), procedure type (phacoemulsification with posterior chamber lens implantation, intravitreal injection, pars plana vitrectomy, laser photocoagulation), diabetes, hypertension, chronic viral hepatitis (including hepatitis B and C), alcohol consumption, and smoking history. The patients' histories of ophthalmologic procedures and hospitalization within 3 months before sample collection were also evaluated. The following measurements were performed: fasting blood glucose, glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels.

2. Methods

1) Sample collection and storage

Specimens were collected from the lower conjunctival

sac by scraping the lower eyelid laterally with a polyester-tipped swab (23-400-122, Fisherbrand) after inversion of the lower eyelid before applying the eye drop anesthetic. No prophylactic antibacterial eye drops were administered before surgery. Immediately after inoculation on 5% blood agar, the specimens were cultured at 37 °C in an incubator (Water-Jacketed CO2 Incubator, Forma Scientific, Inc.) for up to 7 days. The bacterial colonies were plated on fresh 5% blood agar or MacConkey medium to obtain pure colonies, and the strains were classified according to the colony shape. Subsequently, 1 mL of a mixture of 60% glycerol and *Brucella* broth in a 3:7 ratio was dissolved for 1–2 weeks and stored in a –70 °C ultra-low temperature freezer.

2) Bacteria identification and antimicrobial susceptibility testing

A total of 167 frozen samples collected from 135 patients were thawed and re-inoculated on 5% blood agar or MacConkey medium using a 10-μL loop (SPL Life Sciences). A total of 261 strains were identified by subculturing. The bacteria were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics GmbH) or VITEK 2 system (bioMerieux, Marcy l'Etoile). Bacterial identification and susceptibility tests were performed using ID (GP or GN) cards and AST-P600) cards on VITEK-2 equipment, respectively. The minimum inhibitory concentration (MIC, μg/mL) was reported according to Clinical and Laboratory Standards Institute (CLSI) standards [12].

3) Factors related to fluoroquinolone resistance of CoNS in conjunctival flora

The CoNS strains isolated from the conjunctival flora of 68 patients were classified according to fluoroquinolone resistance. Strains that were moderately resistant or resistant to ciprofloxacin, levofloxacin, and/or norfloxacin were categorized as FR CoNS. In contrast, strains that were sensitive to all three fluoroquinolones were categorized as non-FR CoNS. If more than one FR CoNS were identified from one patient, the groups were classified based on CoNS with a high degree of resistance. In addition to the clinical information surveyed on all 68 subjects, the history of statin use within 3 months before sample collection was also investigated.

4) Statistical analysis

For comparisons between two groups, the chi-square or Fisher exact tests were used for categorical variables, while Mann-Whitney *U*-tests were performed for numerical variables. Statistical significance was set at $p<0.05$. Variables that were significant in univariate analysis were reanalyzed in multivariate analysis using the "enter" method to check the influence between variables. The KoreaPlus statistical program (Embedded in SPSS 26.0 Statistics) for Windows (Datasolution Inc.) was used to perform these analyses.

Results

1. Clinical characteristics of the study participants

Among the study participants, 15 (11.1%) had a history of chronic viral hepatitis including hepatitis B and C. Fifteen patients (11.1%) had undergone ophthalmic procedures within 3 months before sample collection (0–7 procedures) and 35 (25.9%) had been hospitalized for any reason (duration, 1–23 days) (Table 1).

Table 1. Demographic characteristics of the patients (n=135)

Characteristic	No. (%)
Age (yr), median (range)	62 (20–88)
Male sex	79 (58.5)
Conjunctival swab culture	
Bacterial growth	107 (82.9)
Ophthalmic procedure	
Phacoemulsification with posterior chamber lens implantation	33 (24.4)
Intravitreal injection	100 (74.1)
Others	2 (1.4)
Ophthalmic disease	
Cataract	33 (24.4)
Diabetic retinopathy	45 (33.3)
Macular dystrophy, macular degeneration	34 (25.2)
Retinal vascular occlusion	16 (11.9)
Glaucoma	21 (15.6)
Others	7 (5.2)
Other diseases and conditions	
Diabetes mellitus	67 (49.6)
Hypertension	38 (28.1)
Viral hepatitis	15 (11.1)
Alcohol drinking	50 (37.0)
Smoking	38 (28.1)
Ophthalmic procedure within 3 mo before sample collection	15 (11.1)
Hospital admission within 3 mo before sample collection	35 (25.9)

2. Types of cultured strains and their antimicrobial susceptibility

Among a total of 167 samples collected from 135 patients, 261 bacterial strains were isolated. There were 192 (73.6%) Gram-positive bacteria and 69 (26.4%) Gram-negative bacteria (Table 2). Antimicrobial susceptibility was tested for 123 of the 192 Gram-positive strains (84 strains of *Staphylococcus epidermidis*, 22 strains of CoNS excluding *S. epidermidis*, 11 strains of *S. aureus*, and 6 strains of *Enterococcus* spp.). Among them, 12.2% (15/123) were sensitive to penicillin, while 70.7% (87/123), 71.5% (88/123), and 61.0% (75/123) of strains were susceptible to ciprofloxacin, levofloxacin, and norfloxacin, respectively. CoNS strains (106 strains) were 68.9% (73/106), 69.8% (74/106), and 58.5% (62/106) susceptible to ciprofloxacin, levofloxacin, and norfloxacin, respectively (Table 3). In 22 patients, two or more strains of the same CoNS species were identified in samples from the same round of sample collection. Among them, 21 had *S. epidermidis*; the other had *Staphylococcus haemolyticus*. Twelve cases showed different antimicrobial susceptibilities among these bacteria, with 54.5% (12/22) of the same type of CoNS showing different susceptibilities.

3. Factors associated with fluoroquinolone resistance in CoNS

Of the 68 patients from which CoNS were isolated, 31 and 37 were in the non-FR CoNS and FR CoNS groups, respectively. The bacteria identified in the 31 non-FR CoNS patients were *S. epidermidis* (27 patients), *Staphylococcus lentus* (2 patients), *S. haemolyticus* (1 patient), and *Staphylococcus capitis* (1 patient), while the 37 FR CoNS patients included *S. epidermidis* (29 patients), *S. haemolyticus* (4 patients), *Staphylococcus hominis* (3 patients), and *S. capitis* (1 patient). Hospitalization before sample collection was slightly higher in the FR CoNS group, but the difference was not statistically significant (p=0.077).

The FR CoNS group was significantly associated with history of statin use within 3 months before sample collection (p=0.016), total cholesterol over than 200 mg/dL (p=0.006), and LDL cholesterol over than 130 mg/dL (p=0.002). The FR CoNS group was significantly associated with a history of viral hepatitis (p=0.006) (Table 4).

Table 2. Microbial isolates from the conjunctiva (n=261)

Microbial	No. (%)
Gram-positive bacteria	192 (73.6)
Staphylococcus epidermidis	87 (33.3)
Corynebacterium spp.	49 (18.8)
CoNS other than *S. epidermidis*	24 (9.2)
Staphylococcus aureus	11 (4.2)
Enterococcus spp.	6 (2.3)
Micrococcus spp.	5 (1.9)
Other Gram-positive bacteria[a]	10 (3.8)
Gram-negative bacteria	69 (26.4)
Ochrobactrum spp.	21 (8.0)
Achromobacter spp.	15 (5.7)
Pseudomonas spp.	12 (4.6)
Brevundimonas spp.	5 (1.9)
Enterobacter spp.	4 (1.5)
Other Gram-negative bacteria[b]	12 (4.6)

CoNS, coagulase-negative *Staphylococcus*.
[a]Other Gram-positive bacteria: *Trueperella* spp. (n=1), *Propionibacterium* spp. (n=1), *Paenibacillus* spp. (n=1), *Microbacterium* spp. (n=2), *Kocuria* spp. (n=3), *Dermabacter* spp. (n=1), *Clostridium* spp. (n=1).
[b]Other Gram-negative bacteria: *Acinetobacter* spp. (n=2), *Proteus* spp. (n=2), *Delftia* spp. (n=2), *Sphingomonas* spp. (n=2), *Stenotrophomonas* spp. (n=2), *Cupriavidus* spp. (n=1), *Morganella* spp. (n=1).

Table 3. Antibiotic susceptibilities of 123 Gram-positive bacteria isolated from conjunctiva

Antibiotic susceptibility	Gram-positive bacteria, No. (%)			
	Staphylococcus epidermidis (n=84)	CoNS other than *S. epidermidis* (n=22)	*Staphylococcus aureus* (n=11)	*Enterococcus* (n=6)
Benzylpenicillin	5 (6.0)	2 (9.1)	2 (18.2)	6 (100)
Ciprofloxacin	59 (70.2)	14 (63.6)	9 (81.8)	5 (83.3)
Levofloxacin	60 (71.4)	14 (63.6)	9 (81.8)	5 (83.3)
Norfloxacin	48 (57.1)	14 (63.6)	9 (81.8)	4 (66.7)
Linezolid	84 (100)	22 (100)	11 (100)	6 (100)
Vancomycin	84 (100)	22 (100)	11 (100)	6 (100)
Tigecycline (n=121)	84 (100)	20 (100)	11 (100)	6 (100)

CoNS, coagulase-negative *Staphylococcus*.

When only statin intake history and total cholesterol >200 mg/dL were included for the multivariate analysis two variables were related to fluoroquinolone resistance; a history of statin intake significantly increased the risk of fluoroquinolone resistance (odds ratio [OR], 4.86; 95% confidence interval [CI], 1.25–18.91; p=0.022) (Table 5).

Discussion

Although prophylactic antibiotic use before and after cataract surgery and intravitreal injection can prevent endophthalmitis, prophylactic ocular antimicrobial administration has increased fluoroquinolone resistance [8]. Some experts argue that these prophylactic eye drops are necessary and that information on the type of conjunctival flora and their antimicrobial susceptibility reported in the community can help to select the appropriate antibacterial agents [4,13]. The present study was designed to provide this information.

In this study, 107 (82.9%) conjunctival swab culture samples from 135 patients were culture positive. The previously reported positivity rates for conjunctival bacteria through traditional culture techniques range from 75%–82% or 14%–86% [1,14,15].

Worldwide, the most common bacterium in the conjunctiva is CoNS, primarily *S. epidermidis*, while *S. aureus*, *Corynebacterium* spp., *Pseudomonas aeruginosa*, and *Haemophilus influenzae* are also common [7,16-22]. Among the conjunctival flora, the reported proportions of CoNS,

Table 5. Multivariate model for predictors of fluoroquinolone-resistant CoNS

Variable	β	SE	p-value	OR (95% CI)
Statin use	1.581	0.693	0.022	4.86 (1.25–18.91)
Cholesterol >200 mg/dL	−1.582	0.758	0.037	0.21 (0.05–0.91)

CoNS, coagulase-negative *Staphylococcus*; SE, standard error; OR, odds ratio; CI, confidence interval.

Table 4. Comparison of clinical characteristics in patients with CoNS as conjunctival flora according to FR

Characteristic	Non-FR CoNS (n=31)	FR CoNS (n=37)	$\chi 2$ or U tests	p-value
Male sex (n=68)	20 (64.5)	23 (62.2)	0.04	0.841
Age (yr)	60.9±14.4	63.9±13.6	500	0.365
Ophthalmic disease				
Cataract	9 (29.0)	15 (40.5)	0.98	0.323
Glaucoma	4 (12.9)	10 (27.0)	2.06	0.151
Other diseases and conditions				
Diabetes mellitus	16 (51.6)	20 (54.1)	0.04	0.841
Hypertension	7 (22.6)	10 (27.0)	0.18	0.673
Viral hepatitis	0	8 (21.6)	7.60	0.006[b]
Alcohol drinking	14 (45.2)	14 (37.8)	0.37	0.541
Smoking	11 (35.5)	15 (40.5)	0.18	0.669
Ophthalmic procedure within 3 mo before sample collection	5 (16.1)	7 (18.9)	0.09	0.764
Hospital admission within 3 mo before sample collection	5 (16.1)	13 (35.1)	3.13	0.077
Statin use	5 (16.1)	16 (43.2)	5.81	0.016
Blood test results[c]				
Cholesterol over 200 mg/dL (n=27, n=27)	12 (44.4)	3 (11.1)	7.48	0.006
HDL less 40 mg/dL (n=24, n=26)	6 (25.0)	11 (42.3)	1.67	0.197
LDL over 130 mg/dL (n=27, n=27)	9 (33.3)	0	10.80	0.002[b]
TG over 150 mg/dL (n=27, n=26)	11 (40.7)	14 (53.8)	0.91	0.339
FBS over 125 mg/dL (n=23, n=21)	12 (52.2)	7 (33.3)	1.59	0.208
HbA1C over 6% (n=15, n=11)	13 (86.7)	10 (90.9)	0.11	0.738

Values are presented as number (%) or mean±standard deviation.
CoNS, coagulase-negative *Staphylococcus*; FR, fluoroquinolone-resistant; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; FBS, fasting blood glucose; HbA1C, glycosylated hemoglobin.
[a]Pearson $\chi 2$ test (categorical variable) or Mann-Whitney U test (numerical variable).
[b]Fisher exact test.
[c]The n values in parentheses are the number of patients in Non-FR CoNS and FR CoNS, respectively.

S. epidermidis, *S. aureus*, *Corynebacterium* spp., and other Gram-positive and Gram-negative bacteria were 33%–77%, 35%–76%, 4%–23%, 0%–45%, 3%–16%, and 6%–20%, respectively; these findings are comparable to the results of the present study, with proportions of 43%, 33%, 4%, 19%, 8%, and 26%, respectively [16,18,23,24].

In a study conducted in Korea in 2000, only 82.5% of the CoNS showed sensitivity to ciprofloxacin before cataract surgery. A 2006 study reported that only 69.2% of CoNS showed ciprofloxacin sensitivity, while 78.7% showed levofloxacin sensitivity among conjunctival flora before cataract surgery [7,25]. The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study reported CoNS sensitivities to levofloxacin of 86.1% and 43.2% in methicillin-sensitive (MS) and methicillin-resistant (MR) strains, respectively [26,27]. The present study did not separately confirm methicillin sensitivity. The sensitivities of CoNS to ciprofloxacin and levofloxacin were 68.9% and 69.8%, respectively. These sensitivities were higher than that of MR CoNS and lower than that of MS CoNS reported previously. Among staphylococcal isolates, the sensitivity of fluoroquinolone in the ocular flora before cataract surgery in Taiwan was 75%–82.5%, which is slightly lower than that reported previously [4]. In this study, 54.5% (12/22) of 22 patients with two or more identical species of CoNS among the samples from the same round were colonized with the same species of CoNS, but with different antimicrobial susceptibilities. More than 40% of cases of the same species of CoNS showed different susceptibilities to antibacterial agents in a previous study of conjunctival flora before cataract surgery [28].

Fluoroquinolones are broad-spectrum bactericidal antibacterial agents used to treat Gram-positive, Gram-negative, and anaerobic bacteria. They are mainly used as prophylactic antibacterial agents before and after ophthalmic surgery. However, among the bacteria that cause eye infections, resistance to fluoroquinolones is on the rise [28].

The results of this study showed that significantly more patients in the FR CoNS group had a history of statin use within 3 months before sample collection (p=0.016), as well as normal total cholesterol and LDL cholesterol levels (p=0.006, p=0.002).

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and are antihyperlipidemic agents widely prescribed worldwide to lower cholesterol. Statins are also known to have antibacterial effects against pneumococci and *S. aureus*, and simvastatin and atorvastatin are the drugs with the most potential as antibiotics. Statins have been thought to block antibiotic resistance by exerting a synergistic effect with existing antibiotics, attenuating virulence factors, strengthening human immunity, or assisting wound healing. However, their widespread use for cardiovascular protection has instead created selective pressure for resistance. Ironically, it also has the potential to promote antibiotic resistance. Current evidence better supports blocking potential antimicrobial resistance, but a role in promoting antibiotic resistance cannot be ruled out. At low antibiotic concentrations (up to several hundred times the MIC), the growth rate of susceptible bacteria is slightly reduced, allowing the growth of multiple new resistant mutant strains and the proliferation of antibiotic-resistant bacteria. Because the maximum plasma concentration that can be achieved at the dose of statins used to treat hyperlipidemia is hundreds to thousands of times lower than the MIC, statins are unlikely to exert significant systemic antibacterial effects. However, a greater concern is that patients with bacteremia may be exposed to low systemic antimicrobial concentrations, which may result in selective pressure for resistance. When bacteria are exposed to antibacterial drugs for a long period of time, the death of susceptible bacteria can be accelerated and resistant bacteria can become dominant. Elucidating the mechanism of antibacterial activity of statins may perhaps clarify their role in antibiotic resistance [10,11]. In addition, statin use may explain the higher proportions of patients with normal total and LDL cholesterol levels in the FR CoNS group than in the non-FR CoNS group. However, due to the small number of participants, the present study could not confirm the relationship between the growth of CoNS resistance to fluoroquinolones and statin use.

Factors known to contribute to the acquisition of fluoroquinolone resistance in *S. aureus* and CoNS include recent ophthalmic surgery before cataract surgery, recent hospitalization, use of fluoroquinolone eye drops within 3 months, treatment history of intravitreal injection, use of systemic antibacterial agents, use of eye drops containing preservatives, use of fluoroquinolone eye drops for 3 months to 1 year, and use of other antibacterial eye drops within 1 year [8]. However, the present study did not identify these factors as related to the acquisition of fluoroquinolone resistance, which was likely due not only to the small number of study

subjects but also to the limitations of a retrospective study based only on medical records from a single institution.

This study has several limitations. Compared to previous studies, statistical significance could not be confirmed for some factors owing to the small number of study subjects. Because this study used a traditional culture method without polymerase chain reaction and genome sequencing, the sensitivity to accurately identify the actual flora was low [29,30]. However, using polymerase chain reaction and genome sequencing, it is difficult to determine whether a bacterium is related to a clinical ophthalmic disease, despite the superior sensitivity of these methods compared to traditional culture methods [22]. In addition, the antimicrobial susceptibility information based on the CLSI criteria used in this study may differ from drug concentrations that can be reached after the administration of ocular antimicrobial agents in local ocular structures, as these are determined based on expected drug concentrations achieved in the serum, plasma, and cerebrospinal fluid [2]. Therefore, it may be difficult to directly apply this sensitivity information to the conjunctival flora of the eye tissue [4,28,31]. Antimicrobial resistance to fluoroquinolones has gradually increased since the 1990s. Although resistance to old-generation fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin) exceeds that of new-generation fluoroquinolones (gatifloxacin and moxifloxacin), the resistance to newer fluoroquinolones is also increasing [2]. However, among the antibacterial eye drops mainly used in clinical practice, this study did not test sensitivity to 4th-generation fluoroquinolones (gatifloxacin and moxifloxacin).

In conclusion, CoNS, including *S. epidermidis*, accounted for 42.5% of the conjunctival flora of patients undergoing cataract surgery and intravitreal injection, with sensitivity to quinolone antibacterial agents ranging from 58.5% to 69.8%. A history of statin use was a significant risk factor for the development of resistance to fluoroquinolones. Additional large-scale studies are necessary to confirm the relationship between statins and fluoroquinolone resistance.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: YRH, SJL. Data curation: YRH, SJL. Formal analysis: CEO. Investigation: YRH, SJL, CEO. Methodology: YRH, SJL. Supervision: SJL. Validation: YRH, SJL. Writing – original draft: YRH. Writing – review & editing: YRH, SJL.

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Orbital complications of acute rhinosinusitis in adults: a 21-year experience

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Background: Orbital complications arising from acute rhinosinusitis (ARS) are a major concern for clinicians and serve as important warning indicators of ARS. Prompt recognition and appropriate management are crucial for preventing potential vision-threatening sequelae. Orbital complications of rhinosinusitis are markedly more common in children than in adults. The aim of this study was to investigate the clinical characteristics and treatment outcomes of orbital complications of ARS in adult patients.

Methods: This retrospective observational cohort study analyzed the medical records of 176 patients admitted for orbital cellulitis/abscess (ICD code: H050) who underwent orbit or paranasal computed tomography from January 2001 to February 2022 at a tertiary hospital.

Results: Eighteen adults with a mean age of 53.2±18.9 years were diagnosed with orbital complications due to ARS: five (27.8%) had preseptal cellulitis, eight (44.4%) had orbital cellulitis, and five (27.8%) had subperiosteal orbital abscess. None of the patients had an orbital abscess or cavernous sinus thrombosis. All patients had unilateral orbital complications (7 right and 11 left) and were managed with intravenous antibiotics for an average of 10.3±6.6 days. Five patients with subperiosteal orbital abscesses underwent intranasal endoscopic drainage at an average of 1.4±1.9 days after admission, while two patients required additional external drainage. Complete recovery was observed in all patients.

Conclusions: Conservative antimicrobial therapy can be effective for treating orbital complications from ARS, and not all adult patients require immediate surgical intervention for subperiosteal abscesses. Nonetheless, careful monitoring is essential, and an ophthalmologist must check patients' visual acuity to prevent irreversible blindness.

Keywords: Abscess; Adult; Cellulitis; Orbital diseases; Sinusitis

Introduction

Acute rhinosinusitis (ARS) is a condition characterized by inflammation of the nasal cavity and paranasal sinuses that typically lasts for up to 12 weeks according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 [1]. ARS is among the top five causes of antibiotic prescriptions, accounting for one in every five reasons for antibiotic prescriptions for adults [2]. Approximately 17% to 21% of adults are diagnosed with ARS each year [3,4]. Orbital complications arising from ARS are a major concern for clinicians, often presenting with periorbital swelling, pain, and potential visual dis-

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turbances. Prompt recognition and appropriate management are crucial in preventing potential vision-threatening sequelae.

While orbital complications of rhinosinusitis are more commonly observed in children, they are also encountered in adults. However, there is limited information on the clinical features and treatment outcomes of orbital complications of rhinosinusitis in adult patients. Therefore, this retrospective observational cohort study aimed to investigate the clinical characteristics and treatment outcomes of adult patients diagnosed with orbital complications due to ARS admitted to Gyeongsang National University Hospital over the past two decades. The study included patients diagnosed with orbital complications such as cellulitis or abscess and evaluated the correlation with rhinosinusitis based on computed tomography (CT) findings.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Gyeongsang National University Hospital (IRB No. 2023-08-013). Informed consent was waived.

Data from 176 patients older than 18 years of age who were admitted for orbital complications such as cellulitis or abscess at Gyeongsang National University Hospital from January 2001 to June 2022 were retrospectively collected from an electronic medical record database. Orbital complications were identified using the International Classification of Diseases, tenth revision (ICD-10) code (H050) occurring at least twice. Among 176 patients, 166 had a history of orbit or paranasal sinus CT. Non-enhanced or enhanced axial and coronal reformatted images were acquired for all cases. Two otorhinolaryngologists (YJJ and WH) who were blinded to patient clinical information and perioperative findings, evaluated the CT images and identified abnormalities in the sinuses and correlations between orbital complications and rhinosinusitis. Seventeen patients who did not show rhinosinusitis on CT were excluded. One hundred and thirty-one patients with orbital complications arising from dacryocystitis (n=114), skin infection (n=15), or other causes (n=2) were also excluded. Preseptal cellulitis, commonly categorized as a skin infection, was included in our analysis as one of the orbital complications originating from ARS, classified according to Chandler's classification I [5]. Finally, eighteen patients were included out of the initial 176 patients (Fig. 1). The continuous data are presented as means±standard deviation and categorical data are presented as number and percentages.

Results

1. Demographic characteristics

A total of 18 patients (8 males and 10 females) with a mean age of 53.2±18.9 years (range, 19–88 years) were included in this study. Pretreatment findings for the enrolled patients according to orbital complications are summarized in Table 1. Among them, seven patients had right-sided involvement and eleven patients had left-sided involvement. Three patients (16.7%) had a history of sinus surgery, and 14 patients (77.8%) were previously healthy. Among the underlying diseases, three patients had hypertension, and one patient was a carrier of the hepatitis B virus.

2. Clinical presentation

The most common chief complaint was periorbital swelling and pain, with mean onset time of 2.2±1.9 days (range, 0–8 days) prior (Fig. 2). Other complaints included upper

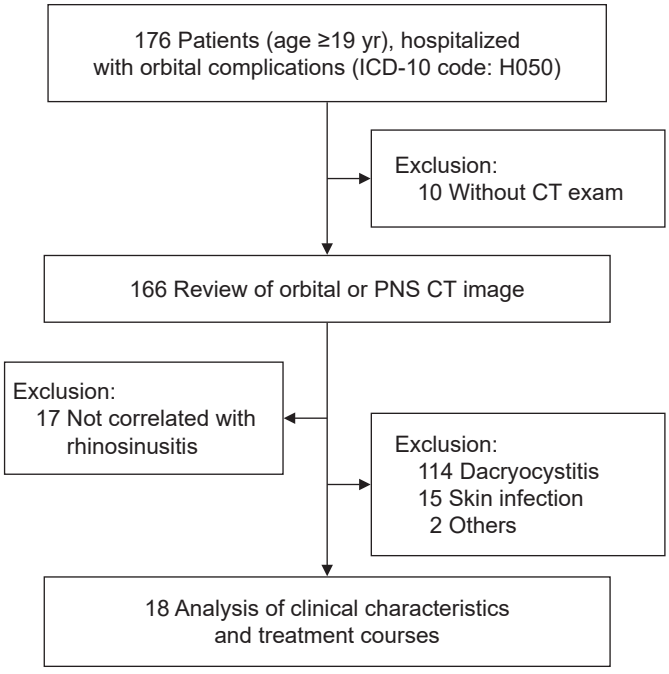

Fig. 1. A schematic illustration of the participant selection process in the present study. ICD-10, International Classification of Diseases, tenth revision; CT, computed tomography; PNS, paranasal sinus.

Table 1. Demographic and clinical characteristics of patients

Characteristic	Preseptal cellulitis	Orbital cellulitis	Subperiosteal abscess	Total
No. of patients	5	8	5	18
Male sex	2 (40.0)	5 (62.5)	1 (20.0)	8 (44.4)
Age (yr)	51.6±23.7 (19–77)	48.9±19.7 (19–77)	64.6±11.4 (51–82)	53.2±18.9 (19–88)
Right side	2 (40.0)	3 (37.5)	2 (40.0)	7 (38.9)
Previous sinus surgery	1 (20.0)	0	2 (40.0)	3 (16.7)
Underlying diseases	0	2 (25.0)[a]	2 (40.0)[b]	4 (22.2)
Duration of periorbital swelling and pain (day)	2.4±1.1 (1–4)	2.5±2.2 (0–8)	1.6±0.9 (1–3)	2.2±1.9 (0–8)
Upper respiratory infection symptoms	0	2 (25.0)	3 (60.0)	5 (27.8)
Toothache	0	2 (25.0)	0	2 (11.1)
Diplopia	1 (20.0)	0	3 (60.0)	4 (22.2)
Reduced visual acuity	0	0	1 (20.0)	1 (5.6)
Involvement of sinuses				
Maxillary sinus	4 (80.0)	8 (100)	4 (80.0)	16 (88.9)
Ethmoid sinus	5 (100)	4 (50.0)	5 (100)	14 (77.8)
Frontal sinus	3 (60.0)	2 (25.0)	3 (60.0)	8 (44.5)
Hospital stay (day)	6.2±3.3 (3–11)	8.5±5.3 (5–22)	15.2±5.5 (9–24)	10.3±6.0 (3–24)

Values are presented as number (%) or mean±standard deviation (range).
[a]Hepatitis B virus (n=1), hypertension (n=1).
[b]Hypertension (n=2).

Fig. 2. Initial clinical presentation. (A) Preoperative photograph showing right periorbital swelling and erythema. (B) Computed tomography scan illustrating a subperiosteal abscess (indicated by an asterisk). The patient provided written informed consent for the publication and use of images.

respiratory tract infection symptoms including cough, rhinorrhea or sputum (n=5) and toothache (n=2). The most common diagnoses were orbital cellulitis (n=8, 44.4%) (Fig. 3B), followed by preseptal cellulitis (n=5, 27.8%) (Fig. 3A), and subperiosteal abscess (n=5, 27.8%) (Fig. 3C). On initial ophthalmology examination, four patients (22.2%) had diplopia, and one (5.6%) had reduced visual acuity.

3. Laboratory findings

Findings from CT scans of paranasal sinus or orbit showed that the maxillary sinus was involved in 16 patients (88.9%), the ethmoid sinus in 14 (77.8%), and the frontal sinus in eight (44.5%). The culture results showed the presence of *Streptococcus pneumoniae* and *Prevotella intermedia* in only two patients each. However, no specific pathogens were identified in the results for the remaining patients (Table 1).

4. Management

The mean hospitalization period was 10.3±6.0 days (range, 3–24 days). Among the patients with pre-septal cellulitis, five were managed with medical treatment only. Among those with orbital cellulitis, seven were managed with medical treatment only, and one required surgical intervention. Among those with subperiosteal abscess, three underwent

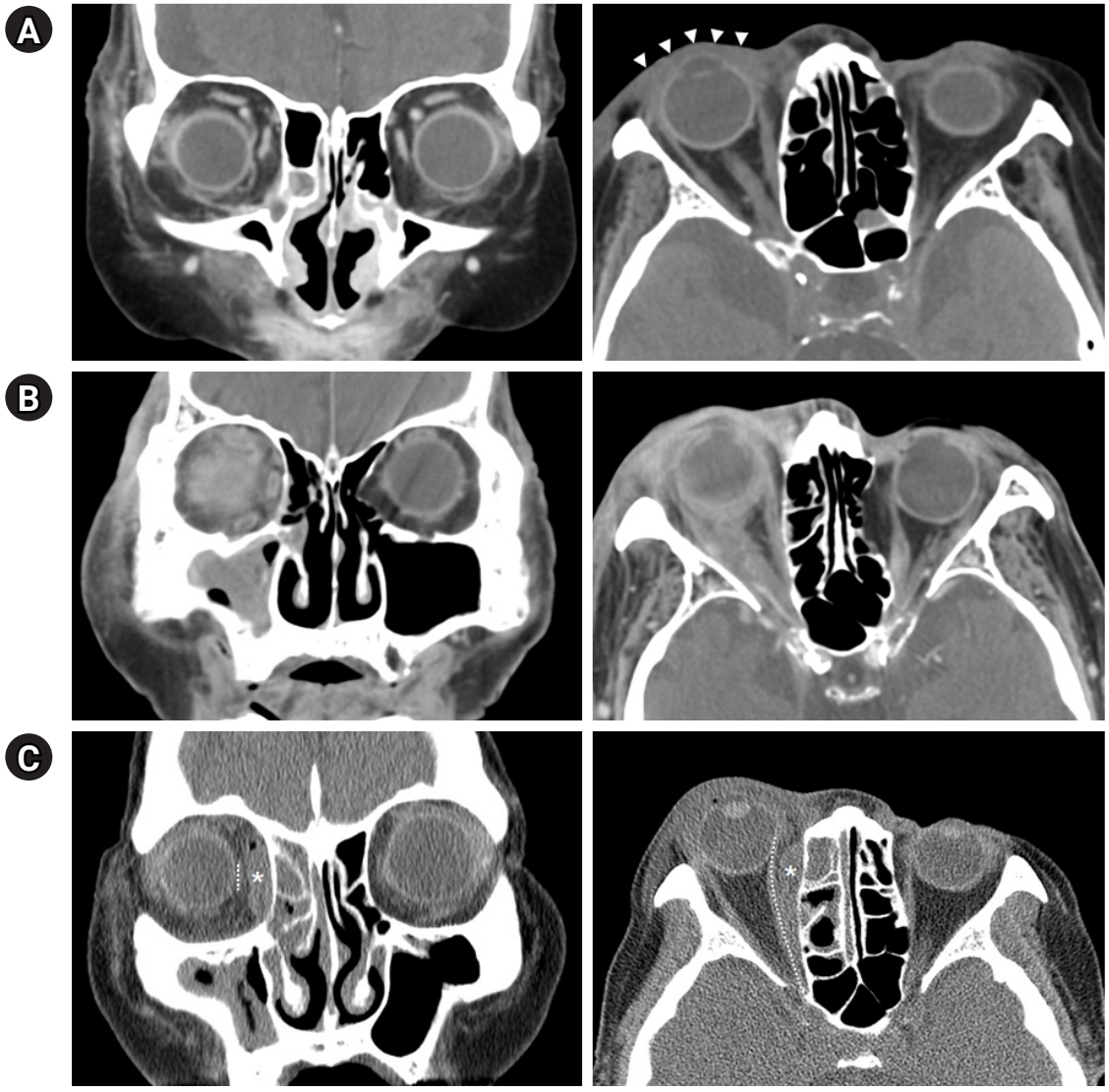

Fig. 3. Representative computed tomography findings of right orbital complications originating from acute rhinosinusitis according to Chandler's classification. (A) Preseptal cellulitis (stage I) displays periorbital soft tissue swelling with inflammation confined to the eyelids and periorbital tissues on the axial view (arrowheads). (B) Orbital cellulitis (stage II) demonstrates the extension of inflammation beyond the eyelids to involve the orbit without abscess formation. (C) Subperiosteal abscess (stage III, marked with an asterisk) is located between the periosteum and the orbital bone, resulting in compression of the right medial rectus muscle (dotted line).

endoscopic sinus surgery, and two underwent both endoscopic sinus surgery and external drainage (Table 2). Ceftriaxone was the most used antibiotic (11 patients), followed by cefotaxime (6 patients) and ampicillin/sulbactam (1 patient). The mean timing of surgical drainage after admission was 1.4±1.9 (range, 0–4 days).

Discussion

In this retrospective observational cohort study, we investigated the clinical characteristics and treatment outcomes of adult patients diagnosed with orbital complications resulting from ARS. Our findings elucidate this relatively unexplored area and provide valuable insights into patient management. Notably, there have been no reported cohort studies specifically focused on adult orbital complications

Table 2. Overview of clinical data related to subperiosteal abscesses

Patient no.	Sex	Age (yr)	Hospital stay (day)	Follow-up (mo)	Gaze restriction	Proptosis (right/left, mm)	Extraocular muscle(s) involved	Orbital fat involved	Sinus involved	Treatment
1	Male	59	16	1.5	Yes	Yes (12/17)	SO, MR, IR, LR	Yes	M, E, F	ESS, EX
2	Female	51	14	3	No	-	MR	No	M, E	ESS
3	Female	82	13	3.5	Yes	Yes (16/13)	SO, SR, MR	Yes	E, F	ESS
4	Female	66	24	1.5	Yes	No (19/18)	MR, IR	Yes	M, E	ESS, EX
5	Female	65	9	1.5	Yes	-	SO, SR, MR	No	M, E, F	ESS

SO, superior oblique; MR, medial rectus; IR, inferior rectus; LR, lateral rectus; SR, superior rectus; M, maxillary sinus; E, ethmoid sinus; F, frontal sinus; ESS, endonasal sinus surgery; EX, external drainage via transconjunctival approach.

of ARS. Furthermore, since 2009, no original reports have been published regarding orbital complications arising from ARS in adults. This cohort study represents the longest observation period conducted at a single institution. Based on data from a previous study on the Korean adult population from January 1985 through December 2007 [6-10], the mean incidence was 1.4 patients per year, ranging from 0.2 to 2.9. Interestingly, our study yielded a similar incidence of orbital complications of ARS in adults.

ARS is a common condition that can lead to serious complications, including orbital complications, which are particularly concerning due to the potential for vision loss or life-threatening outcomes. The increased susceptibility of children to orbital complications can be attributed to several anatomical differences between pediatric and adult populations, compounded by the heightened prevalence of upper respiratory infections in children [11]. Children typically exhibit diploic-type facial bones and thinner bony separation, coupled with increased vascularity, rendering them more vulnerable to the development of orbital complications. Furthermore, previous studies on pediatric populations found male dominance in orbital complications. The demographic characteristics of the study cohort revealed a relatively equal distribution between males and females, with a mean age of 53.2 years. While orbital complications are known to occur more frequently in pediatric populations, our study demonstrates that they can also affect adults, highlighting the importance of understanding this condition in all age groups.

The majority of patients were previously healthy, emphasizing that even individuals without underlying health issues are at risk of developing serious complications following ARS. Numerous studies have explored the various risk factors associated with these complications. A prior investigation suggested that ethmoid sinusitis, male gender, dehiscence of lamina papyracea due to congenital defects or prior sinus surgery, and younger age (below 18 years) were positively correlated with ARS leading to orbital complications. Contrarily, allergic rhinitis did not exhibit any significant association with such complications [12]. Despite the abundance of studies exploring potential risk factors, a clear consensus on the definitive factors contributing to the development of ARS-related orbital complications remains elusive.

The predominant chief complaint among the patients was periorbital swelling and pain, which is consistent with previous literature on orbital complications of rhinosinusitis. In addition to periorbital swelling and pain, patients exhibited orbital symptoms such as diplopia, gaze restriction, and changes in visual acuity. These symptoms demonstrated a potential for rapid progression, underscoring the need for prompt diagnosis and intervention to avoid further deterioration and associated complications. While suspicion of an orbital complication is crucial with such symptoms, CT is considered the gold standard for diagnosis. In terms of imaging findings, CT revealed involvement of the maxillary and ethmoid sinuses in a significant proportion of patients, which is in line with the anatomical proximity of these sinuses to the orbit. Our findings corroborate previous studies, indicating a higher prevalence of orbital complications arising from maxillary and ethmoid sinusitis [12]. Frontal sinus involvement was observed in fewer patients, possibly due to the relatively less common occurrence of frontal sinusitis compared to maxillary and ethmoid sinusitis.

The identification of causative pathogens through culture results showed the presence of *S. pneumoniae* and *P. intermedia*, highlighting the importance of appropriate antibiotic selection in the management of these cases. While pathogens such as *Streptococcus milleri*, *Streptococcus pyo-*

genes, *Streptococcus viridans*, *Staphylococcus aureus*, *Haemophilus influenza*, and various anaerobes are recognized as potential contributors, the isolation of pathogens from abscesses may sometimes prove challenging [13]. In the current study, ceftriaxone emerged as the most frequently prescribed antibiotic, followed by cefotaxime and ampicillin/sulbactam. Antibiotic selection should be guided by the suspected or identified pathogens and their sensitivity profiles to ensure effective treatment.

Appropriate timing of surgical intervention was essential to optimize outcomes for patients requiring drainage procedures. Medical treatment alone was sufficient for some patients, particularly those with preseptal cellulitis, while others required surgical intervention, including endoscopic sinus surgery and external drainage for subperiosteal abscess cases. EPOS 2020 suggests that for orbital complications except for preseptal cellulitis, surgical drainage is recommended if there is no response to intravenous antibiotics within 48 hours [1]. In the present study, surgical interventions were eventually required for five patients with subperiosteal abscess.

Our study has several limitations that should be acknowledged. First, the retrospective nature of the study introduces inherent biases and limitations in data collection. Second, the relatively small sample size may limit the generalizability of our findings to larger populations. Third, the study was conducted at a single institution, potentially affecting the diversity and representation of cases. Nevertheless, this study provides valuable insights into the clinical characteristics and treatment outcomes of adult patients with orbital complications resulting from acute bacterial rhinosinusitis. The findings emphasize the significance of early recognition and prompt management of these complications to prevent severe consequences. Future prospective studies with larger, multicenter cohorts are warranted to further validate and expand on our findings and to develop evidence-based guidelines for managing these challenging cases. Improved understanding and management of adult orbital complications of ARS will contribute to better patient outcomes and reduce the burden of this condition on healthcare systems.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: YJJ. Data curation: YJJ, WJ. Formal analysis: YJJ. Funding acquisition: YJJ. Investigation: WJ, YHJ, HJC, SWK. Methodology: WJ, YHJ, HJC, SWK. Project administration: YJJ. Resources: YJJ. Software: YJJ. Supervision: YJJ. Validation: YJJ. Visualization: YJJ. Writing - original draft: YJJ, WJ. Writing - review & editing: YJJ. Approval of final manuscript: all authors.

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Case report

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Cardiovascular collapse during transcatheter aortic valve replacement in monitored anesthesia care using an end-tidal carbon dioxide monitor: a case report

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Capnography is commonly used to monitor respiration during general anesthesia. However, it has limited utility in patients with respiratory distress during sedation. This case report examines capnography use in a transcatheter aortic valve replacement procedure performed on an elderly woman with severe aortic stenosis. A 73-year-old woman with a history of non-ST-elevation myocardial infarction and congenital heart failure presented with severe dyspnea caused by severe aortic stenosis. Transcatheter aortic valve replacement was preferred over surgery due to her comorbidities. Monitored anesthesia care was administered with a capnogram. During the procedure, the patient was sedated with remimazolam, maintaining a bispectral index range of 60–80 and a score of 2 on the Modified Observer's Assessment of Alertness/Sedation scale. Although irregular breathing patterns and a gradual decrease in oxygen saturation were observed following remimazolam infusion, the patient's respiration eventually stabilized. However, the patient experienced cardiovascular collapse 45 minutes after sedation began. The arterial carbon dioxide pressure measured by arterial blood gas analysis performed just before resuscitation was 68.4 mmHg. After one cycle of resuscitation, the patient recovered. The procedure was successfully performed under general anesthesia, which was replaced with monitored anesthesia care during resuscitation. Although most monitoring devices have similar utility for both general anesthesia and sedation, capnography has limitations for evaluating respiration during sedation, especially for patients with respiratory distress. Therefore, anesthesiologists or medical staff who provide sedation should not neglect periodical arterial carbon dioxide pressure observations via other methods, such as arterial blood gas analysis.

Keywords: Anesthesia; Capnography; Case reports; Hypnotics and sedatives; Resuscitation

Introduction

Capnography is a device used to evaluate a patient's respiration. Its use has increased as the demand for anesthesia outside operating units has greatly expanded. This monitoring technique can help anesthesiologists evaluate the presence and quality of respiration. However, applying an end-tidal carbon dioxide ($EtCO_2$) monitor for particular patients might be less valuable. In this case report, we discuss a woman who received a transcatheter aortic valve replacement in an interventional radiology suite.

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Case

Ethical statements: This study was exempted from review by the Institutional Review Board (IRB) of Busan Paik Hospital, Inje University of College of Medicine (IRB No: 2023-03-012-001). Informed consent was waived.

A 73-year-old woman (144 cm, 40 kg) previously diagnosed with non-ST-elevation myocardial infarction and congenital heart failure 20 years prior was admitted to the emergency department due to dyspnea. Physical examination revealed severe dyspnea, classified as New York Heart Association class 4. Transesophageal echocardiography confirmed severe aortic stenosis and moderate aortic regurgitation. Additionally, the patient had mild to moderate mitral and tricuspid regurgitation and moderate pulmonary hypertension. Pulmonary function tests indicated restrictive lung disease, which caused pulmonary edema and bilateral pleural effusion observed as extensive peribronchovascular consolidation with ground glass opacity and interlobular thickening in an unenhanced chest computed tomography scan. Considering her age, physical examination results, and imaging findings, the short-term risk for open cardiac surgery was 10%, which was too high for a surgical aortic valve replacement. A collaborative heart valve team consisting of cardiologists and thoracic surgeons decided to perform transcatheter aortic intervention.

The anesthesiologists and cardiologists determined that monitored anesthesia care would be the optimal choice based on its association with reduced 30-day mortality, shorter hospital stays, and impracticality of extubation [1]. We applied an automatic blood pressure cuff, electrocardiogram, and pulse oximetry for basic monitoring. We attached a bispectral index signal (BIS) monitor to assess sedation level and non-rebreather oxygen mask with a reservoir bag (#0562 Adult CO2/O2 Sampling Mask, Westme), which allowed side-stream capnograph monitoring with a ventilator (Primus, Drägerwerk AG & Co. KGaA). To prevent air leakage from the gap between the mask and face, we adjusted the nose clip and used silicon tape (Innomed silicone tape, Chinoomed) around the mask. Moreover, the patient's neck was extended with a pillow to maintain airway patency. After the reservoir back was full of 100% oxygen, the oxygen flow was adjusted to 6 L/min. Despite gradual decrease in saturation at the beginning of sedation, oxygen saturation was maintained at 100% during the procedure.

Remimazolam was administered for sedation, with a loading dose of 6 mg/kg/hr over 3 minutes, followed by a maintenance dose of 0.3 mg/kg/hr after the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) reached 2 [2,3]. The BIS range was 60–80. We used remifentanil by the target site infusion method with the Minto model for pain reduction during the procedure, initially targeted at 0.8 ng/cc of an effect-site concentration and maintained at 1.0 ng/cc of effect-site concentration at which self-respiration was well maintained. To manage a sudden drop in blood pressure during rapid ventricular pacing, arterial line, and central venous catheter were inserted. The mean arterial blood pressure (MAP) was maintained above 75 mmHg, and respiration rate measured by capnogram remained regular at 10 breaths/min, with $EtCO_2$ levels at 25–30 mmHg.

We sampled the arterial blood to determine why the arterial blood pressure gradually decreased 45 minutes after sedation began. The pH of the arterial blood was 7.17, and the arterial carbon dioxide pressure ($PaCO_2$) and actual bicarbonate were 68.4 mmHg and 22.4 mmol/L, respectively. While we tried to wake the patient to encourage deep breathing, the MAP dropped below 40 mmHg, and the patient was pulseless, triggering resuscitation (Fig. 1). During resuscitation, the patient was intubated following 50 mg of rocuronium injection and general anesthesia was maintained by sevoflurane. Hyperventilation was applied to reduce $PaCO_2$. Following the conversion from monitored anesthesia care to general anesthesia, the $EtCO_2$ level was 38 mmHg. The patient recovered from cardiopulmonary collapse after one cycle of resuscitation. Arterial blood gas analysis (ABGA) improved (pH 7.31; $PaCO_2$ 44.9 mmHg; actual bicarbonate 22.4 mmol/L) without a sodium bicarbonate injection. The procedure finished successfully, and we extubated the patient after confirmation that ABGA was normal (pH 7.46; $PaCO_2$ 32.9 mmHg; actual bicarbonate 23.6 mmol/L) (Table. 1).

Discussion

$EtCO_2$ monitoring is an essential component of general anesthesia and is recommended for evaluating respiration during sedation [4]. It enables anesthesiologists to detect

the absence of respiration more quickly than pulse oximetry and provides information on the $PaCO_2$ level. However, these advantages are most effective for mechanically ventilated patients, limiting the utility of $EtCO_2$ monitoring to that specific population [5].

Mehta et al. [6] investigated the sensitivity of $EtCO_2$, an indirect measure of respiration, in relation to minute volume, which serves as a direct measurement of ventilation, three groups were compared: patients under general anesthesia, individuals undergoing procedural sedation, and awake volunteers. The procedural sedation group exhibited lower sensitivity than other groups, indicating that minute volume changed less in relation to $EtCO_2$ levels in that group [7].

Sedation may result in a dampened respiratory drive. The low sensitivity may be attributed to the blunting of the respiratory drive, which typically responds to elevated CO_2 levels and is regulated by central and peripheral chemoreceptor activation. Additionally, sensitivity demonstrates a bimodal distribution, with higher sensitivity observed when the depth of sedation approaches that of general anesthesia or while awake [6]. It has been observed that BIS does not reliably indicate the depth of sedation when using remimazolam [8]. Although no intraoperative awareness was reported with a BIS score of 60 or higher during remimazolam administration for general anesthesia, it does

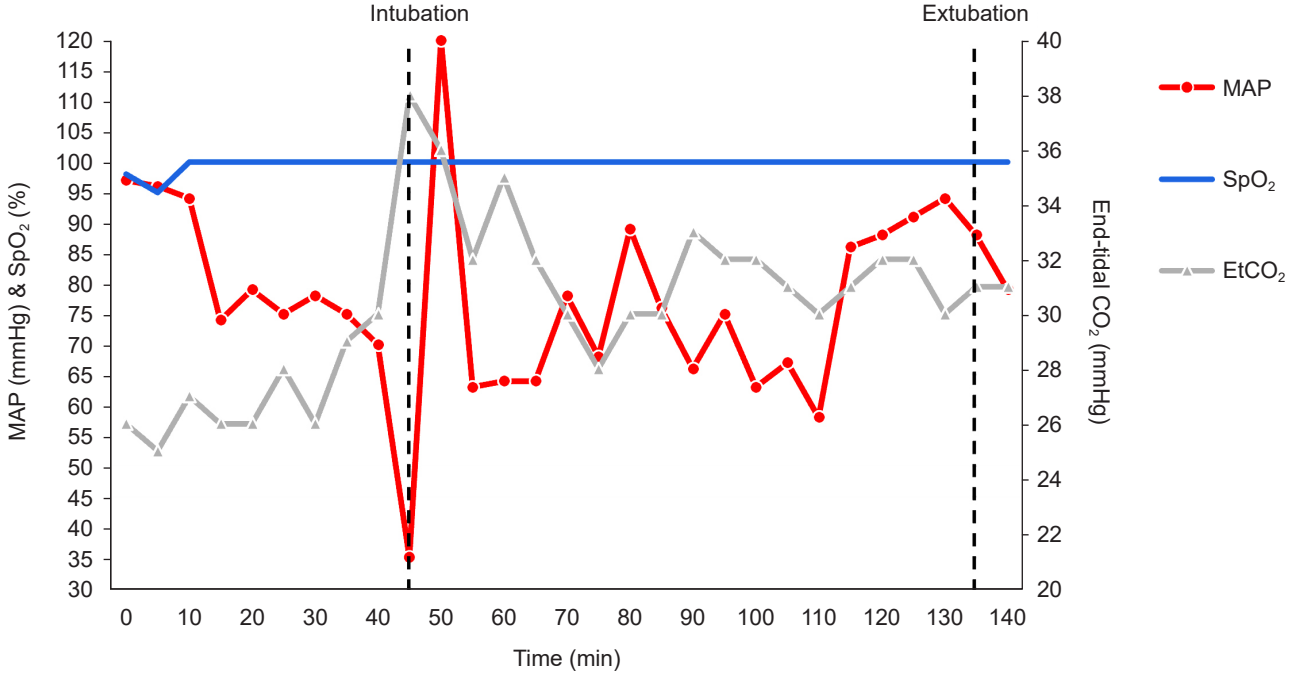

Fig. 1. The MAP gradually decreased until stabilization above 75 mmHg 15 minutes after the initiation of sedation. At 45 minutes after initiation, the MAP decreased to 35 mmHg, at which point the patient required resuscitation. Simultaneously, the patient was intubated, and the $EtCO_2$ value measured using a capnogram was 38 mmHg, whereas the arterial carbon dioxide pressure was 68.4 mmHg. MAP, mean arterial blood pressure; SpO_2, pulse oximetry; $EtCO_2$, end-tidal carbon dioxide.

Table 1. The values of pH, PaO_2, $PaCO_2$, and actual bicarbonate from the arterial blood gas analysis conducted in each situation

Situation	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Actual bicarbonate (mmol/L)
Gradual decrease of mean arterial pressure	7.17	230	68.4	22.4
After recovery from cardiovascular collapse	7.30	246	44.9	22.4
Procedure finished (FiO_2: 0.5)[a]	7.46	113	32.9	23.6

PaO_2, arterial oxygen pressure; $PaCO_2$, arterial carbon dioxide pressure; FiO_2, fraction of inspired oxygen.
[a]The FiO_2 was 0.5 when the procedure was finished, but the patient was not extubated.

not assure definite depth of the sedation [9]. Therefore, it is recommended to evaluate the depth of sedation using additional assessment tools like the MOAA/S scale to ensure more accurate results [2].

Herein, the patient received sedation with remimazolam, maintaining a BIS range of 60–80 and MOAA/S 2 [2,8]. Despite remimazolam having comparable efficacy and safety to propofol [2], irregular breathing patterns were observed following its initiation. Although the regularity of respiration stabilized soon after, the depth of sedation may have been intermediate, resulting in a lower sensitivity of $EtCO_2$ monitoring. Considering these factors, general anesthesia would be preferable to maximize the sensitivity of $EtCO_2$ monitoring.

$EtCO_2$ monitoring is further constrained by challenges associated with predicting $PaCO_2$ based on $EtCO_2$ measurements. Limited studies have demonstrated the usefulness of $EtCO_2$ monitoring as a predictor of $PaCO_2$. However, these studies only analyzed patients with acute asthma attacks, not those with respiratory distress like chronic obstructive pulmonary disease, pneumonia, and congestive heart failure. Also, they used less effective methods to measure the concordance between two factors [10,11]. When using the Bland and Altman plot analysis, the golden standard, $EtCO_2$ monitoring, showed limited effectiveness in predicting $PaCO_2$ in patients with respiratory distress [5].

The observed limitations in predicting $PaCO_2$ using $EtCO_2$ in patients with respiratory distress can be attributed to several factors. First, patients in respiratory distress often exhibit increased physiologic and pathologic dead space compared to healthy individuals. This results in a ventilation-perfusion mismatch, which impairs gas exchange between the alveoli and capillary arteries. Furthermore, shallow and rapid breathing patterns associated with respiratory distress may not allow adequate exhalation, leading to decrease in functional residual capacity. Consequently, the gradient between $EtCO_2$ and $PaCO_2$ was elevated. Although it was difficult to state that the patient who had several cardiopulmonary diseases, had shallow breath because of limited data about minute volume, these underlying conditions might contribute to weakened breathing and a significant degree in ventilation-perfusion mismatch, further complicating the prediction of $PaCO_2$ using $EtCO_2$ measurements.

According to the clinical practice guidelines for diagnostic and procedural sedation [12], $EtCO_2$ monitoring is recommended for preventing hypoxia during sedation. In this context, the application of $EtCO_2$ monitoring for our patient was effective in ensuring adequate oxygenation. However, the patient experienced cardiovascular collapse and demonstrated hypercapnia. The $EtCO_2$ and $PaCO_2$ gradient exceeded 30 mmHg, surpassing the acceptable limit [5]. This emphasizes the importance of not mistaking adequate oxygenation for effective CO_2 elimination. While the cardiovascular collapse in our case was likely due to inadequate exhalation of CO_2, it is possible that the excessive infusion of remimazolam from the beginning of the sedation might have been the underlying cause of the collapse. However, though remimazolam could induce not only respiratory regression but mild depression of mean blood pressure, the amount of remimazolam, infused up to cardiovascular collapse, was not even enough for the depression which was shown in the study [3].

The CO_2 retention in this case may have originated by anesthesiologists relying on $EtCO_2$, thought to reflect respiration during sedation. Other monitoring devices have similar utility in both general anesthesia and sedation. However, during sedation, $EtCO_2$ monitors are limited in evaluating the adequacy of a patient's respiration under respiratory distress. Therefore, medical staff providing sedation should not neglect periodical $PaCO_2$ evaluation by other means, such as ABGA.

Article information

Conflicts of interest

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

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Case report

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Interpedicular approach in percutaneous sacroplasty for treating pain due to direct invasion of rectal cancer into the S3 body: a case report

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Percutaneous sacroplasty is mainly used as an intervention for pain associated with sacral insufficiency fractures or sacral metastatic tumors. However, sacroplasty for managing the pain associated with direct sacral invasion of rectal cancer has been rarely reported. We present a case of a 74-year-old patient who underwent sacroplasty via the interpedicular approach under fluoroscopic guidance to relieve pain resulting from direct tumor invasion into the S3 body. After the procedure, the patient experienced immediate pain relief and did not feel worse pain with ambulation. Aside from peritumoral vascular leakage, no other significant complications occurred immediately post-procedure. Our results suggest that fluoroscopically guided interpedicular sacroplasty is a safe and effective option for relieving the pain associated with direct sacral invasion by rectal cancer.

Keywords: Cancer pain; Case report; Interventional radiology; Neoplasm invasion; Rectal neoplasms

Introduction

Bone invasion of the tumor in the sacrum usually produces pain due to tumor burden, fracture, instability, and neural compression [1]. Pain is a common symptom of sacral tumor invasion and usually occurs in the rectal or perineal region. The direct sacral invasion of rectal cancer is uncommon. In a study of pelvic recurrence, direct sacral invasion accounted for less than 5% of the local recurrence [2]. The two main methods of treating sacral invasion of rectal cancer are radiotherapy and surgical resection. However, the absence of significant complications renders surgical resection difficult, and radiotherapy takes time to relieve pain.

Sacroplasty, cement augmentation of the sacrum, is a safe and effective procedure for treating pain associated with sacral insufficiency fractures and metastatic tumors [3]. Accurate needle placement within the lesion is crucial when performing sacroplasty to treat pain caused by a sacral tumor. Several approaches can be adopted to achieve accurate needle placement to the lesion without complication, but the methods for effectively treating tumor lesions in the lower sacral body are limited. The interpedcular approach

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is a relatively recently introduced method in which the needle is advanced from the sacral hiatus through the sacral body parallel to the anterior edge of the sacrum, providing easy access to the sacral body lesion [4].

However, there are few documented cases of sacroplasty for the treatment of pain caused by rectal cancer directly invading the lower sacral body. We describe a case of sacroplasty performed using the interpedicular approach to manage pain caused by direct invasion of rectal cancer into the S3 body under fluoroscopic guidance, which resulted in immediate pain relief.

Case

Ethical statements: This study was exempted from review by the Institutional Review Board of Kyungpook National University Chilgok Hospital (IRB No. 2023-09-013). Written informed consent was obtained from the patients to participate in the study.

A 74-year-old woman with direct sacral invasion of rectal cancer was referred to our department due to symptoms of intractable perineal pain. She underwent transanal excision followed by neoadjuvant chemoradiotherapy. However, the patient reported escalating pain after neoadjuvant chemoradiotherapy, which scored 10 on the numeric rating scale (NRS), describing it as dull, lancinating, and similar to an electric shock. The pain worsened with ambulation.

Subsequent magnetic resonance imaging (MRI) and computed tomography (CT) scans of the lumbar spine showed rectal cancer invasion into the S3 body; no other lesions causing pain were found (Fig. 1). After consultation with the surgeon, the patient did not agree to undergo surgical tumor resection and receive additional radiotherapy. She felt that the previous radiotherapy had not been effective and thus preferred immediate pain relief. The initial intervention was a caudal epidural steroid injection, which reduced the NRS score to 6. However, the patient complained of persisting pain and wanted additional management. After consultation with her family and obtaining informed consent from her, we decided to perform percutaneous sacroplasty to relieve the pain caused by the direct sacral invasion of rectal cancer.

Prophylactic antibiotic therapy (1 g of cefazolin sodium; Yuhan Corp.) was intravenously administered 30 minutes before the procedure. Before the procedure, the patient's MRI and CT images were carefully reviewed, and the depth from the skin surface to the center of the lesion was determined for the interpedicular approach.

The patient was placed in the prone position to ensure relaxation. The sacrococcygeal region was carefully prepped with 10% povidone-iodine solution, and sterile draping was employed to maintain asepsis. After applying 2 mL of 1% lidocaine to the skin and subcutaneous tissue of the sacral hiatus to induce local anesthesia, a precise incision was made at the sacral hiatus using a scalpel. A 13-gauge bev-

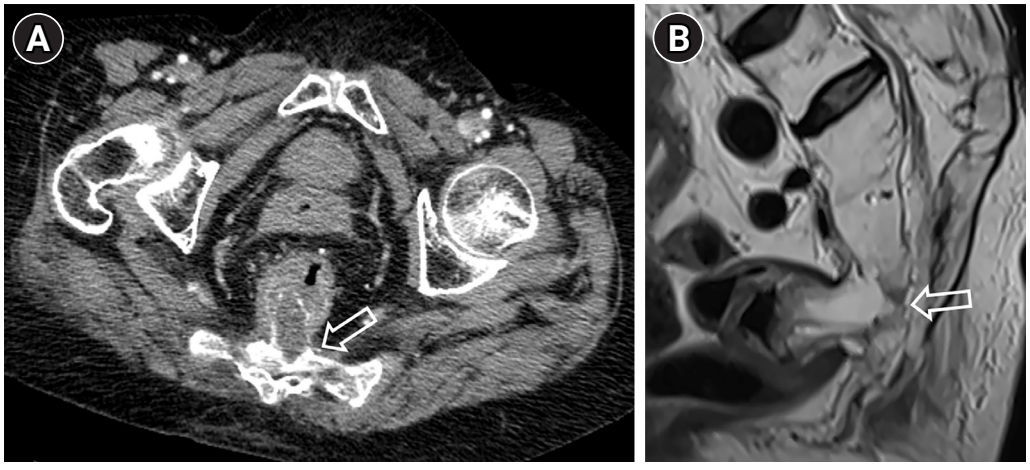

Fig. 1. (A) Axial computed tomography image showing direct sacral invasion of rectal cancer. (B) Sagittal magnetic resonance image showing direct tumor invasion into the S3 vertebral body. Open arrows indicate rectal cancer invasion.

el-edge needle (Manan Medical Products) was then inserted into the skin incision and subcutaneous tissue to reach the periosteum of the bone. After penetrating the posterior wall of the sacral canal, the needle was advanced to the anterior wall of the sacral canal, corresponding to the level of S4 body. Subsequently, the cortex was punctured, and the needle was carefully advanced through the bone until it reached the center of the lesion at the S3 body, maintaining an orientation parallel to the anterior edge of the sacrum. The needle was adjusted according to the sagittal and axial CT and MRI images to ensure accurate needle placement within the lesion under fluoroscopic guidance in multiple projections. After stylet removal, radiopaque contrast media was injected to obtain a tumor venogram, and the needle tip was finely adjusted to minimize peritumoral venous leakage. Polymethyl methacrylate (PMMA) (Exolent Spine, Elmdown LTD) was carefully injected into the lesion under fluoroscopic guidance in both the lateral and anterior-posterior views to ensure complete filling of the lesion and prevent PMMA leakage. Then, 2 mL of PMMA was carefully injected, and subsequent follow-up assessments confirmed optimal lesion filling without significant PMMA leakage to the sacral foramen or canal. Cement injection did not induce clinically significant complications or adverse side effects (Fig. 2).

After the procedure, the patient experienced substantial and immediate pain relief, as evidenced by an NRS score of 2, and did not have worse pain with ambulation on the following day; thus, the patient was eventually discharged. This analgesic effect was maintained until a 4-month follow-up.

Discussion

Sacroplasty, a variant of vertebroplasty, was first introduced in 2000 for the treatment of pain related to sacral metastatic tumors [5]. However, sacroplasty mainly treats osteoporotic insufficiency fracture pain [6]. Several studies have reported that sacroplasty is effective in treating pain related to sacral metastatic tumors [3,7,8]. However, there is little evidence of the efficacy of sacroplasty for pain relief in cases of direct sacral invasion of rectal cancer.

Percutaneous sacroplasty is more complicated than percutaneous vertebroplasty owing to its pyramidal and convex shape and porous structure, the difficulty in visualizing the anterior sacral cortical margin with fluoroscopy, poorly

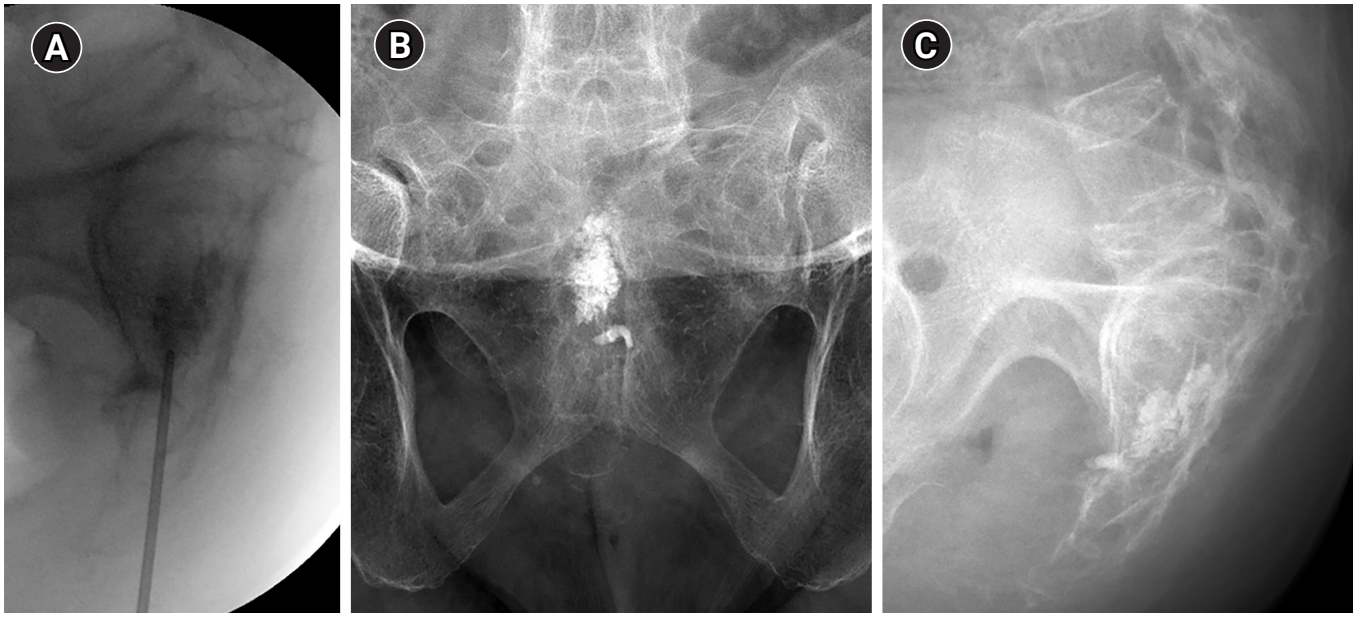

Fig. 2. (A) Fluoroscopic image showing precise needle placement using the interpedicular approach, with the needle tip positioned within the S3 body. Posttreatment frontal (B) and lateral (C) images show the presence of polymethyl methacrylate cement within the S3 body, accompanied by minimal presacral extravasation.

defined fluoroscopic landmarks for bone needle placement, and the risk of sacral nerve root or spinal canal compromise due to cement migration. Nerve root preservation is crucial in sacroplasty. Injury to bilateral L5 nerve roots typically affects ambulatory function, whereas injury to the S2 and S3 nerve roots affects bowel and bladder function [8].

Several approaches can be used for sacroplasty, including posterior (long and short axes), transiliac (lateral), anterior-oblique, and interpedicular approaches. The majority of these techniques were initially developed to access sacral ala lesions [9].

The lateral and anterior-oblique approaches can be employed for sacral body lesions. However, the lateral approach requires passage through the sacroiliac joint and sacral neural foramina zone. It carries a potential risk for nerve root and iliac bone damage, hinders clear visualization, and makes the identification of anatomical landmarks under lateral fluoroscopy difficult.

Similarly, although capable of providing access to the sacral body, the anterior-oblique approach presents challenges when approaching the lower sacral vertebral body due to the curved ventral cortical margin of the sacrum. It also carries a risk of sacral nerve root injury [8,10].

In the present case, we opted for the interpedicular approach, which avoids passage through the sacral neural foramina zone, minimizes the likelihood of ventral cortical sacral wall breakage, and allows for adequate fluoroscopic visualization of the S3 body [7]. We performed sacroplasty without damage to the sacral roots and visceral organs and significant extravasation. After the procedure, the patient immediately experienced pain relief and could ambulate without increasing pain.

The recommended volume of PMMA filling for the cervical, thoracic, and lumbar spine is 2.5, 5.5, and 7.0 mL, respectively [11]. Despite the increasing use of sacroplasty, a recommended volume for the procedure remains undefined. Kortman et al. [9] reported an average bone cement volume of 4.1 mL for sacroplasty, Frey et al. [12] documented a range of 2–5 mL, while Moussazadeh et al. [13] used an average of 6.4 mL for sacroplasty. In a cadaver study, the volume of injected PMMA in sacroplasty does not affect the strength and stiffness of bone [14]. Therefore, injecting an appropriate amount of cement without producing cement leakage, which causes nerve root and lumbosacral plexus damage, is essential.

Pain is a manifestation of neoplastic disease of the sacrum when the lesion causes either bony destruction or neuronal invasion and compression. Bony destruction activates pain receptors of the periosteum. The neurotoxic effect of PMMA and exothermic reaction during cement polymerization are suggested to induce periosteal denervation [15]. Cement injection for internal reinforcement of the trabecular bone can potentially stabilize microfractures within the sacrum effectively [16]. Furthermore, cement injection could induce tumor necrosis and reduce tumor volume, which further contributes to pain mitigation [16].

Pain from neural involvement is typically radicular and radiates along the S1 dermatome if the upper sacrum is involved or in the perineal region if the lower sacral nerve roots are involved. Numbness and paresthesia over the perineum, sacrum, and sole may also be observed with sacral nerve root or sacral plexus compression. In the present case, the patient did not report numbness or radicular pain, and imaging studies revealed no evidence of neuronal involvement. Therefore, sacroplasty was performed to relieve pain.

The pain reduction after sacroplasty seems to be favorable. Andresen et al. [17] demonstrated a sustained reduction in pain for up to 6 months after surgery, and Moussazadeh et al. [13] reported a significant reduction in pain in 80% of patients over an average follow-up of 6.5 months. These reports suggest that sacroplasty provides a favorable reduction in pain compared to radiotherapy, where the reported efficacy in reducing pain is typically 30% to 40% [18].

CT has an advantage over fluoroscopy for accurately placing needle tips in sacroplasty. However, CT does not always provide real-time monitoring during cement injection [4]. Fluoroscopy-only guided sacroplasty has difficulty visualizing sacral foramina [8]. Zhang et al. [8] suggested combining CT and fluoroscopy is the best alternative. However, combining CT and fluoroscopy increases procedure time and radiation exposure. Previous interpedicular approaches of sacroplasty were performed only fluoroscopy guided without complications [4,8]. So, we did sacroplasty using fluoroscopic guidance only.

The two main treatment methods for sacral invasion of rectal cancer are *en bloc* sacrectomy and palliative radiotherapy. *En bloc* sacrectomy as part of pelvic exenteration [19]. This method can increase disease-free survival by up to 33 months. However, it involves longer operation time

and is associated with significant blood loss (ranging from 1 to 7.5 L) and increased morbidity, with over 50% of patients reporting at least one major complication, such as pelvic abscess, sacroiliac joint instability, neurological complications of the lower body, or intractable pelvic girdle pain [19]. Owing to the high morbidity rate and significant risks of complications associated with the *en bloc* sacrectomy, the patient and her family decided against the procedure after consulting the surgeon.

Palliative radiotherapy is an alternative treatment for sacral tumor invasion. Radiotherapy is indicated in patients without spinal instability or acute neurological deterioration. However, it takes time for pain relief to manifest, and radiosensitivity varies among tumor types [20]. Our patient previously received radiotherapy, did not want additional radiotherapy, and complained of severe pain. Thus, we initially considered sacroplasty.

To the best of our knowledge, this is the first report to present percutaneous sacroplasty as an effective procedure for alleviating pain in the case of sacral invasion of rectal cancer. In this case, the interpedicular approach in percutaneous sacroplasty successfully relieved pain without causing significant complications.

In conclusion, sacroplasty using the interpedicular approach for managing pain related to direct sacral invasion of rectal cancer is a safe procedure and can alleviate pain without causing complications.

Article information

Conflicts of interest

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Author contributions

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Case report

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Disseminated herpes zoster with vagus nerve involvement in a kidney transplant recipient: a case report

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Herpes zoster virus infection is common and results in significant morbidity in patients who have undergone solid organ transplantation. Herpes zoster can involve the cranial nerves, and vagus nerve involvement is an infrequent primary manifestation of herpes zoster. Here, we describe a rare presentation of disseminated herpes zoster infection with vagus nerve involvement in a kidney transplant recipient. A 62-year-old man who had undergone kidney transplantation 3 years prior presented to our clinic with sore throat and hoarseness, followed by multiple vesicular-pustular rashes on the face and trunk. Flexible laryngoscopy revealed left paramedian vocal cord paralysis with multiple ulcerative lesions extending from the left pyriform sinus to the epiglottis. Computed tomography of the neck, abdomen, and chest revealed no significant abnormalities that could have caused vocal cord paralysis. We confirmed the diagnosis of disseminated herpes zoster after herpes zoster laryngitis based on positive blood tests and polymerase chain reaction for varicella zoster virus antibodies. The skin rashes and laryngeal ulcers rapidly resolved after treatment with intravenous acyclovir and high-dose steroids. The patient still had persistent dysphagia and microaspiration as assessed by a video fluoroscopic swallowing study, but showed improvement in dysphagia in response to swallowing rehabilitation therapy. This case provides valuable insights into the presenting symptoms of disseminated herpes zoster, which can cause acute vagus neuritis in solid organ transplantation recipients.

Keywords: Case reports; Herpes zoster; Kidney transplantation; Varicella zoster virus infection

Introduction

Varicella zoster virus (VZV) can cause a primary infection known as varicella (chicken pox), which later reactivates into herpes zoster (HZ, shingles) within the sensory neuron body in the dorsal ganglion [1]. HZ is more common in immunocompromised individuals, particularly in those who have undergone solid organ transplantation (SOT), with an incidence of 8% to 11% in the first 4 years [2]. HZ typically presents with prodromal symptoms such as fever, malaise, and burning pain around the unilateral dermatome, followed by erythematous vesicular rashes over several days. The most commonly affected dermatomes in patients with HZ are in the thoracic, trigeminal, cervical, and lumbar regions [3]. Although less common, HZ can also involve the cranial nerves (CN). A retrospective study demonstrated that the trigeminal nerve (CN V, 57.9%), facial nerve (CN VII, 52.1%), and vestibulocochlear nerve (CN VIII, 20%) are commonly affected; however, involvement of the vagus nerve (CN X, 0.9%) is very rare [4].

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Disseminated HZ is a serious complication that occurs more frequently in SOT recipients than in the general population. Previous studies have reported a global mortality rate of approximately 30% in cases of disseminated HZ and a high incidence in SOT recipients [5,6]. HZ typically presents with unilateral dermatomal involvement and subsequently spreads to affect three or more dermatomes, which can lead to serious complications involving the central nervous system or internal organs, such as the gastrointestinal tract, liver, lung, and pancreas [2]. Herein, we present a rare case of disseminated HZ following acute vagus neuritis in a kidney transplant recipient.

Case

Ethical statements: This study was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. 2311-008-133). Written informed consent was waived because the retrospective design of the study.

A 62-year-old man with a history of end-stage kidney disease of unknown cause underwent deceased donor kidney transplantation (KT) 3 years ago. He had no other comorbidity such as hypertension or diabetes, and had been receiving hemodialysis for 6 years before KT. At the time of KT, the patient had no donor-specific antibodies and received induction therapy with basiliximab. Two months after KT, he was treated for T-cell-mediated rejection with methylprednisolone pulse therapy. He had to reduce his immunosuppressive agents because of subsequent cytomegalovirus viremia. The patient was taking prednisolone (2.5 mg daily), mycophenolic acid (180 mg twice daily), and tacrolimus (2 mg twice daily) with trough levels of 4–5 ng/mL. His serum creatinine level has been maintained within the range of 0.9–1.0 mg/dL.

He presented to our clinic with sore throat and hoarseness, followed by multiple vesicular-pustular rashes on the face and trunk (Fig. 1A, 1B). Flexible laryngoscopy revealed left paramedian vocal cord paralysis, with multiple ulcerative lesions extending from the left pyriform sinus to the epiglottis (Fig. 1C). Computed tomography of the neck and chest revealed no significant abnormalities that could have caused vocal cord paralysis. Laryngeal electromyography (EMG) revealed a fibrillation potential in the left thyroarytenoid muscle innervated by the left recurrent laryngeal nerve (RLN). Laboratory data showed a white blood cell of 5,570/μL, C-reactive protein of 0.68 mg/dL, serum creatinine of 1.05 mg/dL, VZV immunoglobulin G of 2.25 (reference, positive: ≤0.90), and immunoglobulin M of 1.4 (reference, positive: ≤1.10), as well as a positive blood test for VZV polymerase chain reaction. Serologies for other viruses that could cause laryngitis were negative (Table 1).

Based on these findings, we diagnosed the patient with disseminated HZ following acute vagus neuritis. We admin-

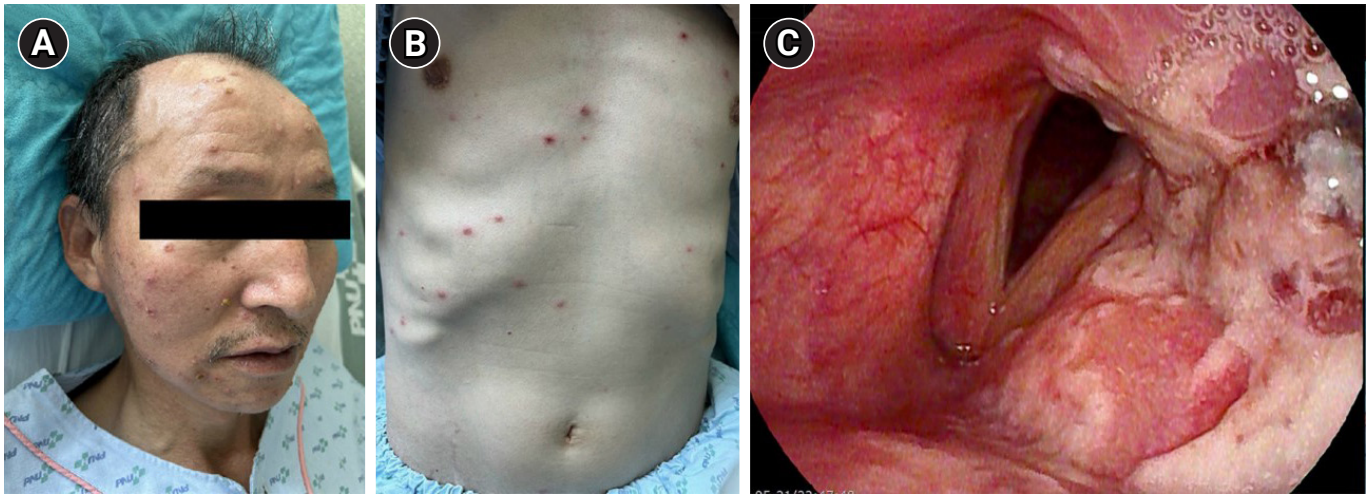

Fig. 1. (A, B) Multiple vesicular-pustular rashes on the face and trunk. (C) Left paramedian vocal cord paralysis with multiple ulcerative lesions extending from the left part of the pyriform sinus to the epiglottis.

Table 1. Serological findings associated with vocal cord paralysis

Variable	Result	Reference value
Varicella zoster IgG	Positive	Negative
Varicella zoster IgM	Positive	Negative
Varicella zoster PCR	Positive	Negative
CMV PCR	Negative	Negative
CMV IgM	Negative	Negative
EBV anti-VCA IgM	Negative	Negative
EBV anti-VCA/EA-D IgG	Negative	Negative
EBV real-time PCR	Negative	Negative
HSV IgG	Positive	Negative
HSV IgM	Negative	Negative
Influenza A virus PCR	Negative	Negative
Influenza B virus PCR	Negative	Negative

Ig, immunoglobulin; PCR, polymerase chain reaction; CMV, cytomegalovirus; EBV, Epstein-Barr virus; anti-VCA, anti-viral capsid antigen; anti-EA-D, anti-early antigen-diffuse; HSV, herpes simplex virus.

istered intravenous acyclovir (10 mg/kg every 8 hours) for 14 days along with 1,000 mL of intravenous normal saline to prevent acyclovir-related nephropathy, and high-dose prednisolone (0.5 mg/kg/day) was given for 7 days, then tapered to 2.5 mg/day to reduce the risk of neurological complications. We also reduced the immunosuppressive agents, including mycophenolic acid (180 mg daily) and tacrolimus (1.5 mg twice daily) with trough levels of 3–5 ng/mL. During hospitalization, his serum creatinine was carefully monitored and the dose of tacrolimus was adjusted according to trough levels (Fig. 2). As a result, there was rapid resolution of skin rashes and laryngeal ulcers (Fig. 3A). However, 2 weeks after the completion of treatment, the patient still experienced persistent hoarseness, dysphagia, and evidence of microaspiration, as assessed by video fluoroscopic swallowing study (Fig. 3B). We injected hyaluronic acid into the paralyzed vocal cord and the patient showed improvement in dysphagia and hoarseness with continuous swallowing and speech rehabilitation therapy.

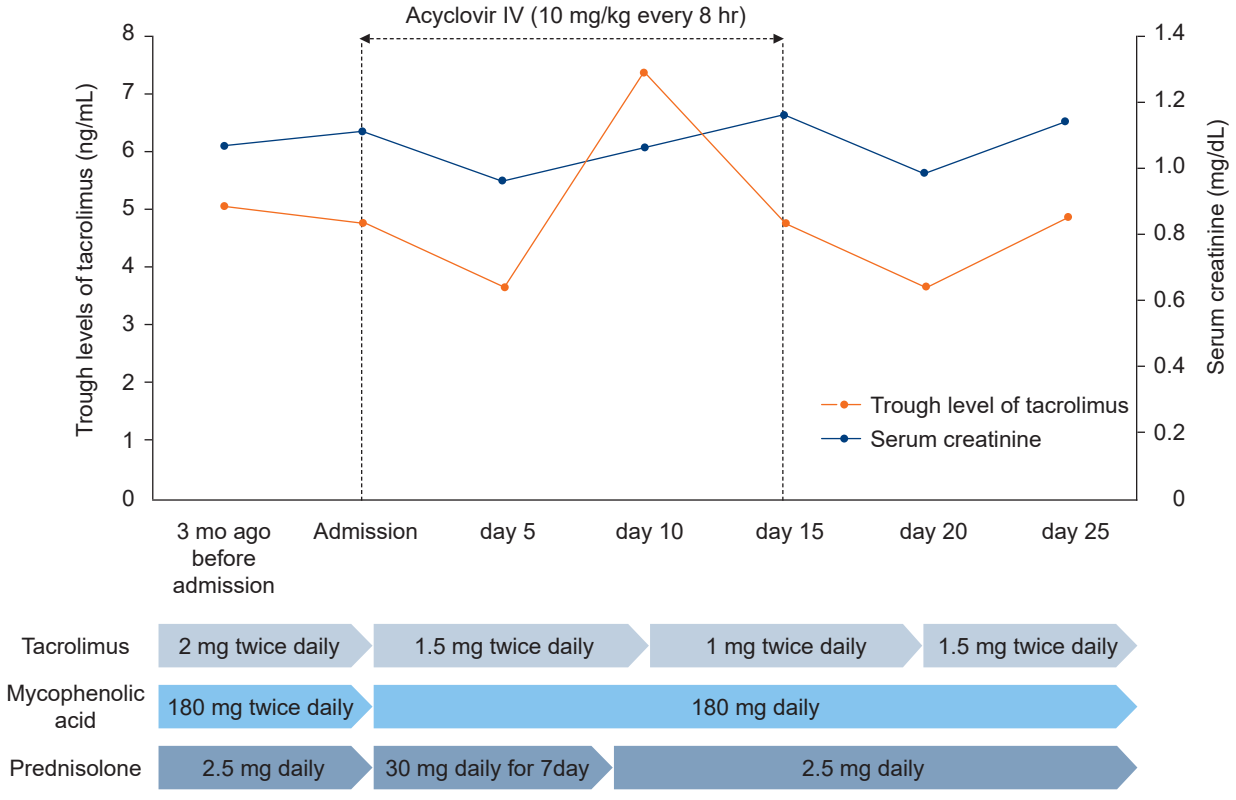

Fig. 2. Changes in serum creatinine, trough levels of tacrolimus, and dose adjustment of immunosuppressive agents during hospitalization. IV, intravenous.

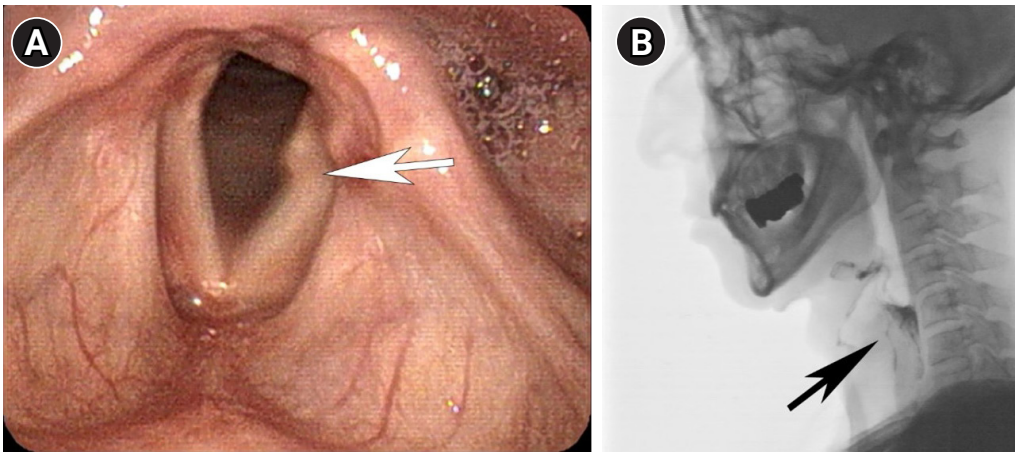

Fig. 3. (A) Persistent vocal cord paralysis despite resolution of laryngeal ulcers (white arrow) 2 weeks after the completion of treatment. (B) Video fluoroscopic swallowing study showing poor pharyngeal constriction with moderate liquid retention and delayed aspiration (black arrow) in the pharyngeal phase.

Discussion

SOT recipients on lifelong immunosuppressive therapy are at high risk of VZV reactivation, which can subsequently lead to disseminated disease or internal organ involvement. A meta-analysis of 6,560 SOT recipients showed that the overall incidence of HZ was 9.1% and that heart transplantation had the highest incidence of HZ (15.2%), followed by lung transplantation (11.0%) and KT (6.7%) [7]. They further demonstrated that a higher incidence of post-transplant HZ was associated with a higher proportion of previous graft rejection.

A previous study reported atypical cases of HZ in KT recipients, including the involvement of CN V (V1), multiple thoracic dermatomes (T2–T5), and disseminated disease with septic shock as primary manifestations [8]. These cases demonstrated that the presentation of HZ may be atypical, and the severity of HZ may vary depending on the degree of immunosuppression in SOT recipients.

In this case, the patient presented with vagus nerve involvement, which is a rare manifestation of HZ. Flexible laryngoscopy revealed unilateral ulcerative lesions on the laryngeal mucosa, suggesting involvement of the internal branch of the superior laryngeal nerve, which originates from the vagus nerve. Additionally, we observed left paramedian vocal cord paralysis, suggesting injury to the RLN, which innervates the laryngeal muscles and originates from the vagus nerve [9].

Several viral etiologies have been reported to cause vocal cord paralysis, including cytomegalovirus, influenza virus, Epstein-Barr virus, herpes simplex virus, and VZV. Of these, VZV and herpes simplex viruses can cause permanent damage [10]. A previous study has revealed that the full recovery rate of HZ-associated vocal cord paralysis is 60% to 62.5% [11].

Laryngeal EMG is a useful tool for evaluating the neurological prognosis of RLN injury. The presence of spontaneous activity, such as fibrillation potentials or positive sharp waves on EMG, indicates a poor prognosis [12]. In this case, 2 weeks after the completion of treatment, the laryngeal EMG revealed a fibrillation potential in the left thyroarytenoid muscle innervated by the RLN, and a subsequent flexible laryngoscopy still showed paramedian vocal cord paralysis. Despite the poor prognosis indicated by the laryngeal EMG, his dysphagia and hoarseness improved with conservative treatments, including injection of hyaluronic acid into the paralyzed vocal cord to correct the incomplete closure of the glottis, and continuous swallowing and speech rehabilitation therapy. Therefore, these conservative treatments are essential for preventing permanent neurological complications in patients with HZ complicated by acute vagus neuritis.

The preferred treatment for HZ in immunocompromised patients is intravenous acyclovir (10 mg/kg every 8 hours) for 7 to 10 days. Administration of intravenous acyclovir within 72 hours of rash onset effectively suppresses disease

progression by inhibiting viral replication and prevents the spread of viral infections to other organs or dermatomes [13]. Of note, a synergistic nephrotoxicity should be considered when intravenous acyclovir is used in combination with a calcineurin inhibitor in SOT recipients [14]. Adequate intravenous hydration is required to prevent the formation of acyclovir crystals, along with careful monitoring of serum creatinine and trough levels of calcineurin inhibitors.

When patients are complicated by VZV-associated neuritis, combination therapy with intravenous acyclovir and high-dose steroids may be helpful. Steroids are known to reduce neural edema through their anti-inflammatory effects, thereby preventing permanent damage. Early initiation of steroid therapy during the course of the disease may improve neurological complications [15,16]. Furthermore, it is necessary to reduce immunosuppressive agents, particularly mycophenolate mofetil or mycophenolic acid, in order to reduce severe complications and mortality [17,18].

To reduce the risk of HZ in SOT recipients, it is ideal to administer the HZ vaccination before organ transplantation, but it is not always guaranteed. Currently, a non-live recombinant zoster vaccine has been demonstrated to be immunogenic and safe, even when administered 4 to 18 months after transplantation [19]. This provides an opportunity to overcome the limitation of being unable to administer a live vaccine to unvaccinated patients after transplantation, thus reducing the risk of HZ.

In conclusion, we encountered a rare case of HZ involving the vagus nerve in a kidney transplant recipient, which subsequently progressed to disseminated disease and may have resulted in serious neurological complications. However, this was minimized by early administration of an antiviral agent with high-dose steroids, and intensive rehabilitation therapy. This case provides valuable insights into the presenting symptoms of disseminated HZ, which can cause acute vagus neuritis in SOT recipients.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: EYS. Data curation: DEK. Visualization: DEK. Supervision: EYS, SHS. Writing – original draft: DEK. Writing – review & editing: DWK, HR, HJK.

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Case report

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Total intravenous anesthesia using remimazolam for patients with heart failure with reduced ejection fraction: a case series

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Patients with heart failure undergoing surgery that requires general anesthesia face substantial perioperative risks; however, clear guidelines are not available for anesthesia management in patients with a reduced left ventricular ejection fraction. Traditional intravenous and volatile anesthetics require careful administration to prevent severe hypotension and bradycardia in patients with heart failure. Remimazolam has emerged as a promising alternative to conventional anesthetics because of its reduced cardiovascular depressive effects. We present three cases illustrating the successful use of remimazolam to induce and maintain general anesthesia in patients with heart failure and reduced cardiac function. Our cases demonstrate the safe use of remimazolam for general anesthesia in patients with heart failure and a reduced ejection fraction.

Keywords: Anesthesia; Case reports; Heart failure; Remimazolam; Ventricular ejection fraction

Introduction

Heart failure is a syndrome frequently encountered by anesthesiologists in the operating room. Patients with heart failure have a high risk of perioperative mortality and morbidity, and anesthesiologists may have difficulty maintaining stable hemodynamic status [1]. Owing to perioperative and postoperative adverse events, it is imperative to exercise caution when patients with heart failure undergo surgery under general anesthesia. However, there are no high-grade recommendations for anesthetic practice in patients with reduced left ventricular ejection fraction (LVEF) [2]. Commonly used intravenous and volatile anesthetics should be administered carefully because of their potential cardiovascular depressant effects, which can lead to severe hypotension and bradycardia, ultimately resulting in cardiovascular collapse in patients with heart failure [1].

Remimazolam (Byfavo; Hana Pharm Co., Ltd.) is an ultra-short-acting benzodiazepine used for sedation and general anesthesia [3]. Reportedly, remimazolam causes fewer cardiovascular depressant effects than conventional propofol induction and inhalational agent maintenance in general anesthesia. However, previous clinical trials did not include patients with severe heart failure, including those undergoing cardiac surgery [3]. Herein, we present three cases in which remimazolam was used to induce and maintain gen-

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eral anesthesia in patients with reduced heart function undergoing both non-cardiac and cardiac surgeries, including cardiopulmonary bypass (CPB).

Case

Ethical statements: This report was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (IRB No. 05-2023-124), which waived the requirement for informed consent given its retrospective nature.

1. Case 1

A 75-year-old man (height: 165 cm; weight: 54 kg) with a history of diabetes mellitus presented to the emergency room with closed tibia and fibula fractures caused by a slip-and-fall incident. Preoperative transthoracic echocardiography (TTE) revealed left ventricular (LV) systolic dysfunction with an ejection fraction (EF) of 35%, possibly due to an old myocardial infarction affecting the anteroseptal and lateral walls. Additionally, mild aortic stenosis was noted, with a transaortic valve maximum velocity (Vmax) of 2.25 m/sec and peak and mean pressure gradients of 20/11 mmHg. Open reduction and internal fixation of the tibia and the fibula were scheduled. After the patient entered the operating room, routine monitoring, including noninvasive blood pressure (BP), electrocardiography, percutaneous oxygen saturation (SpO_2), and bispectral index (BIS), was performed. The vital signs before anesthesia induction were as follows: BP, 126/62 mmHg; heart rate (HR), 65 beats per minute; and SpO_2, 100%. Remimazolam was administered at 6 mg/kg/hr with remifentanil in a target-controlled infusion mode. Once the patient lost consciousness, the infusion rate of remimazolam was adjusted to 1–2 mg/kg/hr to maintain a BIS value between 40–60. Rocuronium 1 m/kg was administered, and intubation was successfully performed. A radial artery catheter and large-bore peripheral line were inserted. Milrinone was started at a dose of 0.5 μg/kg/min to support LV systolic function and, phenylephrine was initiated at 0.3 μg/kg/min to prevent vasoplegia, but was later discontinued due to hypertension. Vital signs remained stable throughout the operation, and no additional vasopressors were required. Transient hypertension during the operation was managed with nicardipine boluses (0.3 mg and 0.2 mg). Upon the end of the operation, flumazenil (0.5 mg, Flunil; Bukwang Pharm Co., Ltd.), and sugammadex (200 mg, Bridion; Merck & Co., Inc.) were given (Fig. 1A). The patient was successfully extubated and transferred to the post-anesthesia care unit without any complications.

2. Case 2

A 53-year-old man (height: 168.7 cm; weight: 67 kg) with a history of diabetes mellitus, end-stage renal disease on peritoneal dialysis, and three-vessel coronary artery occlusive disease with percutaneous stents inserted in the right coronary, left anterior descending, and left circumflex arteries presented to the emergency room with a bimalleolar ankle fracture. Preoperative TTE showed LV akinesia from the mid to basal posterolateral wall and middle inferior wall with moderate LV systolic dysfunction and an EF of 39%, attributed to ischemic heart failure. The patient was scheduled to undergo open reduction and internal fixation of the bimalleolar fracture. Routine monitoring of noninvasive BP, electrocardiography, percutaneous oxygen saturation, and BIS was performed. The initial vital signs before anesthesia induction were as follows: BP, 140/83 mmHg; HR, 85 beats per minute; and SpO_2, 98%. Remimazolam was administered at a dose of 6 mg/kg/hr with remifentanil infusion. Once the patient became unconscious, the remimazolam dose was adjusted to 1–2 mg/kg/hr to maintain a BIS value between 40–60. Rocuronium 0.7 m/kg was administered, and intubation was successfully performed. Vital signs remained stable throughout the operation, and no additional vasopressors or inotropes were required. At the end of the surgery, flumazenil (0.5 mg) was administered along with sugammadex (100 mg) (Fig. 1B). The patient was extubated and transferred to the post-anesthesia care unit without complications.

3. Case 3

A 64-year-old man (height: 170 cm; weight: 65 kg) with hypertension, dyslipidemia, stage 2 chronic kidney disease, and severe aortic stenosis underwent elective aortic valve replacement with thoracotomy for minimally invasive cardiac surgery. The patient presented with symptoms of dyspnea that had progressed over 3 months before the operation, reaching New York Heart Association class IV. Preoperative TTE revealed severe degenerative aortic stenosis with a transaortic Vmax of 5.3 m/sec, peak and mean pressure gradients of 111/59 mmHg, and mild aortic regurgitation. While there was no definite regional wall motion abnormality, severe LV systolic dysfunction was

evident, with an EF of 30%. Moderate resting pulmonary hypertension and right ventricular dysfunction were also observed. Before the operation, a radial artery catheter was inserted for continuous arterial BP monitoring. After standard monitoring, remimazolam was initiated at 6 mg/kg/hr along with remifentanil infusion. When the patient became unconscious, the infusion rate of remimazolam was adjusted to 1–2 mg/kg/hr to maintain a patient-state index between 25–50. Rocuronium (0.8 mg/kg) was administered for intubation, and norepinephrine was administered to maintain BP. Surgery commenced, and remimazolam was continuously infused to maintain a patient-state index between 25–50, even during CPB. Dobutamine and milrinone were both started at a dose of 0.5 μg/kg/min after the aortic cross-clamp was released to support cardiac function. At the end of the surgery, sugammadex (200 mg) and flumazenil (0.5 mg) were administered, and extubation was performed in the operating room (Fig. 1C). The patient was transferred to the intensive care unit without postoperative complications. The following day, the patient was transferred to the general ward and discharged from the hospital on postoperative day 4.

Discussion

Patients with reduced LVEF have risk for intraoperative hypotension and bradycardia [4]. In the presence of reduced LVEF, systolic BP, and pulse pressure are dependent on LV stroke volume, while mean arterial pressure and diastolic BP are dependent on the degree of peripheral vasodilatation [5]. Many anesthetic agents decrease myocardial contractility and systemic vascular resistance, resulting in hypotension and reduced coronary perfusion. This can be particularly risky for patients with reduced EF. While anesthetic goals in patients with advanced heart failure and reduced EF should focus on avoiding hypotension to

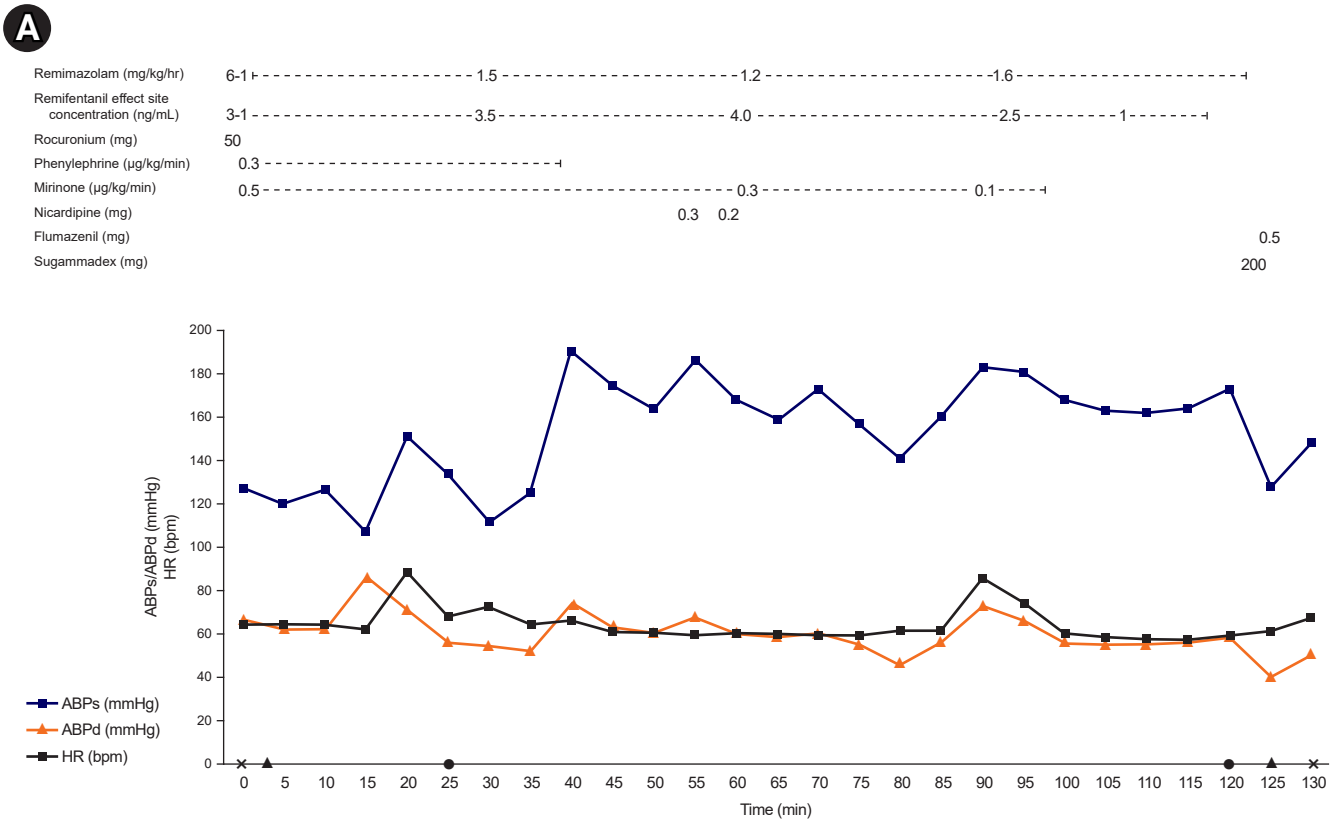
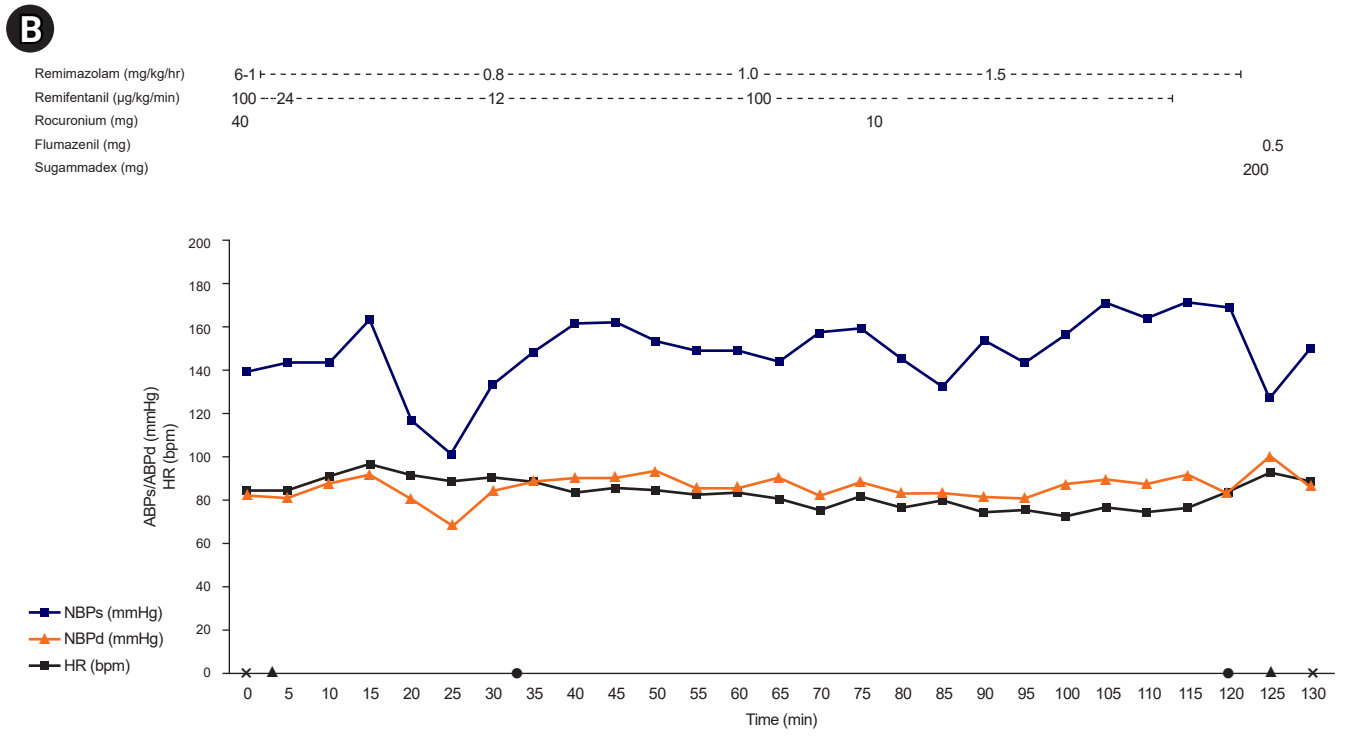


Fig. 1. Changes in hemodynamic status under general anesthesia. (A) Case 1. (B) Case 2. (C) Case 3. ABPs, systolic artery blood pressure; ABPd, diastolic artery blood pressure; bpm, beats per minute; HR, heart rate; ×, beginning or ending of anesthesia; ▲, endotracheal intubation or extubation; ●, start or end of surgery (Continued to the next page).



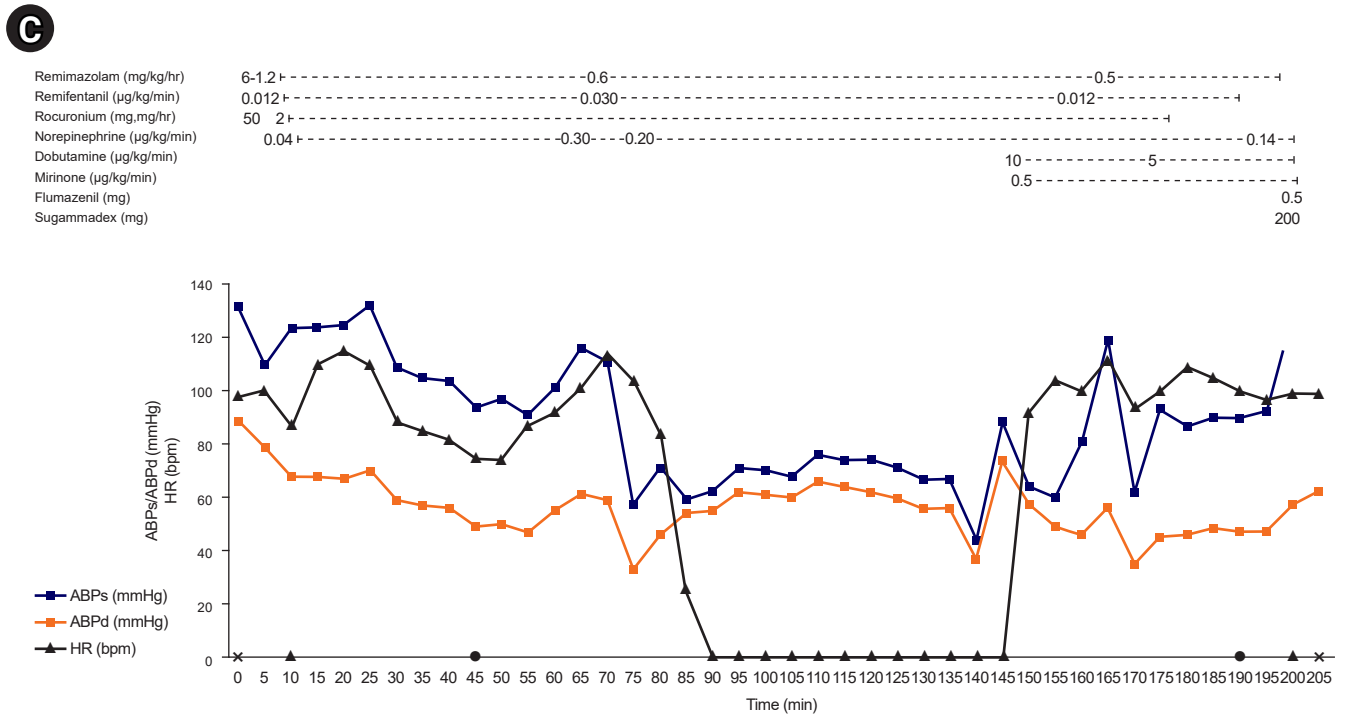


Fig. 1. (Continued from the previous page)

maintain coronary perfusion and cardiac output, it is worth noting that there are no definitive anesthetic guidelines for patients with heart failure [1]. In our three cases, although cardiac output was not continuously monitored during surgery, the patients remained hemodynamically stable under remimazolam anesthesia, with the use of relatively low doses of vasopressors and inotropic agents.

Propofol is commonly used to induce and maintain anesthesia. However, through direct activation of the chloride channel of GABAA receptors, propofol rapidly inhibits cardiac contractility and reduces preload due to vasodilation. This can lead to fatal circulatory failure. However, benzodiazepines induce a mild allosteric response that increases the affinity of GABA for the receptor, and therefore have relatively less vasodilatory and myocardial depressant effects [6]. Remimazolam, whose effect can be reversed by flumazenil, causes less hypotension during general anesthesia than during conventional inhalational anesthesia [3]. This effect could be particularly valuable in patients with severe heart failure or those undergoing cardiac surgery. However, few case reports have documented the use of remimazolam in cardiac surgery and in patients with heart failure [7,8].

In a study by Nakanishi et al. [9], when remimazolam was administered at a rate of 6 mg/kg/hr to induce anesthesia, the mean arterial pressure decreased slightly until consciousness was lost. Furthermore, in a study involving healthy patients, when the administration rate of remimazolam was adjusted to 5 mg/min for 5 minutes, 3 mg/min for the next 15 minutes, and 1 mg/min for an additional 15 minutes, the average arterial pressure decreased by approximately 24% [10]. The induction dose of remimazolam is generally 12 mg/kg/hr, but successful anesthesia induction is possible with 6 mg/kg/hr; therefore, a lower dose is recommended for the elderly or patients with American Society of Anesthesiologists class 3 or higher [11]. In our cases, we used a dose of 6 mg/kg/hr for induction, and observed no adverse events, such as anesthesia recall or induction failure. Similarly, there are other case reports on the use of remimazolam in patients with heart failure and severe aortic stenosis undergoing cardiac surgery using a dose of 6 mg/kg/hr without complications [7,8]. However, further studies are required to determine a suitable induction dose for patients with reduced EF.

Despite these hemodynamic advantages, there may be concerns about the occurrence of awareness due to a slightly high BIS during general anesthesia using remimazolam. The range of the BIS index for maintaining an appropriate depth of anesthesia when using remimazolam is approximately 60–70; therefore, the appropriate range is unclear [12]. However, according to a study by Liu et al. [13], hemodynamic stability can be maintained even by maintaining a BIS of 40–60 under remimazolam anesthesiaFormatting.... Remimazolam has the advantage of being predictable in anesthesia induction and emergence due to its rapid onset of action and short contact-sensitive half-life. However, delayed awakening of more than 30 minutes has been reported to occur in approximately 8% of cases [14]. Flumazenil can be used to antagonize remimazolam; however, caution must be exercised against rapid increases in BP, as vascular resistance may rapidly increase [8].

In conclusion, our three cases demonstrate that remimazolam can be safely used for general anesthesia in patients with heart failure and reduced EF for hemodynamic stability. However, BIS monitoring for awareness prevention and careful use of flumazenil during reversal are necessary. Clinical trials involving these patient populations are also required to establish clear dosage guidelines.

Article information

Conflicts of interest

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

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Author contributions

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