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Aims and scope

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Editorial

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Congenital mild ptosis might not influence visual function in esotropia patients

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See "Stereopsis and clinical features of esotropia patients accompanied by congenital mild ptosis" by Heeyoung Choi, Su-Jin Kim, Seungahn Yang, Kwang Eon Hane

Childhood is critical for the development of visual function. Insufficient exposure to visual stimuli during this period can lead to conditions such as amblyopia and reduced stereopsis, which do not improve in adulthood. Ptosis is a cause of deficient visual stimuli, and studies have shown that the incidence of strabismus is higher in patients with ptosis than in the general population [1,2]. A previous study reported the prevalence of strabismus in children with eyelid ptosis [3]. However, insufficient research has explored the development of visual function in cases of congenital mild ptosis that does not cover more than half of the eye. It is essential to carefully monitor such patients and repeatedly assess whether a therapeutic intervention is necessary. Therefore, research on the development of visual function in patients with mild ptosis accompanied by strabismus will provide meaningful insights in clinical practice.

This article published in *Kosin Medical Journal* [4] compared the visual function of patients with simple esotropia and those with esotropia accompanied by ptosis, building upon previous research by the same group that compared visual acuity and stereopsis between patients with simple exotropia and those with exotropia accompanied by ptosis [5]. These two studies found that in patients with esotropia, ptosis did not affect visual function, including stereopsis, whereas in those with exotropia, ptosis led to a reduction in distance stereopsis and suppression. However, it is important to note that factors such as the timing of strabismus onset and the duration of the condition can influence the development of visual function [6]. Therefore, standardizing the onset, angle, and duration of strabismus is essential for drawing definitive conclusions. In this current study on esotropia, a sub-analysis was conducted based on the degree of ptosis (0<marginal reflex distance 1 [MRD1]≤1 and 1<MRD1≤2). Mild ptosis did not affect stereopsis. However, the study did not differentiate between distance and near vision, which could limit the findings since convergence at near distances might have a lesser impact on the development of stereopsis. Additionally, the study did not differentiate between various subtypes of esotropia, such as accommodative esotropia, non-accommodative esotropia, and congenital esotropia. This omission makes it challenging to generalize the results to all forms of esotropia.

Nevertheless, ongoing research, including this study, is likely to contribute to the understanding of visual acuity

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and visual function development in patients with simple esotropia and those with esotropia accompanied by ptosis. Despite several limitations—including its retrospective nature, small sample size, lack of data on post-surgical binocular function, absence of lateralization analysis of ptosis, and no consideration of esotropia types—this study provides valuable suggestions for future research. Nonetheless, the strength of this research lies in its quantitative assessment of binocular function in esotropia patients with congenital ptosis compared to esotropia-only patients.

To enhance the quality and reliability of data, future research should focus on conducting prospective studies and expanding the sample size through multicenter, large-scale studies to improve statistical power and generalizability. Additionally, it is crucial to investigate potential improvements in binocular function following ptosis surgery, particularly if reductions in visual functions, including stereopsis, are observed across various degrees of ptosis. It is also important to perform lateralization analyses to compare visual outcomes between affected and unaffected eyes. Finally, investigating the effects of different types of esotropia on visual acuity and stereoacuity will provide a more comprehensive understanding of the condition.

In conclusion, this study highlights the importance of understanding the development of visual function in patients with esotropia and ptosis. Despite its limitations, the research offers valuable insights and proposes directions for future studies.

Article information

Conflicts of interest

Chang Zoo Kim 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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Review article

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The ethics of using artificial intelligence in medical research

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The integration of artificial intelligence (AI) technologies into medical research introduces significant ethical challenges that necessitate the strengthening of ethical frameworks. This review highlights the issues of privacy, bias, accountability, informed consent, and regulatory compliance as central concerns. AI systems, particularly in medical research, may compromise patient data privacy, perpetuate biases if they are trained on nondiverse datasets, and obscure accountability owing to their "black box" nature. Furthermore, the complexity of the role of AI may affect patients' informed consent, as they may not fully grasp the extent of AI involvement in their care. Compliance with regulations such as the Health Insurance Portability and Accountability Act and General Data Protection Regulation is essential, as they address liability in cases of AI errors. This review advocates a balanced approach to AI autonomy in clinical decisions, the rigorous validation of AI systems, ongoing monitoring, and robust data governance. Engaging diverse stakeholders is crucial for aligning AI development with ethical norms and addressing practical clinical needs. Ultimately, the proactive management of AI's ethical implications is vital to ensure that its integration into healthcare improves patient outcomes without compromising ethical integrity.

Keywords: Artificial intelligence; ChatGPT; Compliance; Ethics; Social responsibility

Introduction

As insights into the relationship between research and technology rapidly evolve, new nuances in ethical concerns have emerged [1]. Historically, ethics in medical research has primarily focused on the security and protection of human subjects. However, with the increasing use of advanced technologies in contemporary research, expanding our ethical considerations has become necessary [2]. This shift requires addressing additional dimensions to ensure enhanced ethical safeguards in human research.

Currently, the forefront of technology, particularly artificial intelligence (AI) and its specific applications such as ChatGPT (generative pre-trained transformer, OpenAI), is becoming increasingly relevant in discussions of ethical issues related to medical research [3,4]. These technologies present unique challenges that necessitate a re-evaluation of ethical frameworks to ensure they are adequately addressed. Furthermore, the acceptance of ethical issues in medical research varies across cultural backgrounds and

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generations of researchers [5-8]. This cultural and generational divide has influenced perspectives on medical ethics, leading to various manifestations in research practices concerning ethical issues.

However, researchers continue to face challenges in evaluating the performance of studies incorporating AI [9-11]. In this review, we examine articles that discuss the ethical issues arising in medical research involving such technologies. We aimed to reflect on these debates and propose potential resolutions (Fig. 1).

Methods

This review examines recent studies addressing ethical issues in medical research. Given the significant impact of these ethical considerations on the direction of medical research, we thoroughly analyzed the norms and strategies related to ethics accountability. Our methodology employed a holistic approach, encompassing all academic disciplines and levels, with a specific focus on sourcing evidence from medical institutions and hospitals. To identify the relevant articles, we meticulously searched for keywords and themes that include AI, ChatGPT, autonomy, privacy, confidentiality, accountability, fairness, regulatory compliance, informed consent, and liability across medical databases, including PubMed and Google Scholar. Our objective was to identify emerging trends, burgeoning areas of interest, such as AI, and the evolving focus on ethics in medical research over time.

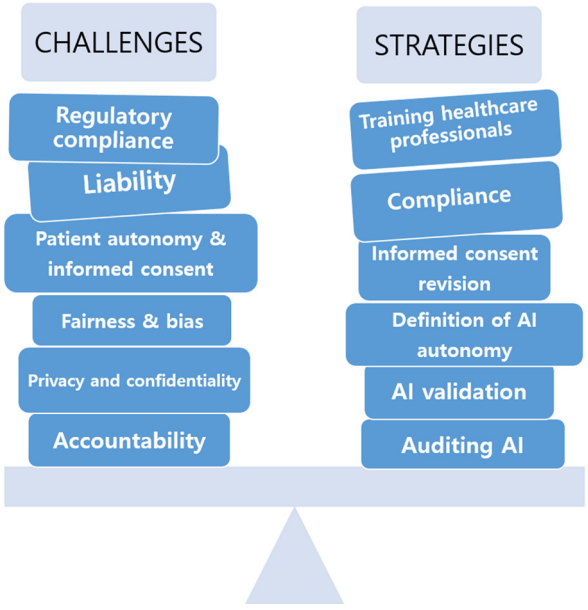

Fig. 1. Balancing challenges and strategies for artificial intelligence (AI) integration in healthcare.

Ethical challenges in medical AI

1. Privacy and confidentiality issues

The use of AI and representative applications such as ChatGPT in medical research raises several ethical concerns that need to be addressed [12]. Key among these is the privacy and confidentiality of patient data [13-16]. Ensuring that the patient information used to train and operate AI models is handled securely and responsibly is crucial, especially when it involves sensitive health data [17]. This includes paying careful attention to how data are collected, stored, and shared.

2. Accountability issues

The opacity of AI models, particularly deep-learning systems, is also a concern [18]. These "black box" systems often do not provide easy insights into their decision-making processes, which can complicate clinical decision-making and accountability [19]. For its effective use in medicine, AI processes must be transparent and explainable [20-22].

3. Bias and fairness issues

Another critical issue is bias and fairness [23-25]. AI systems can unintentionally perpetuate or even worsen existing biases if trained on nondiverse or nonrepresentative datasets. This could lead to biased treatment recommendations or diagnostic outcomes, disproportionately affecting marginalized groups.

4. Informed consent and patient autonomy issues

Informed consent and patient autonomy are further areas of concern [26,27]. Patients may not fully comprehend the extent of AI's role in their diagnosis or treatment, potentially affecting their ability to make informed health-related decisions [28]. Additionally, as AI increasingly handles tasks traditionally performed by humans, medical professionals could become overly reliant on AI, potentially leading to the deskilling of the workforce [29,30]. This could diminish the healthcare workers' ability to make nuanced decisions without AI assistance [31,32].

5. Liability issues

Determining the liability when AI systems err remains a complex challenge [33]. The question of who is responsible for AI-related misdiagnosis or treatment failure continues to spark debate [34,35]. The use of AI could require redefining standards of care and adjusting the legal definitions of negligence and malpractice [36]. Large language model (LLM) AI might produce "hallucinations" or unreliable outputs, which could mislead clinicians and lead to potential malpractice [37]. LLM AI-generated advice may be treated similarly to other forms of third-party medical advice, which have historically had mixed acceptance in terms of establishing standard care in legal terms.

6. Regulatory compliance issues

Regulatory compliance is another significant issue [38,39]. AI tools must adhere to medical laws and regulations such as the Health Insurance Portability and Accountability Act (HIPAA) in the United States [40], which protects patient privacy, and the General Data Protection Regulation (GDPR) in Europe, which governs data protection [41,42]. However, the setup of research environments should adapt based on each nation's unique medical infrastructure and level of industrial support [43].

Addressing these ethical issues is crucial for the responsible development and application of AI in healthcare to ensure that it enhances patient outcomes without compromising ethical standards or patient trust.

7. Cultural differences and perceptions of ethics in AI and medical research

Finally, cultural differences profoundly influence how doctors, patients, and their families handle ethical dilemmas in medicine [44-46]. A comparative study of medical professionalism in China and the United States highlighted notable cultural distinctions and parallels between the two nations, examining Chinese practices such as family consent and familism, alongside the contentious issue of patient autonomy [47]. Furthermore, Western and Asian cultures significantly differ in their emphasis placed on patient rights [48]. Navigating these cultural variances is essential for international collaboration in AI and medical research, ensuring that technologies are developed and utilized in a manner that respects diverse ethical standards and values.

Strategies for resolving ethical issues in AI use in medical research

Initially, determining the level of autonomy that AI should have in completing tasks is crucial, particularly in relation to their impact on patient outcomes [49,50]. The extent of AI autonomy varies significantly depending on the severity and importance of these tasks. Thus, a consensus is needed on the extent to which AI autonomy will be granted in clinical decision-making processes [51]. Ultimately, the role of AI—whether as an assistive aid or autonomous agent—must first be clearly defined [52]. For example, simpler and well-defined tasks such as administrative duties and data management are more suitable for AI automation [53]. By contrast, complex decision-making tasks that require human empathy and understanding should remain under human control [54,55].

To ensure the accuracy of the decisions made by AI, its performance must be rigorously validated [56]. Clinical trials to evaluate these processes should be conducted before AI systems are used in practice [57]. Once these systems are commercially available and implemented in clinical practice, a continuous monitoring process is crucial to ensure that the AI systems operate as intended [58,59]. Several rigorous methods have been employed to validate AI systems for healthcare applications and to ensure their efficacy and safety [60]. Trial validation involves deploying systems in their intended clinical environments to monitor the real-time performance and user interactions. Simulation test systems in virtual environments that mimic complex medical scenarios provide a safe platform for evaluating potential risks without endangering patients. Model-centered validation focuses on the AI model itself using data-driven techniques to verify its predictive accuracy and reliability across diverse clinical datasets. Additionally, expert opinion plays a crucial role as healthcare professionals assess the system's practicality and adherence to medical standards. These multifaceted validation approaches are critical for integrating reliable AI tools into medical practice and ultimately enhancing patient care and clinical outcomes.

As mentioned previously, regulations and ethical guidelines are essential to ensure that AI tools comply with health privacy laws and meticulously protect patient data. The implementation of AI auditing processes should be guided by ethical standards that prioritize patient welfare and equity

[61,62]. Healthcare providers must understand the decision-making processes of AI tools to make informed judgments regarding how AI-influenced outcomes affect patient care [63]. This includes ensuring that all processes implemented using AI obtain informed consent from patients concerning AI involvement in their care, the information it processes, and its influence on their treatment.

To implement these processes in practice, revising current consent processes to explicitly inform patients about how AI is used in research and treatment and detailing both the benefits and risks is vital. Consent must be informed and voluntary, with clear options for opting out [64]. Aligning these guidelines with international standards has promoted global consistency [65]. Transparency and explainability should be emphasized to enable both clinicians and patients to understand AI decisions, thus building trust and facilitating informed clinical decision-making [21,66,67]. Openly publishing details on AI training processes, datasets, and performance metrics is essential.

Training healthcare professionals is necessary to ensure safe AI applications in patient care [68]. They must learn to use AI tools safely and accurately [69]. As AI is expected to take over many tasks currently performed by healthcare providers, the risk that human skills may diminish remains high. Consequently, health professionals should focus more on areas in which AI systems cannot make accurate final decisions because of the irreplaceable nature of certain tasks [70]. This necessitates clear protocols to define the depth and range of AI involvement in patient care. The entire process involves risks that can affect patient outcomes. Therefore, establishing a backup system for AI tools is crucial to prepare for scenarios where tracing the decision-making process is possible [71,72]. A trial-and-error period seems inevitable as AI continues to develop and improve. The role of AI must be adjusted based on real-world requirements and evolving ethical standards. It is important for AI systems to enhance healthcare services without compromising patient safety and prognosis.

Compliance with data protection regulations such as the GDPR and HIPAA is essential. Establishing comprehensive data governance frameworks is crucial for dictating the collection, storage, and use of patient data, thereby ensuring anonymity and safeguarding against breaches. Robust anonymization methods are vital for protecting patient information prior to its use in machine learning training. Furthermore, securing patient consent, maintaining data integrity, and implementing secure data management and storage protocols is imperative to adhere to relevant legal standards [73]. Various methods have been introduced to ensure that images remain useful for medical research and diagnosis while removing personally identifiable information to protect patient privacy, such as de-identifying facial features in magnetic resonance images, encrypting patient identifications, and modifying personal data fields [74,75].

To reduce bias, AI models should be trained using diverse datasets representing various demographics, and regular audits of AI systems for biases and discrepancies in performance across different groups are necessary to ensure broad applicability and fairness [76]. Addressing bias in AI systems is also necessary to ensure that they deliver trustworthy and fair results, which necessitates a continuous effort to identify and mitigate potential biases in AI systems to ensure that they are accurate and equitable [77]. To evaluate fairness, the “fairness score” and “bias index” were introduced, and the researchers suggested that fairness certification is crucial for the broader acceptance and trustworthiness of AI systems [78].

Defining the accountability clearly for AI decisions in a clinical setting is essential. This task encompasses AI developers, healthcare providers, and organizations that deploy AI solutions. AI tools must embody transparency to facilitate proper regulation and meet societal demands for accountability, particularly when unexpected outcomes arise [79]. Legislative initiatives, such as the Algorithmic Accountability Act of 2022 in the U.S. and the European Union AI Act, propose comprehensive measures. These legislative frameworks mandate that developers extensively evaluate the impact of their AI systems, including potential biases and discriminatory outcomes [80]. There is a pressing need for precise definitions of risk and accountability in the AI domain. Additionally, standardizing risk governance methods for practical industrial applications is crucial. We must clearly define AI-related risks and develop standardized risk governance and management strategies that are applicable across the sector. Five characteristics are essential for AI risk-management methodologies: balance, extendibility, representation, transparency, and long-term orientation. These attributes ensure that AI systems are accountable, sustainable, and ethically aligned with clinical needs and societal expectations [81].

Encouraging collaboration between technologists, ethicists, healthcare providers, and patients is crucial for a holistic approach to AI development and implementation [16,67,82]. This has led to better-designed AI systems that respect ethical norms and are more effective in clinical settings. Although no singular global legal framework specifically governing the use of AI in healthcare exists [83], adopting these strategies can help address the ethical risks associated with deploying AI technologies, such as ChatGPT, in medical research. By implementing these measures, we can enhance the benefits of AI while reducing its potential harm.

Cross-cultural training provides researchers and professionals with workshops, seminars, and programs that promote cultural competence and ethical sensitivity [84,85]. Global ethical standards should be developed to honor local values while upholding international norms. Collaborative international research encourages partnerships to enhance mutual understanding and integrate diverse ethical perspectives [86]. Community engagement involves public consultations and advisory panels to gain local insights, helping researchers grasp cultural nuances [87,88]. Transparent communication ensures information about AI and medical research is clear and culturally appropriate. Ethics reviews should include cultural experts to tackle potential cultural and ethical issues. Finally, adaptive technology design enables the customization of AI systems and research protocols to various cultural settings, supporting multiple languages and flexible interfaces [89].

Engaging a diverse array of stakeholders in the development of policies and guidelines for AI and medical research is crucial. Including ethicists, technologists, patients, and practitioners from varied backgrounds ensures that these guidelines are comprehensive and that AI systems are capable of nuanced decision-making. This inclusive approach is vital for crafting policies that address the multifaceted impacts of AI technologies across different segments of society [90,91]. Moreover, the implementation of robust feedback mechanisms is essential for the ongoing refinement of AI systems. Such mechanisms enable stakeholders to report on how AI applications affect their lives, providing critical insights that can lead to enhancements in both functionality and ethical alignment [92]. Participatory design plays a pivotal role in AI development by involving end users and patients directly in the design and testing phases. This strategy results in innovations that are not only user-friendly but also deeply align with the diverse needs and values of various user groups [93].

Conclusion

The integration of AI technologies like ChatGPT into medical research offers substantial transformative potential but also poses significant ethical challenges. These include concerns related to privacy, bias, accountability, informed consent, regulatory compliance, and liability. To responsibly deploy AI in healthcare, it is crucial to establish a clear ethical framework that defines AI's role in clinical decision-making, ensuring it enhances transparency and patient trust.

This entails rigorous validation through clinical trials, ongoing post-implementation monitoring, and the creation of comprehensive data governance frameworks that prioritize privacy and security. Moreover, developing diverse datasets is essential to reduce bias and promote equitable healthcare outcomes. Engaging a wide range of stakeholders, including technologists, ethicists, healthcare providers, and patients, will ensure the ethical alignment of AI systems and their alignment with actual clinical needs.

Ultimately, by maintaining high ethical standards and fostering a collaborative development environment, AI can be leveraged to make significant advances in healthcare that are both innovative and ethically responsible.

The future of AI in healthcare is poised to enhance clinical decision-making, patient care, and operational efficiencies significantly but it requires careful management to address potential ethical, regulatory, and practical challenges. Overall, the prospective view is one of cautious optimism, advocating for a balance between leveraging the potential benefits of AI in medical research while diligently addressing the ethical and practical challenges that accompany such technology.

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Conflicts of interest

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Non-pharmacological treatments for insomnia: a focus on components of cognitive behavioral therapy for insomnia

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Insomnia is a prevalent disorder that affects 4% to 22% of the population in the United States. While cognitive behavioral therapy for insomnia (CBT-I) remains the gold standard for non-pharmacological treatment, accessibility barriers exist owing to a shortage of trained professionals and high costs. This review examines the efficacy of the individual components of CBT-I as stand-alone interventions to improve treatment accessibility, digital CBT-I, and other non-pharmacological interventions. Guidelines from organizations such as the American Academy of Sleep Medicine and, European Sleep Research Society, along with recent meta-analyses, support the effectiveness of these components as stand-alone treatments. Sleep restriction therapy and stimulus control therapy show promise as effective interventions. Although recommended by certain guidelines, relaxation therapy has yielded mixed results. Sleep hygiene education, a common component of CBT-I, has not demonstrated significant efficacy as a stand-alone treatment. Cognitive strategies have shown promise in recent studies. Sufficient clinical evidence supports the efficacy of digital CBT-I in treating insomnia. Internationally, various platforms for digital CBT-I have already been developed and are in use, and in South Korea, some digital CBT-I software programs have received digital therapeutic device approval in 2023. This review highlights the potential of individual components of CBT-I as effective stand-alone interventions for insomnia, as well as digital CBT-I, emphasizing their importance for improving the accessibility of non-pharmacological insomnia treatments in clinical settings where full CBT-I may not be available.

Keywords: Behavior therapy; Cognitive behavioral therapy; Insomnia

Introduction

Insomnia is a common disorder with a prevalence ranging from 4% to 22% in the United States [1]. It is characterized by difficulties in initiating or maintaining sleep or early morning awakening, accompanied by daytime dysfunction despite adequate opportunities for sleep. Diagnosis is based on criteria from the International Classification of Sleep Disorders, 3rd edition or the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [2,3].

Insomnia treatment is categorized into pharmacological and non-pharmacological methods, primarily represented by cognitive behavioral therapy for insomnia (CBT-I). Although various hypnotic/sedative drugs are available, they are recommended only for short-term use (less than 4 weeks) to avoid dependency or tolerance [4]. Additionally, especially in older adults, pharmacological treatments carry increased risks of falls, confusion, and physical dependence [5], and studies have explored their potential associations with cognitive decline [6]. Thus, CBT-I is considered the

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most effective and safest treatment for insomnia [4].

Guidelines from the American Academy of Sleep Medicine (AASM), European Sleep Research Society, and other professional sleep associations recommend CBT as a first-line treatment for chronic insomnia in adults of all ages [7-9]. Pharmacological treatments are recommended only when CBT-I is insufficient [4,8,9].

CBT-I is a multicomponent therapy consisting of various strategies to correct cognitive errors related to sleep, along with behavioral therapy strategies such as sleep restriction therapy (SRT) and stimulus control therapy (SCT), and additional elements such as relaxation techniques and sleep-related education, including sleep hygiene [10]. CBT-I is typically conducted over 4–8 sessions by certified health professionals [9]. It is a safe therapy with lasting effects and only transient initial side effects such as daytime drowsiness or fatigue [8]. Despite its effectiveness and safety, CBT-I may face accessibility barriers due to a shortage of trained professionals in some regions, higher out-of-pocket costs compared with pharmacological treatments, and the need for extended time and effort [8,9,11]. Particularly in South Korea, commercialization requires national insurance coverage, but meeting the criteria for insurance allowance is challenging. Even when national insurance allowance is approved, the cost is often low. Moreover, the treatment requires a significant time commitment, making it less appealing, and the lack of trained professionals make its clinical application even more difficult [12].

Recently, some individual components of CBT-I, such as SRT and SCT, have been considered as useful independent therapies for insomnia [4,8,9]. This article aimed to review the literature including the clinical practice and individual effectiveness of each component of CBT-I, considering their potential for improving accessibility to non-pharmacological treatments for insomnia in clinical settings.

Sleep restriction therapy

SRT is a therapy that readjusts the bed-sleep association through sleep time restrictions [10,13,14]. This therapy is decided by sufficient discussion with the patient, based on at least 1 week of sleep diary data. The treatment process involves several steps: (1) setting a fixed wake-up time that aligns with the lifestyle of the patient; (2) restricting time in bed to approximate the average total sleep time (TST; minimum 5 hours); (3) refraining from lying down outside designated sleep times and attempting to stay awake; and (4) adjusting time in bed weekly based on sleep efficiency, increasing by 15 minutes if efficiency is above 85% to 90% or decreasing by 15 minutes if efficiency falls below 80%. Patients are informed about the potential initial side effects, such as daytime drowsiness, and are cautioned to avoid activities with a high injury risk [9,10,15].

The 2021 AASM guidelines conditionally recommend SRT as a stand-alone treatment for chronic insomnia in adults, based on six randomized controlled trials (RCTs) [8]. This recommendation is supported by the 2023 World Sleep Society (WSS) [9]. Additionally, the 2023 update of the European Insomnia Guidelines suggests the efficacy of SRT for the treatment of insomnia [4]. A 2021 meta-analysis of eight RCTs showed that SRT effectively improves insomnia severity and sleep continuity in the short term, with post-treatment effect sizes as large as CBT-I [16]. A 2024 component network meta-analysis of 241 RCTs found SRT to be potentially beneficial for insomnia treatment (incremental odds ratio [iOR], 1.49; 95% confidence interval [CI], 1.04–2.13), associated with improvements in subjective sleep quality, sleep efficiency, and wake after sleep onset (WASO) [17].

Stimulus control therapy

SCT seeks to decondition the incorrect association between the bed/bedroom and wakefulness and restore the connection with sleep. It involves instructions such as [8,10,18]: (1) lying in bed only when sleepful; (2) leaving the bed if unable to sleep (after about 10–15 minutes); (3) using the bed only for sleep and sexual activity; (4) waking up at the same time every morning; and (5) avoiding naps. Although SCT is a relatively easy method to manage, some instructions, such as “get out of bed if you cannot sleep,” may need to be modified for safety in patients at high risk of fall, such as those with limited mobility or those using sedatives [9,10,18,19].

The latest (2021) AASM guidelines conditionally recommend SCT as a stand-alone treatment for insomnia, based on eight additional studies [8]. This recommendation is supported by the 2023 WSS [9]. The 2023 update of the European Insomnia Guideline update also acknowledges the effectiveness of SCT for treatment of insomnia [4]. A

2023 network meta-analysis confirmed the individual effectiveness of SCT in insomnia treatment, despite variations in guideline details, showing associations with increased TST, decreased sleep onset latency, and WASO [18]. A meta-analysis conducted in the same year highlighted a slightly greater impact of SCT on sleep onset latency and TST outcomes than other cognitive and behavioral interventions, although methodological limitations precluded definitive conclusions [20]. A 2024 component network meta-analysis found SCT to be potentially beneficial for insomnia treatment (iOR, 1.43; 95% CI, 1.00–2.05) and is associated with improvements in sleep latency, SE, and subjective sleep quality [17]. A systematic review and meta-analysis in 2024 analyzed 11 studies comparing SCT alone with comparative therapies. Studies that combined stimulus control with other CBT-I components (e.g., sleep hygiene) were excluded, thereby expanding the evidence for SCT as a stand-alone therapeutic element [20].

Relaxation therapy

Insomnia is a disorder characterized by excessive arousal or difficulty in controlling arousal [21], and relaxation training aims to reduce pre-sleep anxiety and arousal. Techniques include physical relaxation methods to reduce physical tension (e.g., progressive muscle relaxation and diaphragmatic breathing) and cognitive relaxation methods to reduce cognitive arousal (e.g., meditation and guided imagery) [8,10]. Currently, evidence does not support the superiority of any one technique [4]. Relaxation therapy requires consistent practice and is better to practice during daytime and low-stress periods until patients become proficient [10].

Based on five studies, the 2021 AASM guidelines conditionally recommend relaxation therapy as a stand-alone treatment for insomnia [8], with endorsement from the WSS in 2023 [9], and the 2023 update of the European Insomnia Guidelines [4]. Conversely, a component network meta-analysis in 2024 suggested that relaxation therapy might potentially yield adverse outcomes (iOR, 0.81; 95% CI, 0.64–1.02) [17].

Psychoeducation and sleep hygiene

Sleep hygiene and psychoeducation provide general recommendations and theoretical rationales for lifestyle and environmental factors that promote or hinder sleep [4,8,10,22]. Sleep hygiene includes maintaining an appropriate bedroom environment; regular routines; exercise; medications; limiting fluid intake before sleep; alcohol; caffeine; eating regularly; not looking at the clock in bed; and refraining from napping during the day. Psychoeducation may also include the roles and functions of sleep, circadian rhythm regulation models, normal sleep components, and age-related changes in sleep patterns. However, sleep hygiene behaviors may sometimes act as safety-seeking behaviors in patients with insomnia [4,8,10].

The 2021 AASM guidelines recommend against the use of sleep hygiene as a stand-alone therapy due to insufficient evidence [8], a position supported by the 2023 WSS [9]. Similarly, a 2024 component network meta-analysis found sleep hygiene education to be non-essential (iOR, 1.01; 95% CI, 0.77–1.32) [17]. However, sleep hygiene remains a common component of CBT-I and may be helpful in a comprehensive multicomponent treatment approach.

Cognitive strategies

Cognitive arousal is considered a fundamental prerequisite for insomnia, and mental events, dysfunctional sleep efforts, and heightened emotions are also common [4,23,24]. Many cognitive strategies have been developed to address these issues and are provided as a component of CBT-I in most studies [7,10,23,25]. Cognitive strategies include cognitive control, which is a method of clearing excessive thoughts before bed; imagery training, which is effective at reducing the racing mind at bedtime; paradoxical intention, which is designed to prevent counterproductive sleep efforts (a willingness to try to stay awake rather than fall asleep); and cognitive restructuring, which modifies common misconceptions about sleep and reconstructs dysfunctional beliefs about insomnia and its daytime consequences, using Socratic questioning and behavioral experiments [4,10,26].

The 2021 AASM guidelines do not recommend cognitive therapy or paradoxical intention as stand-alone therapies owing to insufficient evidence [8]. In the case of cognitive therapy, as mentioned above, most is integrated into CBT-I multicomponent treatment, and the evidence was assessed as insufficient because no studies have compared cognitive therapy monotherapy with a control group. However, the

AASM task force noted that cognitive therapy could be considered an alternative treatment if CBT-I is unavailable [8]. Additionally, the 2023 update of the European Insomnia Guidelines suggests the efficacy of paradoxical intention as a stand-alone therapy for insomnia [4]. The 2024 component network meta-analysis of 241 RCTs found cognitive restructuring to be beneficial for insomnia treatment (remission iOR, 1.68; 95% CI, 1.28–2.20) [17].

Digital CBT-I

Digital therapeutics are technologies based on software designed to prevent, manage, or treat diseases [27,28]. CBT-I is based on a structured manual and involves manual-based education and training over a certain period, therefore, it is suitable for implementation as an internet or smart device-based digital therapeutic device [12,29], Sufficient clinical evidence support that digital CBT-I can be effective in treating insomnia [4]. Using digital CBT-I allows patients to overcome the spatial and temporal constraints of visiting healthcare facilities and provides the potential to offer treatment to more patients at a lower cost. Additionally, it allows for the recording and monitoring of whether education and training are effectively applied in patients' real lives and can offer personalized feedback and treatment [12,30]. Therefore, in the Korean clinical environment where resources for face-to-face CBT-I are limited, digital CBT-I may be considered a powerful clinical alternative for non-pharmacological treatment of insomnia [12,29].

Internationally, various digital CBT-I programs such as Sleepio and CBT-I Coach are already in use [12,30]. Recently in South Korea, digital therapeutic software aimed at treating insomnia such as AIMED's Somzz and WELT's SLEEP Q were developed and approved by the Ministry of Food and Drug Safety in 2023 [12], and started non-covered prescriptions in psychiatric hospitals in 2024. However, they have not yet been widely used. The actual non-covered cost of Somzz in clinical settings is around 200,000 KRW (1 USD=1,400 KRW), but the Health Insurance Review & Assessment Service has set the non-covered standard cost at 25,390 KRW, which could dampen enthusiasm for developing and supplying digital CBT-I.

Other cognitive behavioral intervention

Third wave therapies such as mindfulness, acceptance and commitment therapy (ACT) are being considered as treatment for insomnia [4]. Mindfulness-based treatments for insomnia have shown significant therapeutic benefits in two meta-analyses [31,32]. However, there are still few studies, and further researches on long-term effects are needed. ACT has only been studied in small-scale RCTs. While some studies suggest that ACT may be effective compared to active control groups [33-35], larger-scale RCTs are required to confirm these findings.

Other therapeutic interventions

Other non-pharmacological approaches for insomnia include exercise therapy, light therapy, repetitive transcranial magnetic stimulation, and acupuncture. However, most studies are of very low quality, and reported results are based on a small number of studies, limiting their interpretation [4,36].

Several studies including meta-analyses have reported on the effects of exercise on insomnia [37-46]. The types of exercises studied include yoga, aerobic exercise, and Tai Chi. However, results have been inconsistent, and many studies suffer from poor methodological quality; thus, further high-quality research is needed [4,36].

A meta-analysis conducted in 2023 on the effects of light therapy on insomnia suggested it as potentially effective compared to placebo for both objective and subjective WASO [47]. However, due to significant heterogeneity in research methods such as choice of light wavelength and exposure time, consistent conclusions are difficult to draw; further research is needed. The European insomnia guideline update in 2023 suggested that integrating exercise therapy or light therapy into CBT-I might provide additional benefits [4].

For repetitive transcranial magnetic stimulation and acupuncture, some studies have reported subjective sleep improvement in insomnia patients, however, results for physiological indicators had tendency to show either insignificant or mixed results [36,43]. Methodological limitations further restrict interpretation [4]. Moreover, in acupuncture studies, high redundancy in publications citing the same original study may have led to overestimation of its effects [36].

Conclusions

CBT-I remains the gold standard for the treatment of insomnia and is a safe and effective approach with long-term benefits that extend beyond the treatment period. However, despite the proven efficacy of CBT-I, several barriers, including limited access to trained professionals and poor patient compliance, continue to challenge its broader implementation. Particularly in South Korea, gaps between evidence and practice are evident due to various clinical challenges. The lack of resources including the shortage of trained professionals, administrative hurdles in fee setting, and the intensive time and effort required for multicomponent CBT-I make it more challenging to effectively utilize multicomponent CBT-I. Addressing these limitations by exploring the independent use and accessibility of the CBT-I components may enhance treatment options, particularly in regions or settings where comprehensive CBT-I may not be feasible. Currently, individual components such as SRT and SCT are promising stand-alone interventions. Evidence suggests that each component of CBT-I—SRT, SCT, relaxation therapy, and cognitive strategies—independently contributes to significant improvements in insomnia. Digital CBT-I could also enhance the accessibility of non-pharmacological treatments for insomnia if supported by realistic administrative measures such as appropriate insurance allowance settings. A general summary of non-pharmacological treatments for insomnia is shown in Table 1. Further research focusing on the individual and combined effects of CBT-I components, as well as innovative delivery methods, could be helpful in improving accessibility and providing viable non-pharmacological insomnia treatment options to a broader population

Table 1. Non-pharmacological treatments for insomnia: a focus on components of CBT-I

	Treatment method	Advantages and disadvantages
CBT-I	A multicomponent therapy consisting of various strategies to correct cognitive errors related to sleep, along with behavioral therapy strategies and additional elements Typically conducted over 4–8 sessions by certified health professionals	Advantages: sufficiently proven to be effective, having safety and long-lasting effect Disadvantages: shortage of trained professionals, higher out-of-pocket costs, need for extended time and effort
SRT	Behavioral therapy that readjusts the bed-sleep association through sleep time restrictions	Effective and safe except for initial transient side effect such as daytime drowsiness
SCT	Behavioral therapy that deconditions the incorrect association between the bed/bedroom and wakefulness and restores the connection with sleep	Safe and effective
Relaxation therapy	Aims to reduce pre-sleep anxiety and arousal	Mixed outcomes: the 2021 AASM guidelines conditionally recommend it
Psychoeducation and sleep hygiene	Provide general recommendations and theoretical rationales for lifestyle and environmental factors that promote or hinder sleep	A common component of CBT-I Insufficient evidence: The 2021 AASM guidelines recommend against its use as a stand-alone therapy
Cognitive strategies	Cognitive control, a method of clearing excessive thoughts before bed; imagery training, effective at reducing the racing mind at bedtime; paradoxical intention, designed to prevent counterproductive sleep efforts; and cognitive restructuring, which modifies common misconceptions about sleep and reconstructs dysfunctional beliefs about insomnia and its daytime consequences	Insufficient evidence as stand-alone therapy because cognitive strategies have been integratively used in CBT-I
Digital CBT-I	Software designed to prevent, manage, or treat insomnia based on CBT-I	Advantages: potential to increase the accessibility of non-pharmacological treatments for insomnia: overcome constraints of visiting healthcare facilities; potential to offer treatment to more patients at a lower cost; be applied in patients' real lives and can offer personalized feedback and treatment Disadvantages: need for realistic administrative measures such as appropriate insurance allowance settings and requirement for caution regarding personal information

CBT-I, cognitive behavioral therapy for insomnia; SRT, sleep restriction therapy; SCT, stimulus control therapy; AASM, American Academy of Sleep Medicine.

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Zonula occludens proteins and their impact on the cancer microenvironment

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Zonula occludens (ZO) proteins serve as scaffolding proteins that provide structural support at cell junctions and the cytoplasmic surface, acting as bridges between integral membrane proteins and the cytoskeleton. In addition to their structural functions, they also regulate cell growth and proliferation. Recent studies have shown that ZO proteins are involved in various diseases, including cancer. Specifically, ZO proteins influence the growth and development of cancer cells in the tumor microenvironment. These proteins perform various functions in the tumor microenvironment through processes such as angiogenesis, inflammatory responses, epithelial-mesenchymal transition, and interactions with mesenchymal stem cells. The mechanisms of these actions may vary depending on the type of cancer and environmental conditions. Ongoing research explores several signaling pathways involving ZO proteins. These insights suggest that new therapeutic approaches may be considered to slow down cancer growth and development within the tumor microenvironment. Despite continuing research on the cellular and *in vivo* roles of ZO proteins, the current understanding of how these signaling mechanisms function within the tumor microenvironment *in vivo* remains limited. In this review, we introduce the characteristics and regulatory mechanisms of ZO proteins in the cancer microenvironment, explore their potential to suppress cancer cell environments, and examine their roles *in vivo*.

Keywords: Animals; Biological phenomena; Neoplasms; Tumor microenvironment; Zonula occludens

Introduction

Tight junctions, adherens junctions, and desmosomes serve as important protective barriers in multicellular organisms and are present in epithelial and endothelial cells. Tight junctions play a crucial role in regulating communication and transport between cells, involving proteins such as claudins, occludins, cingulin, protein associated with LIN7 1, multiple PDZ domain (postsynaptic density protein of 95 kDa, Drosophila disc large tumor suppressor, and zonula occludens [ZO]-1 protein) crumbs cell polarity complex component, and ZO-1, ZO-2, and ZO-3. ZO proteins are key to the formation of tight junctions between cells, interacting directly with the PDZ domain and the C-terminus of claudins. They also regulate various signaling pathways in cancer cells [1]. Representative cancer types associated with ZO proteins include breast cancer [2], liver cancer [3], colon cancer [4], bladder cancer [5], non-small cell lung cancer [6] and gastrointestinal stromal tumors [7]. The expression pattern of ZO proteins

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varies depending on the type of cancer, demonstrating their influence on various malignancies. Recent studies have shown that ZO proteins play a critical role not only in cancer itself but also in the cancer microenvironment. The cancer microenvironment refers to the tissues and proteins surrounding cancer cells, including tumor cells, tumor stromal cells, endothelial cells, immune cells, collagen, and the extracellular matrix. Cancer cells, at the center of the cancer microenvironment, regulate the functions of these cellular and non-cellular components through a complex signaling network, thereby exploiting non-malignant cells to benefit tumor growth [8]. Furthermore, in the cancer microenvironment, ZO proteins exhibit cancer-specific properties. For example, they have been reported to suppress epithelial-mesenchymal transition (EMT) and influence the cancer microenvironment in lung cancer [9], while promoting tumor angiogenesis in breast cancer [10]. These findings suggest that ZO proteins significantly impact the cancer microenvironment. However, further research is needed to fully understand the effects of ZO proteins on other proteins and signaling pathways within the cancer microenvironment. This review therefore aims to explore the relevance of ZO proteins in the cancer microenvironment and examine their mechanisms of action.

ZO proteins in the cancer microenvironment

ZO proteins are located between transmembrane proteins and the actin cytoskeleton, where they form structural support, regulate cell adhesion, and bind to actin, occludin, and claudin. However, recent studies have reported that ZO proteins are involved not only in several diseases but also in the cancer microenvironment [11]. Therefore, it is necessary to explore the various mechanisms by which ZO proteins act in cancer, beyond their previously known roles.

Cancer forms a complex ecosystem composed of tumor cells and numerous normal tissue cells, collectively known as the cancer microenvironment. This environment includes various immune cells, cancer-associated fibroblasts, endothelial cells, perivascular cells, and other tissue cells. These cells play crucial roles in tumor development, and the composition and function of the cancer microenvironment vary depending on the tumor's location, the characteristics and stage of the cancer cells, and patient-specific factors. Various cells within the cancer microenvironment can either suppress or support tumor growth [12]. The expression of ZO proteins can influence factors related to the cancer microenvironment and vice versa. A recent study reported that knockout of tight junction protein 1 (*Tjp1*) and tight junction protein 2 (*Tjp2*), which are ZO protein genes, significantly increased cell proliferation, migration, invasion, tumor growth, and metastatic potential. Next-generation sequencing analysis revealed that genes related to the cell cycle, cell migration, angiogenesis, and cell-cell adhesion were significantly affected [13].

In the cancer microenvironments studied thus far, ZO protein-related factors include angiogenesis, inflammatory response, EMT, and mesenchymal stem cells. Angiogenesis, the process by which new blood vessels form from existing ones, is essential for the growth and metastasis of cancer cells. The inflammatory response refers to the body's reaction to tissue damage or antigen invasion, and chronic inflammation contributes to cancer development. EMT is the process by which epithelial cells lose their adhesion to neighboring cells, gain mobility, and acquire invasiveness, transforming into mesenchymal cells. Mesenchymal stem cells are multipotent stromal cells that can differentiate into various cell types and play a significant role in cancer cell metastasis and invasion. In the cancer microenvironment, these cells can differentiate into stromal cells, such as cancer-associated fibroblasts, and influence tumor progression [14-16]. Therefore, this discussion will delve into the role of ZO proteins in these cancer microenvironment factors.

1. Angiogenesis

Recent studies have reported that ZO proteins are involved in angiogenesis [10]. Angiogenesis is the process by which new blood vessels are formed from existing ones, and it is important for growth and development, wound healing, and granulation tissue formation. However, in cancer, tumor cells may utilize surrounding blood vessels to receive nutrients and metastasize, or they may be involved in the formation of new blood vessels, contributing to the malignancy of the tumor. Growth factors such as vascular endothelial growth factor, fibroblast growth factor (FGF), and epidermal growth factor are essential for angiogenesis. Among these, FGF has been reported to be associated with ZO proteins. In one study, human dermal microvascular endothelial cells with suppressed ZO-1 expression were in-

jected subcutaneously into C57BL/6 mice to create a Matrigel plug model. It was observed that suppression of ZO-1 led to decreased angiogenesis along with a reduction in FGF expression [17]. Additionally, ZO-1 has been reported to indirectly promote angiogenesis in breast and lung cancer by regulating cytokines such as CXC motif chemokine ligand 8 and interleukin (IL)-8 [10]. These findings suggest that ZO proteins in the cancer microenvironment regulate peripheral factors such as growth factors and cytokines or participate in mechanisms that induce angiogenesis in cancer cells, thereby influencing the growth and invasion of tumors.

2. Inflammation response

Inflammatory responses are protective mechanisms of innate immunity, mediated by nonspecific immune cells, blood vessels, and inflammatory mediators. They play a crucial role in protecting cells and preventing tissue damage. Diseases related to inflammation include inflammatory bowel disease, asthma, and chronic obstructive pulmonary disease, and numerous studies have shown that these diseases are linked to ZO proteins [18-22]. Recent studies highlighted the influence of ZO proteins on inflammatory responses in the cancer cell environment. For instance, research has confirmed the association of ZO-1 with carcinogenesis and tumorigenesis in hepatocellular carcinoma (HCC). It was observed for the first time that ZO-1 levels were significantly elevated in HCC patients and positively correlated with inflammatory markers, suggesting that inflammatory responses may elevate plasma ZO-1 concentrations. This finding indicates that ZO-1 could serve as a potential biomarker [23]. In non-small cell lung cancer, which accounts for 80%–85% of lung cancer cases, an association with ZO proteins has also been reported. A previous study demonstrated that the nuclear content of ZO-1 influences the regulation of various inflammatory chemokines. The study further showed that CD8+ cytotoxic T cells and FOXP3+ immunosuppressive regulatory T cells, which are abundant in lung cancer, were correlated with the nuclear expression of ZO-1. This suggests that ZO-1 may be involved in recruiting immune cells to the nucleus of cancer cells by altering tumor cell secretions, thereby promoting tumor progression [6]. Moreover, the importance of ZO proteins has been confirmed in other lung cancers. In studies of lung adenocarcinoma and lung squamous cell carcinoma, it was found that the expression of ZO-1 and ZO-2 was low. When Calu-1 cells (human lung squamous cell carcinoma cells) with reduced ZO-1 or ZO-2 expression were co-cultured with M0 macrophages, M2-like polarization was induced. Conversely, when M0 THP-1 cells (human monocytic cells) were co-cultured with cells expressing ZO-1 or ZO-2, M2 differentiation was significantly reduced. This suggests that abnormal expression of ZO-1 and ZO-2 may play a role in lung cancer development and the regulation of the cancer microenvironment [9]. These findings suggest that ZO proteins are closely involved in inflammatory response within the cancer microenvironment. However, additional research is needed to better understand the mechanisms and roles of ZO proteins in inflammatory responses occurring in the environment surrounding cancer cells.

3. Epithelial-mesenchymal transition

ZO proteins have also been reported to be associated with EMT in the cancer cell environment. EMT is an invasive process that occurs in many types of cancer, characterized by increased cell mobility as epithelial cells acquire mesenchymal cell traits, leading to cancer metastasis. The first step of EMT involves the disassembly of cell-cell contacts in epithelial cells, which are connected by tight junctions, adherens junctions, and desmosomes. Among these, ZO-1 plays a critical role in regulating tight junctions and adherens junctions by influencing cytoskeletal assembly and dynamics. Based on this, it has been reported that RNA binding motif protein 38 promotes EMT by regulating the transcriptional expression of ZO-1 in breast cancer [24]. Another study found that the overexpression of insulin-like growth factor I receptor (IGF-IR) during primary breast cancer development affected ZO-1 overexpression as part of the mechanism that regulates cell-to-cell adhesion via E-cadherin. This suggests that ZO-1 is involved in strengthening the connection between the E-cadherin complex and the actin cytoskeleton through activated IGF-IR, thereby regulating cell-to-cell adhesion [25]. Furthermore, the association between ZO proteins and EMT has also been reported in melanoma cells. Although ZO-1 expression is generally reduced in most cancers, leading to increased cancer cell motility, ZO-1 expression is elevated in melanoma cells. In these cells, ZO-1 is highly co-expressed with N-cadherin, a mesenchymal marker, promoting melanoma

carcinogenesis [26]. These findings confirm the critical role of ZO proteins in EMT within the cancer microenvironment and suggest that this role should be investigated across a broader range of cancer types.

4. Mesenchymal stem cells

Mesenchymal stem cells are multipotent stem cells with the ability to differentiate into osteoblasts, chondrocytes, and adipocytes. These cells promote tumor growth in various types of cancer. Additionally, mesenchymal stem cells have been observed to migrate from the bone marrow to the breast cancer microenvironment, where they differentiate into stromal cells such as fibroblasts. Based on this, a study was conducted to elucidate the intrinsic mechanism by which bone marrow-derived mesenchymal stem cells aggregate in the breast cancer microenvironment, with a focus on the role of ZO-1. The research team confirmed that ZO-1 plays a crucial role in mediating the collective migration of mesenchymal stem cells in breast cancer cells and in converting transforming growth factor-β. They discovered that ZO-1 aggregates in adherens junctions at the contact points between mesenchymal stem cells. Additionally, it was found that ZO-1 cooperates with α-catenin to regulate adherens junctions through the SRC homology 3 and guanylate kinase 1 domains of the ZO-1 protein. This mechanism suggests that ZO-1 can influence the migration of mesenchymal stem cells [27]. This study is the first to report the direct involvement of ZO proteins in mesenchymal stem cells within the cancer microenvironment. Until recently, only indirect influences of ZO proteins on mesenchymal stem cells in damaged human pulmonary microvascular endothelial cells had been studied [28]. Therefore, further investigation into the role of ZO proteins in mesenchymal stem cells and their new functions in the cancer microenvironment is warranted.

5. Other factors and ZO protein associations

ZO proteins have also been shown to be associated with other factors present in the tumor microenvironment. One such factor is glucocorticoids. Glucocorticoids play an important role in central nervous system disorders associated with an impaired blood-brain barrier (BBB), such as edema, brain tumors, and multiple sclerosis. In a study testing the hypothesis that dexamethasone (DEX) treatment enhances the recovery of a BBB model composed of mouse brain endothelial cells in vitro, it was confirmed that ZO-1 expression increased during DEX treatment and recovery, suggesting a structural role for ZO-1 in BBB recovery [29]. Additionally, transcription factors can influence the tumor microenvironment. ZO-1-associated nucleic acid-binding protein (ZONAB), a transcription factor, promotes cell proliferation and the expression of proliferating cell nuclear antigen by shuttling between tight junctions and the nucleus. ZONAB has been reported to be a key component of the transcriptional network that senses epithelial cell density and regulates the transition between proliferation and differentiation [30]. One study confirmed that overexpression of ZONAB increased cell density in mature monolayers, while loss of ZONAB or overexpression of ZO-1 decreased cell density [31]. Furthermore, it was revealed that ZONAB interacts with cyclin-dependent kinase 4 (CDK4), accumulates in the nucleus, and promotes cell proliferation, suggesting that tight junctions may regulate CDK4 nuclear localization and cell proliferation through the ZONAB/ZO-1 pathway [32]. These findings confirm that various factors regulate or interact with ZO proteins in the cancer microenvironment. It can be considered that ZO proteins not only act independently but also in conjunction with other factors, thereby significantly influencing the cancer cell environment.

Defense mechanisms in the cancer microenvironment using ZO proteins

As mentioned above, ZO proteins play various roles in the cancer microenvironment and can accelerate cancer progression and development. Therefore, targeting ZO proteins to defend against mechanisms occurring in the cancer microenvironment could potentially suppress the development of cancer cells. ZO proteins contain a PDZ domain that controls intercellular communication and polarization, protein transport, and protein metabolism. This domain is critical for protein complex formation and stability, establishing an important link between extracellular stimuli detected by transmembrane receptors and intracellular responses. It has also been proposed as a potential therapeutic target for various diseases [33]. Previous studies have reported that deletion or modification of the PDZ domain in ZO proteins can affect inflammatory responses and EMT processes [18,34,35]. Specifically targeting the PDZ domain

of ZO proteins in cancer therapy could, therefore, provide a means to inhibit cancer progression.

The expression of ZO proteins can also be regulated using natural compounds. Natural products, derived from substances found in nature and synthesized chemically, are often used in basic research and as health supplements. Recent studies have shown that natural compounds affect the cancer microenvironment [36-38]. In addition, among these natural products, curcumin and resveratrol have been reported to influence the expression of ZO proteins. Curcumin, the main active compound in turmeric, has anti-inflammatory properties. In a study investigating the effects of curcumin on intestinal damage and the intestinal mucosal barrier, it was reported that pretreatment with curcumin increased the expression of ZO-1, restoring the epithelial structure and protecting the intestines from damage [39]. Resveratrol, a compound produced by plants in response to stressors like mold or pests, has anticancer, antiviral, and antiaging effects. In a study on the anti-inflammatory properties of resveratrol for the treatment of ulcerative colitis, it was found that resveratrol reduced the expression of ZO-1 and inhibited the Notch receptor 1 (Notch1) pathway in the HT-29 cell (colon adenocarcinoma) model of inflammation induced by lipopolysaccharide. This inhibition led to a reduction in the expression of the inflammatory factors IL-6 and tumor necrosis factor-α, suggesting that resveratrol can regulate the ZO-1 protein by weakening the Notch1 pathway [40]. Therefore, controlling the expression of ZO proteins using natural products could potentially prevent the progression and development of cancer by counteracting mechanisms within the cancer microenvironment.

Ongoing research projects

To date, ZO proteins have been widely studied in various diseases, including cancer. In particular, research related to metastasis and invasion has primarily focused on how ZO proteins link cells and transmit signals between themselves [41,42]. Recently, studies have progressed from cellular-level research to *in vivo* studies using mice with knocked-out ZO proteins. These studies have confirmed that ZO proteins play critical roles in pathophysiology, structure, and mor-

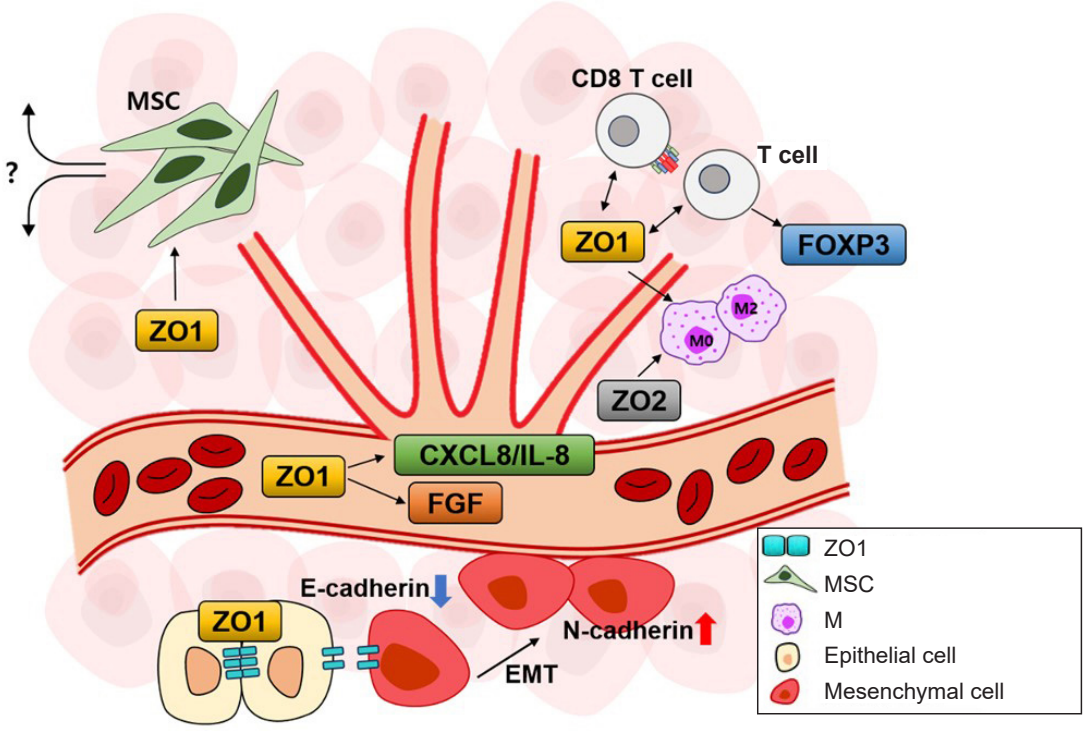

Fig. 1. Schematic representation of the function of ZO proteins in the cancer microenvironment. MSC, mesenchymal stem cell; ZO, zonula occludens; M, macrophage; FOXP3, forkhead box P3; CXCL8, CXC motif chemokine ligand 8; IL-8, interleukin 8; FGF, fibroblast growth factor; EMT, epithelial-mesenchymal transition.

phology [43,44]. However, the exact mechanisms through which ZO proteins contribute to morphological or physiological functions *in vivo* remain unclear. Therefore, further research is needed to investigate the mechanisms of action of ZO proteins *in vivo* and their effects on the cancer microenvironment.

Conclusions

ZO proteins play a crucial role in the cancer microenvironment. These proteins form a structural support around cancer cells, regulating cell adhesion and interacting with various cells to influence cancer development and metastasis. Notably, ZO proteins perform various functions through angiogenesis, inflammatory response, EMT, and interactions with mesenchymal stem cells (Fig. 1). However, since the mechanisms of action may vary depending on the type of cancer and environmental conditions, a defensive strategy tailored to the cancer-specific roles of ZO proteins is necessary. Additionally, the specific mechanisms of ZO protein activity *in vivo* and their impact on the cancer microenvironment have not been fully elucidated, warranting further research.

Article information

Conflicts of interest

Hee-Jae Cha 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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Author contributions

Conceptualization: HJC. Investigation: MHK. Supervision: HJC. Writing - original draft: MHK. Writing - review & editing: HJC. All authors read and approved the final manuscript.

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Efficacy of intravesical gemcitabine instillation compared with intravesical Bacillus Calmette-Guérin instillation for non-muscle invasive bladder cancer

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Background: Intravesical Bacillus Calmette-Guérin (BCG) instillation is the most effective treatment for reducing intravesical recurrence in non-muscle invasive bladder cancer (NMIBC). However, due to the recent global shortage of BCG, there is an increasing need for alternative treatments. This study aimed to retrospectively compare the outcomes of patients treated with intravesical gemcitabine instillation and BCG instillation as initial treatment options for NMIBC.

Methods: Seventy-eight patients with NMIBC who underwent transurethral resection of bladder tumors between January 2022 and September 2023 were reviewed. Of these, 42 patients received intravesical gemcitabine instillation, and 36 patients received BCG instillation. Recurrence-free survival (RFS) was analyzed, along with tumor multiplicity, grade, T stage, size, and bladder storage time after instillation, which could influence RFS.

Results: The mean follow-up period was 18.7 months for the gemcitabine group and 20.6 months for the BCG group. Recurrence occurred in 46.15% of patients (52.38% in the gemcitabine group and 38.92% in the BCG group). Tumor characteristics, including multiplicity, grade, stage, and size, were not significantly different between the two groups. The mean RFS was 15.92 months in the gemcitabine group and 19.84 months in the BCG group, with no statistically significant difference (p=0.397). However, gemcitabine instillation caused more severe bladder irritation, with shorter bladder storage time.

Conclusions: Intravesical gemcitabine and BCG instillation yielded comparable RFS outcomes. However, gemcitabine led to more severe bladder irritation, highlighting the need for further studies to optimize its application.

Keywords: BCG vaccine; Gemcitabine; Intravesical instillation; Non-muscle invasive bladder neoplasms

Introduction

Non-muscle invasive bladder cancer (NMIBC) accounts for about 70% to 75% of all bladder cancers [1]. Its recurrence rate within 1 year is about 50% [2]. If appropriate treatment is not received for NMIBC, the cancer may progress and invade the muscle layer or metastasize. Therefore, effective treatment for NMIBC is very important in the overall treatment strategy for bladder cancer.

Currently, one of the most commonly used methods for treating NMIBC is intravesical Bacillus Calmette-Guérin (BCG) instillation. BCG, a type of live attenuated vaccine, can induce an immune response that plays a role in inhibiting the growth of cancer cells [2]. Although the efficacy of

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BCG instillation has been proven in many studies [3,4], a significant number of patients experience side effects from BCG treatment, with some not responding to the treatment [4].

Recently, as global supply of BCG has become insufficient, many medical institutions are seeking alternative treatments. The shortage of BCG supply is due to various factors such as production issues, increased demand, and supply chain limitations [5]. In this context, gemcitabine is being considered as an alternative [6]. Gemcitabine is an anticancer agent that can inhibit the repair of DNA in cancer cells and suppresses the growth of cancer cells [7]. As an alternative to BCG intravesical instillation, intravesical gemcitabine instillation is being considered for treating NMIBC. It is known to have fewer side effects and higher tolerance in patients than BCG instillation [8]. However, direct comparative studies on the efficacy of these two treatments are limited. Therefore, the purpose of this retrospective study was to compare patients with NMIBC who received BCG intravesical instillation and those who received gemcitabine intravesical instillation. Recurrence rates of the two treatments were evaluated. Their long-term utility was also explored.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kosin University Hospital (IRB No. KUGH 2024-08-033). It was conducted in accordance with the recent Declaration of Helsinki. Informed consent was waived by the IRB.

This retrospective study targeted a cohort of 78 patients who received complete resection of visible tumors in the bladder via transurethral resection of bladder tumors from January 2022 to September 2023. These patients were diagnosed with NMIBC. They received intravesical BCG or gemcitabine instillation therapy. Among them, 42 patients received intravesical gemcitabine to reduce bladder recurrence and 36 patients received intravesical BCG. The BCG therapy involved weekly intravesical BCG instillations for 6 weeks, while the gemcitabine therapy involved weekly intravesical gemcitabine instillations for 6 weeks. The maintenance therapy for BCG was administered every 6 months for 3 consecutive weeks for up to 2 years. For gemcitabine, maintenance therapy was administered once a month for up to 1 year as a general principle. Clinical data of patients were collected retrospectively through electronic medical records. Collected data items included demographic information (age, sex), tumor characteristics (number, size, grade), recurrence after treatment, and bladder storage time after instillation (BST). These collected data were analyzed using statistical software SPSS version 28 (IBM Corp.). Recurrence rates and recurrence-free survival (RFS) time between the two groups were compared and analyzed. Recurrence rates and RFS were compared using Kaplan-Meier survival analysis. Differences between groups were evaluated using the log-rank test. Adverse event rates were compared using the chi-square test. Statistical significance was set at $p<0.05$.

Results

Among a total of 78 patients, 42 were in the gemcitabine instillation group and 36 were in the BCG instillation group. The mean age of all patients was 72.6 years (range, 53–93 years). It was 73.1 years for the gemcitabine group and 71.9 years for the BCG group. The median follow-up period for all patients was 20.0 months (range, 9–29 months). It was 19.5 months for the gemcitabine group and 20.0 months for the BCG group. Eleven patients in the gemcitabine group (26.2%) and three patients in the BCG group (8.3%) had tumors larger than 2 cm, showing a significant ($p=0.040$) difference between the two groups. For BST, three patients in the gemcitabine group (7.1%) and 31 patients in the BCG group (86.1%) had a storage time of more than 2 hours, showing a significant difference between the two groups ($p<0.001$). Other characteristics showed no significant differences between the two groups (Table 1). During the follow-up period, 36 patients (46.2%) experienced bladder recurrence, including 22 (22/42, 52.4%) patients in the gemcitabine group and 11 (14/36, 38.9%) patients in the BCG group. The mean RFS (mRFS) was 15.92 months in the gemcitabine group and 19.84 months in the BCG group. The difference in mRFS between the two groups was not statistically significant ($p=0.397$) (Fig 1). Three patients in the gemcitabine group (3/42, 7.1%) and 31 patients in the BCG group (31/36, 86.1%) had a BST of more than 2 hours, indicating more severe bladder irritation symptoms in the

Table 1. Baseline characteristics

Variable	Gemcitabine (n=42)	BCG (n=36)	*p*-value
Sex			0.363
Male	36 (85.7)	28 (77.8)	
Female	6 (14.3)	8 (22.2)	
Age (yr)	73.1±9.5	71.9±8.9	0.576
Follow up (mo)	19.5 (9–26)	20.0 (9–29)	0.117
Initial T stage			0.111
Ta	15 (35.7)	7 (19.4)	
0	27 (64.3)	29 (80.5)	
Tumor multiplicity	26 (61.9)	22 (61.1)	0.943
Initial grade			0.650
Low grade	2 (4.8)	1 (2.8)	
High grade	40 (95.2)	35 (97.2)	
Initial CIS	0	2 (5.6)	
Tumor size			0.040
>2 cm	11 (26.2)	3 (8.3)	
<2 cm	31 (73.8)	33 (91.7)	
Progression	4 (9.5)	1 (2.8)	0.225
BST			<0.001
<1 hr	22 (52.3)	1 (2.8)	
<2 hr	17 (40.4)	4 (11.1)	
≥2 hr	3 (7.1)	31 (86.1)	

Values are presented as number (%), mean±SD, or median (range).
BCG, Bacillus Calmette-Guérin; CIS, carcinoma *in situ*; BST, bladder storage time after instillation; SD, standard deviation.

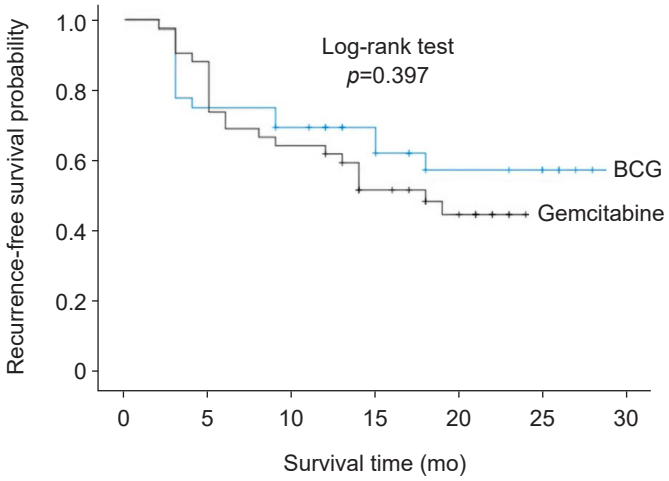

Fig. 1. Gemcitabine versus BCG: recurrence-free survival. Kaplan-Meier curve compares recurrence-free survival between gemcitabine and BCG groups. No significant difference was observed (p=0.397). BCG, Bacillus Calmette-Guerin.

gemcitabine group. In the gemcitabine group, no patients (0/42) reported any adverse effects during or after treatment. In contrast, in the BCG group, three patients (3/36, 8.3%) experienced adverse effects, including lower urinary tract symptoms (LUTS) such as increased urinary frequency and a urinary urgency. Despite these side effects, no patients discontinued treatment. The difference in adverse event rates between the gemcitabine and BCG groups was not statistically significant (p=0.056).

Discussion

Several studies have investigated the efficacy of intravesical instillation therapies such as gemcitabine and docetaxel in BCG failure cases of NMIBC. Skinner et al. [9] have reported a 1-year recurrence rate of 72% and an mRFS of 6.1 months after intravesical gemcitabine was administered to BCG failure patients. Di Lorenzo et al. [10] have also reported a recurrence rate of 52.5% and an mRFS of 3.9 months when intravesical gemcitabine was administered to BCG intractable patients. Although studies on first-line intravesical instillation therapies are limited, Bendary et al. [11] have reported no significant difference in recurrence rate between first-line gemcitabine and BCG groups (p=0.66), showing similar results to our study. Various agents such as docetaxel, mitomycin C, and adriamycin have been suggested as potential alternatives to BCG [12-14], although BCG has been traditionally preferred due to its effectiveness, especially in high-grade tumors and carcinoma *in situ*. Recently, due to BCG shortage, there is an increasing need to use alternative agents as first-line or BCG substitutes [5]. However, studies comparing these alternatives to BCG are insufficient. Although the present study was a retrospective study, we could see that the efficacy of gemcitabine intravesical instillation therapy was comparable to that of BCG intravesical instillation therapy in NMIBC patients as a first-line treatment (gemcitabine instillation mRFS, 15.92 months; BCG instillation mRFS, 19.84 months; p=0.397) (Fig. 1).

Among individuals known to be at risk of bladder cancer recurrence [15,16], there was no difference in tumor multiplicity, tumor grade, or tumor T stage (Ta, T1), although there was a difference in tumor size between the two groups (Table 1). However, there was no significant difference in

mRFS between the two groups (Fig. 1). Larger-scale research is needed to confirm these findings. In the study by Cambier et al. [15], the sample size was large at 762 individuals, which might explain such different results compared to the present study. While the efficacy of gemcitabine and BCG instillations was similar in terms of RFS, the adverse event profiles differed between the two groups. Notably, no patients in the gemcitabine group reported any adverse effects, whereas 8.3% of patients in the BCG group experienced mild LUTS, including increased urinary frequency and urinary urgency. Although the difference in adverse event rates between the two groups was not statistically significant (p=0.056), this trend suggests that BCG treatment may be associated with more frequent adverse effects. Clinically, these results underscore the importance of monitoring tolerability, as even mild adverse effects can influence patient comfort and treatment adherence. In this study, patients were allowed to refrain from urination for up to 2 hours after BCG and gemcitabine instillation. Most patients in the BCG group were able to hold for 2 hours after drug administration. However, in the gemcitabine group, only 7.1% of patients could hold for more than 2 hours and only 47.5% could hold for more than 1 hour. The actual toxicity was higher and more severe in the BCG group [11,17]. The gemcitabine group had less toxicity and shorter BST. This indicates that to increase effectiveness, research on appropriate BST, gemcitabine administration methods, administration concentration, and oral LUTS medication are needed. Research on the treatment sequence after failure of 1st line gemcitabine intravesical instillation is also necessary. In conclusion, this study compared efficacies of gemcitabine and BCG intravesical instillation methods in NMIBC patients through retrospective analysis. Both treatment methods showed similar RFS. Considering the issue of BCG supply shortage, gemcitabine could be a viable alternative. However, further research on methods to maintain drug retention in the bladder for a sufficient period after instillation is needed to enhance its effectiveness.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: TSK, DHK, SHK. Data curation: DHK. Formal analysis: DHK. Investigation: TSK, DHK, SHK, SBK. Methodology: TSK, DHK, SHK. Project administration: TSK. Resources: TSK, DHK. Software: DHK. Supervision: TSK, SHK. Visualization: DHK. Writing - original draft: DHK. Writing - review & editing: TSK, DHK, SHK, SBK. All authors read and approved the final manuscript.

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Stereopsis and clinical features of esotropia patients accompanied by congenital mild ptosis

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Background: To evaluate binocular function and clinical features in patients with esotropia (ET) accompanied by congenital ptosis.
Methods: Clinical records of 44 ET patients with congenital ptosis (ET-ptosis group) and 71 age-matched ET patients without ptosis (ET only group) who presented for eye examination between January 2016 and December 2021 were retrospectively reviewed. Best-corrected visual acuity (BCVA), magnitude of esodeviation and stereopsis at the first visit were reviewed. Stereopsis and other clinical features of the two groups were compared.
Results: The mean (±standard deviation) age of overall patients was 5.7 (±1.9) years. The margin reflex distance 1 (MRD1) of patients with ptosis was greater than 0 but less than or equal to 2, indicating that mild ptosis was included. There was no significant difference in the distribution of age, sex, spherical equivalent refractive errors, BCVA, or magnitude of ET (at distance or near) between the two groups (all $p>0.05$). Furthermore, stereopsis and the number of patients with amblyopia did not differ significantly between the two groups. The magnitudes of esodeviation, near stereopsis and BCVA did not differ significantly between the 0<MRD1≤1 group and the 1<MRD1≤2 group.
Conclusions: In patients with ET and congenital mild ptosis, stereopsis and visual acuity were not different from those in ET only patients. The presence of coexisting mild ptosis might not have a further deleterious impact on binocular function in ET patients.

Keywords: Amblyopia; Congenital ptosis; Esotropia; Depth perception; Esotropia

Introduction

Congenital ptosis represents an eyelid malposition that can result in cosmetic, functional and psychosocial problems in children. It is commonly accompanied by significant ocular abnormalities or consequences [1]. Amblyopia, strabismus, and refractive errors are substantially more common in congenital ptosis patients than in the general population [1-5]. Strabismus has an estimated prevalence of 1% to 5% in the general population [6,7]. It has been reported that the prevalence of strabismus is 10.3% to 32% in patients with congenital ptosis, which is at least four times higher than the prevalence in the general population [2,3,8].

When strabismus and ptosis coexist, ptosis can negatively affect stereopsis and vision in patients with strabismus. Our previous study has revealed that the presence of coexisting ptosis can have a further deleterious impact on binocular function in patients with intermittent exotropia

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(IXT) [9]. The ptotic eyelid can occlude visual input and disrupt control or fusion. The IXT-ptosis group had worse distance stereoacuity and a larger proportion of patients had suppression on the Bagolini test than the IXT-only group. Therefore, patients with IXT accompanied by ptosis had worse binocular function than IXT-only patients [9]. However, stereopsis and other clinical characteristics of esotropia (ET) accompanied by congenital ptosis compared to ET without ptosis have not been reported yet. Thus, the purpose of this study was to compare binocular function and clinical features in ET patients with congenital ptosis to those without ptosis.

Methods

Ethical statements: This study was approved by the IRB of Pusan National University Yangsan Hospital (IRB No. 63804). Patient consent was waived due to a retrospective study.

1. Study design and subjects

Medical records of 44 patients aged 4 to <10 years who had been diagnosed with ET accompanied by congenital ptosis (ET-ptosis group) were reviewed retrospectively. The control group included 71 age-matched patients who were diagnosed with ET, but without congenital ptosis (ET only group)

Consecutive children aged 4 to <10 years (at the first visit) with previously untreated ET (other than refractive correction) and congenital ptosis who met the following criteria were eligible for this study: (1) any type of ET or esophoria at distance and near, (2) esodeviation with magnitude of deviation measuring 10 prism diopters or greater at distance or near based on measurements by the prism and alternate cover test (PACT). Exclusion criteria were as follows: (1) presence of ocular abnormalities (including glaucoma and congenital cataract) or optic nerve abnormalities, (2) prior strabismus surgery, intraocular or refractive surgery, and (3) significant neurologic diseases such as cerebral palsy.

2. Clinical evaluations

Records of patients were reviewed if they had undergone assessments of best-corrected visual acuity (BCVA), stereoacuity, ocular alignment, marginal reflex distance 1 (MRD1), and cycloplegic refraction at the first visit. Charts of all ET cases with congenital ptosis during the time interval at one hospital were reviewed. Cases with missing information were excluded. BCVA was measured monocularly and followed the age-based testing protocol using the Early Treatment Diabetic Retinopathy Study chart. MRD1 is a measurement in millimeters from light reflex on the patient's cornea to the level of the center of the upper-eyelid margin with the patient gazing monocularly in the primary position [10]. Patients with mild congenital ptosis (0<MRD1≤2) were included. MRD1 was measured when patients looked at the target monocularly because MRD1 could be affected by eyeball deviation.

Near stereoacuity was assessed using the Titmus stereoacuity test (circles, animals, and fly) and the Randot Preschool stereo test at 40 cm. The eyelid was lifted up during stereoacuity testing when needed. In addition, ocular alignment was assessed using the cover/uncover test and the PACT at distance (4 m) and near (33 cm). Coexisting vertical deviation was defined as a constant deviation in all directions with a primary gaze angle of deviation of 4 prism diopters or greater [11]. During the assessment of stereoacuity and PACT, patients were corrected for BCVA. Amblyopia was defined as a visual acuity of 20/40 or worse and a difference in vision between eyes of two or more lines on a vision chart. Severe amblyopia was defined as a visual acuity of 20/100 or worse and moderate amblyopia was defined as a visual acuity of 20/100 to 20/50.

3. Outcome measures

Primary outcome measures were comparisons of stereopsis and clinical features between ET-ptosis and ET-only groups. The secondary outcome measures were comparison of stereopsis and office-based control scores between the patients in the 0<MRD1≤1 and 1<MRD1≤2 groups.

4. Statistical analysis

Descriptive statistics was used for age, sex, BCVA, refractive errors, magnitude of deviation and stereoacuity. Pearson's chi-square test was used for categorical variables and independent samples t-test was employed to compare continuous numerical variables. Before performing the *t*-test, normality of data was assessed. All *p*-values provided were obtained using a two-tailed test. IBM SPSS ver. 23.0 (IBM Corp.) was used for all statistical analyses. Stereoacuity was

Table 1. Stereopsis and clinical features in patients with ET-ptosis group and the ET-only group

Characteristic	ET-ptosis (n=44)	ET-only (n=71)	*p*-value
Age (yr)	6.1±2.3	5.5±1.7	0.25
Sex (male:female)	23:21	32:39	0.45
Cycloplegic refraction, OD (D)			
Spherical	2.42±1.33	1.57±1.84	0.84
Cylinder	1.14±0.63	1.21±1.13	0.50
Spherical equivalent	2.97±1.60	2.17±2.40	0.70
Cycloplegic refraction, OS (D)			
Spherical	2.22±1.05	1.27±2.00	0.66
Cylinder	1.24±0.59	1.27±1.06	0.49
Spherical equivalent	2.84±1.34	1.91±2.53	0.52
BCVA (logMAR)			
Right eye	0.27±0.09	0.31±0.28	0.06
Left eye	0.44±0.14	0.31±0.34	0.63
Magnitude of esodeviation (PD)			
At distance	17.9±6.6	20.0±12.6	0.44
At near	18.6±7.9	23.7±11.4	0.06
Stereopsis (log arcsec)			
Titmus test	2.86±0.45	2.93±0.32	0.73
Randot preschool stereo test	2.95±0.31	2.89±0.39	0.49
Oblique muscle overaction	1 (2.3)	8 (11.3)	0.10
Dissociated vertical deviation	3 (6.8)	5 (7.0)	0.97
Coexisting vertical strabismus	10 (22.7)	8 (11.3)	0.16
Latent nystagmus	4 (9.1)	9 (12.7)	0.28
Amblyopia	16 (36.4)	35 (49.3)	0.39
Severe	5 (11.4)	8 (11.3)	0.99
Moderate	11 (25.0)	27 (38.0)	0.30

Values are presented as mean±standard deviation or number (%).
ET, esotropia; OD, oculus dexter; D, diopter; OS, oculus sinister; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; PD, prism diopter.

converted into a log scale for analysis. For the purpose of statistical analysis, no measurable stereopsis was coded as 3.2 log seconds of arc [12]. Statistical significance was defined as a *p*-value less than 0.05.

Results

The mean and standard deviation age of patients (n=115) was 5.7±1.9 years. There were 55 males and 58 females in the cohort. Of these 115 patients, 44 had ET with congenital ptosis and 71 did not have congenital ptosis. The MRD1 of patients with ptosis was greater than 0 but less than or equal to 2, indicating that mild ptosis was included. There was no statistically significant difference in age, sex, refractive errors or BCVA between the two groups (Table 1). Magnitude of esodeviation at distance and near did not differ significantly between the two groups (at distance, 17.9±6.6 vs. 20.0±12.6, *p*=0.44; at near, 18.6±7.9 vs. 23.7±11.4, *p*=0.06). Numbers of patients with inferior oblique overaction, dissociated vertical deviation, latent nystagmus and coexisting vertical strabismus were not significantly different between the two groups either (inferior oblique muscle overaction, 1 [2.3%] vs. 8 [11.3%], *p*=0.10; dissociated vertical deviation, 3 [6.8%] vs. 5 [7.0%], *p*=0.97; coexisting vertical strabismus, 10 [22.7%] vs. 8 [11.3%], *p*=0.16; latent nystagmus, 4 [9.1%] vs. 9 [12.7%], *p*=0.28). The number of patients with amblyopia did not differ significantly between the two groups either (n=16 [36.4%] in the ET-ptosis group vs. n=35 [49.3%] in the ET-only group, *p*=0.39). Near stereoacuity, which was measured using the Randot stereo test and the Titmus test, did not differ significantly between the two groups either (Titmus test, 2.86±0.45 vs. 2.93±0.32, *p*=0.73; Randot stereo test, 2.95±0.31 vs. 2.89±0.39, *p*=0.49) (Table 1).

Table 2. Comparison of characteristics according to margin reflex distance 1

Characteristic	0<MRD1≤1 (n=20)	1<MRD1≤2 (n=24)	*p*-value
BCVA (logMAR)			
Right eye	0.30±0.11	0.24±0.07	0.51
Left eye	0.46±0.16	0.42±0.12	0.72
Magnitude of esodeviation (PD)			
At distance	18.4±6.8	17.4±6.2	0.70
At near	19.4±8.1	18.0±7.6	0.85
Stereopsis (log arcsec)			
Titmus test	2.90±0.34	2.84±0.32	0.64
Randot test	2.86±0.33	3.03±0.37	0.47
Amblyopia	8 (40.0)	7 (29.2)	0.26
Severe	4	1	
Moderate	4	7	

Values are presented as mean±standard deviation or number (%).
MRD1, margin reflex distance 1; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; PD, prism diopter.

The magnitudes of esodeviation, near stereopsis and BCVA did not differ significantly between the 0<MRD1≤1 group and the 1<MRD1≤2 group. Although the number of patients with severe amblyopia tended to be greater in the 0<MRD1≤1 group than in the 1<MRD1≤2 group, the difference between the two groups was not significant (*p*=0.14) (Table 2).

Discussion

In this retrospective study, we compared stereopsis and other clinical features between the ET-ptosis group and the ET-only group. The mean stereopsis at near and the number of patients with amblyopia did not differ significantly between the two groups. Mild ptosis had no additional negative effect on stereopsis and amblyopia in patients with ET.

Binocular perception of depth is the highest form of binocular vision and important for some professions such as pilots and ophthalmic surgeons who need high degree of hand-eye coordination [13]. Maturation of stereopsis rapidly develops at 8 to 18 months of age [14]. Many studies have shown that patients with IXT have different degrees of damage to their binocular function [11,15,16]. Generally, near stereoacuity is normal in patients with IXT, while distance stereopsis is often worse than in normal controls [15]. Other studies have suggested that some patients with IXT have a decline in near stereopsis [16]. In our previous study, distance stereoacuity was significantly impaired when ptosis coexisted with IXT. However, near stereoacuity of the patients was not affected by ptosis [9]. A larger proportion of patients had suppression on the Bagolini test in the IXT-ptosis group than in the IXT-only group. Also, a higher proportion of patients in 0<MRD1≤1 group had suppression on Baolini test compared to the 1<MRD1≤2 group. Furthermore, office-based control scores at distance tended to be slightly worse in the IXT-ptosis group than in the IXT-only group. In IXT patients, the presence of coexisting ptosis can have a further deleterious impact on binocular function [9].

Infantile ET is related to a higher incidence of amblyopia and impaired binocular sensory function. In a recent prospective study, 129 children who were diagnosed with infantile ET by 6 months of age and followed up for at least 5 years were found that, even though more than 90% of these children were treated for amblyopia during follow-up, less than 10% exhibited persistent amblyopia at the final visit, with majority of persistent cases of amblyopia being mild [17]. In contrast, treatment for binocular sensory impairment is rarely successful. Even with optical correction and early surgery, less than 0.5% of this prospective cohort had normal stereoacuity by the age of five, and over 60% had no stereoacuity at all [17]. This study excluded patients who had strabismus surgery, hence infantile ET was not included.

The onset of an initially intermittent nasalward misalignment in patients with accommodative ET typically starts between the ages of 18 and 48 months. Accommodative ET often leads to impaired binocular sensory function, despite its late development. Even when accommodative ET in children was diagnosed in its earliest stage, more than 40% showed impaired stereoacuity [18]. In this study, ptosis had no further deleterious impact on stereoacuity in ET patients. This was due to the inclusion of mild ptosis in this study. Therefore, mild ptosis had no effect on stereoacuity in ET patients who already had poor stereoacuity.

Amblyopia has been found to be more common in patients with congenital ptosis caused by astigmatism or other refractive errors and/or the visual axis obstruction [8]. In the study of Hornblass et al. [19], they found a significant relationship between the severity of ptosis and the development of amblyopia. Preoperative MRD1 ≤–1 mm, preoperative lid fissure ≤4.5 mm, preoperative anisometropia, and postoperative astigmatism were associated with amblyopia in congenital ptosis after frontalis sling surgery [20]. Amblyopia is uncommon in IXT patients unless there is severe anisometropia [21]. The reported incidence of amblyopia in patients with infantile ET ranges between 30% and 75% [22-27]. The high prevalence of amblyopia in ET is due to asymmetry between the nasal and temporal hemiretina. In ET, the fovea in the deviating eye competes with the more powerful temporal hemiretina in the non-deviating eye, resulting in amblyopia [11,28]. In this study, the number of patients with amblyopia did not differ between the ET-ptosis group and the ET-only group. Amblyopia already occurs frequently in patient with ET, and coexisting mild ptosis did not have a further negative impact on their vision.

This study has some limitations. First, this was a retrospective review of medical records, which could inherently limit the quality of data. Second, the sample size was also relatively small. Third, this study does not disclose whether binocular function would improve after ptosis surgery. Fourth, this study did not analyze the lateralization of ptosis, so it was not possible to compare the vision of the eye with and without ptosis. Finally, this study did not analyze the type of ET, so the effect on visual acuity and stereoacuity according to the type of ET was not analyzed. However, the strength of this study was its quantitative evaluation of binocular function in ET patients with congenital ptosis

compared to ET-only patients.

In conclusion, stereoacuity and visual acuity did not differ between the ET-ptosis group and the ET-only group. The presence of coexisting mild ptosis might not have a further deleterious impact on stereopsis or visual acuity in patients with ET.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: SJK. Data curation: SAY, KEH, Formal analysis: SAY, KEH. Investigation: KEH. Methodology: SJK. Project administration: SJK. Resources: SJK, HC. Supervision: HC. Writing - original draft: SJK, SAY, KEH. Writing - review & editing: SJK, HC. All authors read and approved the final manuscript.

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Diagnostic significance of transcranial Doppler ultrasonography in patients with subarachnoid hemorrhage and cerebral vasospasm

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Background: This study investigated the accuracy and usefulness of transcranial Doppler (TCD) ultrasonography as a diagnostic method in patients with subarachnoid hemorrhage (SAH) and cerebral vasospasm.

Methods: This retrospective study collected data from January 2022 to December 2023 at our institution, targeting patients with SAH caused by rupture of a cerebral aneurysm. TCD and brain computed tomographic angiography (CTA) were performed to diagnose cerebral vasospasm. The vessel diameters on CTA at the time of SAH occurrence and CTA 1 to 2 weeks after the occurrence were compared, and TCD was performed on a daily basis from 3 to 14 days after the occurrence of ictus.

Results: Among 152 patients with non-traumatic SAH over a 2-year period, 143 patients with SAH caused by ruptured cerebral aneurysms were enrolled. The mean age was 59.28±13.27 years. The modified Fisher grade was a statistically significant predictor of cerebral vasospasm (p<0.05). In addition, the Hunt-Hess grade also showed statistical significance (p<0.05). TCD showed high accuracy in predicting vasospasm. The sensitivity was 0.93 (95% confidence interval [CI], 0.87–0.97), specificity was 0.89 (95% CI, 0.81–0.96), positive predictive value was 0.91 (95% CI, 0.85–0.96), and negative predictive value was 0.91 (95% CI, 0.84–0.95).

Conclusions: TCD showed high accuracy in predicting the diagnosis of cerebral vasospasm. TCD is considered an essential diagnostic tool in the neurological management of cerebral vasospasm, which is a potentially fatal complication in SAH patients.

Keywords: Subarachnoid hemorrhage; Ultrasonography, Doppler, transcranial; Vasospasm, intracranial

Introduction

Subarachnoid hemorrhage (SAH), a disease caused by rupture of a cerebral aneurysm, is fatal itself and may lead to severe neurological impairment or death [1,2]. Various complications may occur during the treatment of SAH patients, but cerebral vasospasm (CV), a representative complication, is highly likely to be accompanied by delayed cerebral ischemia (DCI), requiring careful neurological monitoring and treatment [3,4]. CV is a narrowing of the diameter of the cerebral artery, which is reversible and self-limited [5]. CV, a complication of SAH, occurs 3 to 14 days after rupture of the cerebral aneurysm. CV is a narrowing of the cerebral artery diameter, and it is not fatal to the patient alone. However, DCI accompanying CV may have fatal consequences for the patient [6,7]. The incidence of CV confirmed on angiography of computed

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tomography (CT) is approximately 50% to 70% in SAH patients with ruptured cerebral aneurysms [8,9]. Not all patients with angiographically occurring CV develop symptoms. Approximately 30% to 40% of these patients develop symptoms due to DCI, which may result in fatal neurological consequences such as loss of consciousness, hemiplegia, and speech disorders [4,10,11]. Rapid and accurate screening of CV is necessary to avoid DCI, a serious complication of SAH that causes significant symptoms in patients. The most important point in the treatment of neurologically critically ill patients is the symptoms of patients. In cases of SAH, the symptoms of patients are identified through intensive care in the neurological intensive care unit. When DCI occurs due to CV, mood changes such as irritability, confusion, and lethargy may occur, and other symptoms such as headache, focal weakness, speech impairment, and decreased consciousness may also occur [8,12]. When these symptoms occur, CV should be diagnosed and ruled out by using various diagnostic methods. Among the various methods, the most commonly used methods are brain CT angiography (CTA) and transcranial Doppler (TCD). Brain CTA has limitations due to side effects from radiation exposure and the use of contrast agents [9]. In particular, TCD is a good diagnostic tool for early detection of CV in various aspects [13]. First of all, in terms of usage, it has advantages for both patients and practitioners. Its noninvasiveness, measurability at the bedside without moving the patient, and its low cost enable daily measurements (3 to 14 days) during the CV risk period [14]. When the mean blood flow velocity of the middle cerebral artery (MCA) is measured and the measured value is 120 cm/sec or higher, CV may be suspected diagnostically. If CV is suspected after the TCD test, additional brain CTA may be performed to confirm CV through imaging studies. TCD is known to be an accurate diagnostic tool with high sensitivity and specificity [15]. This study investigates the actual patient group of the institution to find out the correlation between TCD and CV and whether it is valuable to perform the test on a daily basis.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kosin Medical Center (IRB No. KUGH IRB 2024-08-021). Written informed consent was waived.

1. Patient

The data was collected from a single institution for a total of 2 years from January 2022 to December 2023. A study was conducted for 2 years targeting non-traumatic SAH patients, and a total of 152 patients were enrolled. This study selected cerebral aneurysm rupture-related SAH patients, and those who did not undergo TCD testing were excluded. Their condition was poor when they first visited the emergency room, and they died within 3 days of admission. A total of 143 patients were enrolled in the study, and this study was conducted as a retrospective study.

2. Clinical management

At the time of admission, the Hunt-Hess grade was recorded through a neurological examination of the patient before surgical or interventional procedures, and the modified-Fisher grade was also recorded through an initial brain CT. All patients underwent emergency conventional surgical treatment (surgical clipping, trapping and bypass) or endovascular intervention (coiling, stent assisted coiling, trapping) and were treated in the neurological intensive care unit. All patients also received brain CT and CTA prior to treatment. All patients received continuous neuromonitoring in the neurological intensive care unit. Neurological examinations and urine output were checked on an hourly basis, and vital signs were monitored continuously. The euvolemic principle was applied in the treatment of patients, and normal systolic blood pressure was used as the reference point for care. Immediately after admission to the intensive care unit, oral nimodipine 60 mg was administered every 4 hours. When the patients showed high intracranial pressure, decompressive craniotomy, external ventricular drainage, or lumbar drainage was additionally performed. TCD tests were performed on a daily basis from the 3rd day to the 14th day. If the patients did not show neurological changes, showed TCD flow velocity lower than 120 cm/sec, or did not show significant changes in TCD flow velocity within a day (differences of more than 50 cm/sec), brain

CT+CTA was performed on the 7th and 14th days. In cases of radiological CV with no difference in neurological symptoms, induced hypertensive treatment was used. In cases of DCI onset accompanied by CV, brain CT was performed to identify low-density lesions and confirm the diagnosis. If the patient had neurological symptoms along with CV, the patient received active treatment as soon as possible. Trans-femoral cerebral angiography (TFCA) was performed as an emergency procedure through a trans-femoral approach in the angiography room to determine the degree of spasm in the major cerebral vessels. Afterwards, nimodipine was diluted with normal saline and injected through a microcatheter. After confirming the degree of recovery of vessel diameter, hypervolemic and induced-hypertension treatment was performed in the neurological intensive care unit.

3. Diagnostic techniques

TCD tests performed daily were performed at the bed side by trained nurses. The device used for the Doppler ultrasound examination at our institution was PMD 150 digital transcranial Doppler system (Spencer Technologies). The figures were checked through each temporal lobe on both sides. TCD figures were measured daily and stored in a computer database in the neurological intensive care unit. When a TCD flow velocity figure was 120 cm/s or higher or showed a difference of 50 cm/sec or higher within 24 hours, the system reported it directly to the attending physician. The results were obtained by measuring the temporal bone area, which is the thinnest area, and measuring both the left and right sides. Blood flow velocity was measured in both the MCA and the anterior cerebral artery using a 2-MHz portable hand-transducer probe.

4. Statistical analysis

Statistical analysis was performed using the SPSS 25.0 for windows (IBM Corp.). The correlation between TCD measurements and Hunt-Hess grade and modified Fisher grade was statistically evaluated using the Mann-Whitney *U*-test. The chi-square and Fisher exact tests were used for categorical variables according to their characteristics. The results of TCD were presented as percentages with 95% confidence intervals (CI). The criterion for indicating statistical significance was p-value <0.05 in all analyses.

Results

This retrospective study collected data over 2 years from January 2022 to December 2023, and a total of 143 patients was included in the criteria. The mean age was 59.28±13.27 years. Females accounted for 83 patients, or 58% of total patients. The most common location of the cerebral aneurysm causing SAH was the anterior communicating artery, accounting for 49 cases (34.3%) of the total patients, followed by the bifurcation of the MCA and the posterior communicating artery. When the cerebral artery location was largely divided into anterior and posterior, aneurysm ruptures in the anterior circulation accounted for 128 cases (89.5%). In this study, cerebral aneurysms located in the posterior circulation were located in the posterior inferior cerebellar artery, basilar artery, superior cerebellar artery, and vertebral artery (Table 1). Hunt-Hess grade and modified Fisher grade data were also collected through neurological examination and brain CT at the time of admission of SAH patients (Table 2). In cases of Hunt-Hess grade, the neurological examination results of the patients showed that grade III, a drowsy level of consciousness, and grade IV, a stupor level of consciousness, respectively accounted

Table 1. Characteristics of patients and locations of aneurysms

Characteristic	Value (n=143)
Age (yr)	59.28±13.27
Female sex	83 (58.0)
Location of aneurysm	
Anterior circulation	128 (89.5)
Posterior circulation	15 (10.5)
A-com	49 (34.3)
MCA bifurcation	39 (27.3)
P-com	25 (17.5)
PICA	8 (5.6)
Distal ACA	7 (4.9)
Para-clinoid segment of internal cerebral artery	4 (2.8)
Anterior temporal artery	3 (2.1)
Basilar artery	3 (2.1)
SCA	2 (1.4)
VA	2 (1.4)
Internal cerebral artery bifurcation	2 (1.4)

Values are presented as mean±standard deviation or number (%).
A-com, anterior communicating artery; MCA, middle cerebral artery; P-com, posterior communicating artery; PICA, posterior inferior cerebellar artery; ACA, anterior cerebral artery; SCA, superior cerebral artery; VA, vertebral artery.

Table 2. Level of consciousness and degree of hemorrhage on computed tomography (n=143)

Grade	No. (%)
Hunt-Hess grade	
I	5 (3.5)
II	15 (10.5)
III	50 (35)
IV	53 (37)
V	20 (14)
Modified Fisher grade	
I	5 (3.5)
II	2 (1.4)
III	60 (42)
IV	76 (53.1)

Table 3. Methods of treating subarachnoid hemorrhage patients

Method	No. (%)
Conventional surgical treatment	36 (25.2)
Clipping of aneurysm	32 (88.9)
Trapping and bypass	4 (11.1)
Interventional endovascular treatment	107 (74.8)
Coiling	102 (95.3)
Trapping of parent vessel	5 (4.7)

Table 4. Occurrence of cerebral vasospasm confirmed by CTA and TCD

	Vasospasm, No. (%)	
	Yes	No
CTA	95 (66.4)	48 (33.6)
TCD	97 (67.8)	46 (39.9)

CTA, computed tomographic angiography; TCD, transcranial Doppler.

Table 5. Correlation between consciousness level and cerebral vasospasm as confirmed by computed tomographic angiography

Hunt-Hess grade	Cerebral vasospasm, No. (%)	
	Yes	No
Grade I	1 (20.0)	4 (80.0)
Grade II	8 (53.3)	7 (46.7)
Grade III	28 (56.0)	22 (44.0)
Grade IV	40 (75.3)	13 (24.7)
Grade V	18 (90.0)	2 (10.0)
p-value	<0.05	

Table 6. Relationship between the amount of hemorrhage and the presence or absence of IVH on brain CT and CV

Modified-Fisher grade	Cerebral vasospasm, No. (%)	
	Yes	No
Grade I	2 (40.0)	3 (60.0)
Grade II	1 (50.0)	1 (50.0)
Grade III	36 (60.0)	24 (40.0)
Grade IV	56 (73.6)	20 (26.4)
p-value	<0.05	

IVH, intraventricular hemorrhage; CT, computed tomography; CV, cerebral vasospasm.

for 35% and 37% of the total patients, accounting for 72% of the total patients. In cases of modified-Fisher grade, grade III, in which SAH volume was 1 mm or more on CT and intraventricular hemorrhage was present, accounted for 42% (60 patients), the largest group. The criteria for treatment selection in SAH patients were the location and size of the cerebral aneurysm, the age of patients, and the overall condition, and were selected between conventional surgical methods and endovascular intervention. In cases where the volume of intracerebral hemorrhage was large or hydrocephalus was present that intracranial pressure was high, conventional surgical methods enabling decompressive craniotomy were selected (Table 3). In brain CTA taken from 3rd to 14th day, CV occurred in 84 patients (58.7%) compared to the initial CTA, and in cases of TCD, it was confirmed that the flow velocity value of the MCA was 120 cm/sec or higher, which was confirmed in 86 patients (60.1% of the total patients) (Table 4). The Hunt-Hess grade records related to the level of consciousness of the patients at the time of ictus were checked to confirm the correlation between CV and grade, and a statistically significant correlation was confirmed (Table 5). Analysis of the correlation between modified-Fisher grade and CV, which are related to the amount of bleeding and the presence or absence of intraventricular hemorrhage on brain CT, also obtained statistically significant values (Table 6). A validation study was conducted to confirm the accuracy of initial screening using TCD in patients suspected of CV. In patients diagnosed with CV on TCD, vasospasm was confirmed on actual CTA in 92.7% of cases, and in patients with normal TCD values, CTA was also normal in 89.1% of cases, showing a significantly high probability of accuracy and obtaining statistically significant values (Table 7). The utility of TCD screening as a diagnostic tool prior to confirmation of CV by CTA was excellent that the sensitivity of 0.93 (95% CI, 0.87–0.97),

Table 7. The correlation between CTA and TCD for cerebral vasospasm

CTA	TCD, No. (%)		*p*-value
	Vasospasm	Normal	
Vasospasm	90 (92.7)	5 (10.9)	<0.01
Normal	7 (7.3)	41 (89.1)	

CTA, computed tomographic angiography; TCD, transcranial Doppler.

specificity of 0.89 (95% CI, 0.81–0.96), positive predictive value of 0.91 (95% CI, 0.85–0.96), negative predictive value of 0.91 (95% CI, 0.84–0.95). According to the results of this study, TCD showed high numerical values in all areas.

Discussion

When SAH occurs due to rupture of a cerebral aneurysm, patients have high morbidity and mortality. SAH patients may develop various complications, such as rebleeding, cerebral infarction, and hydrocephalus, and one of the most fatal complications is CV [16,17]. CV stands for transient cerebral vasoconstriction and may occur from 3 to 14 days after ictus. However, this constriction of cerebral blood vessels itself does not cause harm to the patient. CV may cause and result in cerebral ischemia, and this DCI may bring critically fatal consequences to the patient. Patients may experience a variety of symptoms, including headache, decreased consciousness, hemiparesis, aphasia, and dysarthria, and if DCI progresses further, it may lead to death. DCI, a complication that occurs as a result of CV, requires rapid screening and appropriate treatment [18-20]. Accurate and rapid diagnosis and appropriate treatment have a positive effect on the prognosis of SAH patients [21]. The purpose of this retrospective study was to investigate the diagnostic value of appropriate and early TCD monitoring. In this study, females were slightly more prevalent (58%) in the SAH patient group, the location of the cerebral aneurysm was much more common in the anterior circulation (89.5%), and the most common location was the anterior communicating aneurysm (34.3%). These results were not significantly different from other previously conducted papers [21,22]. The results of the research showed that the Hunt-Hess grade, which indicates the level of consciousness of SAH patients, and the modified-Fisher grade, which indicates the degree of hemorrhage in brain CT, were statistically significant predictors of CV. Oxyhemoglobin in blood clots derived from SAH is a key role in CV. It is known that methemoglobin and superoxide anion radicals and lipid peroxidation caused by oxyhemoglobin lead to damage of endothelial cells and smooth muscle cells, resulting in decreased endothelial nitro oxide and increased endothelin-1, which in turn causes cerebral vessel spasm [23-25]. When SAH occurs due to rupture of a cerebral aneurysm, patients show high morbidity and mortality. SAH patients may develop various complications, such as rebleeding, cerebral infarction, and hydrocephalus, and one of the most fatal complications is CV [16,17]. CV stands for transient cerebral vasoconstriction, and it may occur from 3 to 14 days after ictus. However, this constriction of cerebral blood vessels in itself does not cause harm to the patient. CV may cause and result in cerebral ischemia, and this DCI may have highly fatal consequences for the patient. Patients may experience a variety of symptoms, including headache, decreased consciousness, hemiparesis, aphasia, and dysarthria, and further progress of DCI may lead to death. DCI is a complication that occurs as a result of CV, and it requires rapid screening and appropriate treatment [18-20]. Accurate and rapid diagnosis and appropriate treatment have a positive effect on the prognosis of SAH patients [21].

When a patient presents with neurological changes due to CV, CTA of brain, and TFCA become the gold standard for diagnosis. However, brain CTA has several disadvantages. First, there is the risk of having to move the patient from the intensive care unit to the CT room, and it also may involve radiation exposure and complications from contrast agents. Although TFCA is the most reliable and accurate method for diagnosing CV, it has more dangerous disadvantages than CTA. TFCA is an invasive procedure, and infection, vascular dissection, cerebral infarction may occur during the procedure [26-29]. From this perspective, TCD is considered to be a highly effective diagnostic tool for predictive diagnosis of CV. Like several previous studies [5-7,21,22], this study confirms and highlights these advantages of TCD.

TCD was effectively used for the early detection of CV and had a diagnostic value in predicting the onset of DCI caused by CV. TCD also reduces the risk to patients, saves time until CV diagnosis, and ultimately reduces complications. TCD, which measures the mean blood flow velocity of the MCA using the thinnest part of the temporal bone as a window, is known to have high sensitivity and specificity around 90% [14,15,30].

In the current study, the sensitivity and specificity of TCD were significant high at 93% and 89%, respectively, and such a result ultimately led to the rapid diagnosis of CV and prompt and appropriate treatment of DCI patients. Several previous studies have reported that the mean blood flow velocity of the MCA measured by TCD shows a correlation in patients with asymptomatic CV [7,18], symptomatic CV [16], and DCI [19]. The crucial point is the utility of TCD in patients with symptomatic CV and DCI. In patients with SAH caused by cerebral aneurysm rupture, the occurrence rate of DCI ranges from 10% to 20% [3-5,7]. Patients with ischemic damage show a high probability of developing neurological deficit, and TCD is an excellent diagnostic tool for the early detection of such patients. Patients with DCI caused by CV require brain CTA, medical treatment, and TFCA followed by intra-arterial vasodilator administration, balloon angioplasty, or angioplasty using an intravascular stent. As TCD is easily available at the bedside on a daily basis, it saves time and cost for these systems. Despite these various advantages, there are also disadvantages to the TCD technique. Depending on the skill level of each individual performing the test, there may be differences in the test results, and in cases where the temporal bone is thick, measurement may be difficult.

This study has several limitations. First, it is a retrospective cross-sectional study. Second, this study was conducted in a single center, so the generalizability of the results cannot be guaranteed. Multicenter studies are needed to apply the results to a larger population.

Brain CTA or TFCA is essential for confirming CV. As shown in Table 7, CTA identified CV in 92.7% of cases when the TCD result was 120 cm/sec or higher. The results of this study imply that it is reasonable to use mean blood flow velocity of MCA via TCD for monitoring CV based on reliable data with statistical confidence. These high predictive diagnostic results of TCD provide a rapid treatment protocol for CV patients with symptoms and contribute to saving the time for an appropriate treatment. TCD does not require movement of the critically ill patient, and this effective, accurate, and inexpensive test should be used on a daily basis for 3 to 14 days in cases of CV risk.

Article information

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

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Author contributions
All the work was done by JHP.

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Comparative analysis of Access PCT and Elecsys BRAHMS PCT assays for procalcitonin measurements

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Background: Procalcitonin (PCT) is a crucial biomarker for diagnosing sepsis and managing antibiotic therapy. This study evaluated the analytical performance and comparability of the Access PCT and Elecsys BRAHMS PCT assays.

Methods: The precision, detection capability, linearity, and reference range of both assays were assessed. A comparative analysis included 182 patient samples categorized into four risk groups to compare the results between Access PCT and Elecsys BRAHMS PCT assays.

Results: The Access PCT assay demonstrated precision within the manufacturer's threshold, and its detection capabilities were verified. This assay exhibited excellent linearity and appropriate reference intervals. Comparative analysis indicated that the Access PCT assay reported higher overall PCT levels than the Elecsys BRAHMS assay, with high agreement between the assays (κ=0.941). However, the biases varied across different PCT concentration intervals.

Conclusions: Both the Access PCT and Elecsys BRAHMS PCT assays performed robustly with notable concordance but varying biases at different concentration intervals. The observed biases require careful consideration in clinical decision-making, especially when adopting novel assay systems. Standardizing the calibration across different platforms is recommended to improve assay comparability.

Keywords: Agreement; Limit of detection; Linearity; Precision; Procalcitonin

Introduction

Since the introduction of procalcitonin (PCT) as a potential diagnostic marker of sepsis in 1993, its role in clinical practice has expanded significantly. In 2005, Food and Drug Administration (FDA) approval of the first automated PCT assay, the BRAHMS PCT KRYPTOR produced by Thermo Fisher Scientific, marked a significant advancement in this field [1]. This approval supported extensive research on the clinical utility and efficacy of PCT, thereby expanding its application beyond initial diagnosis of systemic infections. Currently, PCT assays are integral to managing antibiotic therapy, diagnosing pneumonia and postoperative infections, and as prognostic markers in intensive care unit patients at high risk of infection [2].

The initial automated method was developed using re-

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agents and antibodies from BRAHMS GmbH assay, setting a standard that subsequent FDA-cleared methods continued to follow, predominantly through using BRAHMS antibodies [3,4]. However, in recent years, several non-BRAHMS methods have emerged in clinical laboratories, including the latex-based immunoturbidimetric assay by Diazyme, fluorescence immunoassay by Boditech, particle-enhanced turbidimetric immunoassay by Diasys, and paramagnetic particle chemiluminescent immunoassay by Beckman Coulter [4,5]. These assays utilize unique monoclonal antibodies targeting PCT, which differ from those used in BRAHMS methodologies [6].

Although BRAHMS PCT KRYPTOR was the first FDA-accredited automated method and is regarded as a substitute for the reference method, a lack of established reference materials, methodologies, and harmonization across platforms remains [7,8]. This discrepancy is evident in the variability observed both within the BRAHMS assays and when comparing BRAHMS and non-BRAHMS assays, and is often attributed to differences in calibrators or the underlying principles of the methods [9]. These variations have implications for clinical decision-making, particularly regarding the applicability of consistent cutoff values across various clinical conditions and assay methods.

The bias inherent in these assays is well documented, but not consistent; it varies with the concentration of PCT, thus complicating the interpretation of results across a range of clinical scenarios [10]. Most studies have attempted to describe this bias comprehensively across all concentrations [11], data comparing methods specifically based on cutoff points remain sparse.

In the present study, we evaluated the Access PCT immunoassay using DxI 800 (Beckman Coulter), a paramagnetic particle chemiluminescence immunoassay. The analytical performance (precision, detection capability, linearity, carry-over, and reference range) was compared with that of the Elecsys BRAHMS PCT assay conducted on a Cobas e 601 (Roche Diagnostics International). In addition, we assessed the compatibility of the Access PCT assay with laboratories where BRAHMS methods have previously been utilized, considering varying PCT concentrations.

Methods

Ethical statements: The protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (No. KUGH 2019-09-025). This study was performed in accordance with the Declaration of Helsinki. Informed consent was waived.

1. Evaluation of precision

To assess precision, we evaluated the coefficient of variation (CV; %) using commercially available quality control (QC) materials, specifically MAS Omni-IMMUNE Immunoassay Controls (Thermo Fisher Scientific Inc.). The concentrations for the QC materials were set at 0.53, 3.68, and 29.20 μg/L, representing low, intermediate, and high concentrations, respectively. Each QC material was tested over a period of 20 days, with two runs daily and two replicates per run, based on the protocols of the Clinical and Laboratory Standards Institute (CLSI) EP15-A3 [12,13]. We calculated the CV% values for repeatability and within-laboratory precision by comparing these values with the manufacturer's suggested CV% values listed in the product insert. Statistical analyses were conducted using the Analyse-it software (version 5.90; Analyse-it Software Ltd.).

2. Limits of blank, detection, and quantitation verification

The limits of blank (LoB), limits of detection (LoD), and limits of quantitation (LoQ) were verified based on the CLSI guideline EP12-A2 [14]. To verify the LoB and LoD, we repeated the tests for both blank and low-concentration patient samples 20 times. In addition, to confirm the LoQ, we tested five patient samples with concentrations close to the manufacturer's claimed LoQ. Each sample was tested ten times to assess whether the test results were within the permissible total error.

3. Validation of linearity

Linearity validation was conducted based on CLSI guidelines EP06-ED2 [15]. A high-concentration patient sample was serially diluted with the low-level material at ratios of 4:0, 3:1, 2:2, 1:3, and 0:4. Each of the five dilutions was tested in duplicate. The data were analyzed as outlined in CLSI EP06-ED2. The allowable deviation from linearity (ADL) for each of the five levels was calculated and deviations from linearity were assessed. If the deviation was within the calculated ADL, the linearity of the assay was validated.

4. Verification of reference intervals

We verified the manufacturer's reference interval for PCT (0–0.065 μg/L) using samples obtained from a healthy population. Residual blood specimens originally collected during routine health screenings, unrelated to the current research, were utilized. Participants met criteria for a "healthy" status, including being aged 18–50 years. Twenty samples were obtained from Kosin University Gospel Hospital and analyzed based on CLSI guideline EP28-A3 [16]. This process was designed to confirm whether the reference interval was appropriate for our patient population.

5. Assessment of carry-over

Carry-over was evaluated by sequentially testing a high- and low-level sample, each tested four times. The results from the high-level samples were labeled H1–H4, and those from the low-level samples were labeled L1–L4. The carry-over rate (%) was calculated using the equation below. The acceptable criterion for carry-over was set to <1% [17].

$$\text{Carry} - \text{over rate}(\%) = \frac{\text{L1} - (\text{L3} + \text{L4})/2}{(\text{H3} + \text{H2})/2 - (\text{L3} + \text{L4})/2} \times 100$$

6. Comparative evaluation of PCT assays

We collected 190 anonymized patient samples from Kosin University Gospel Hospital for the comparative evaluation of the PCT assays. Samples were transferred to serum separator tubes, divided into two aliquots, and analyzed separately. One aliquot was tested in a routine laboratory using the Elecsys BRAHMS PCT assay, whereas the other was analyzed using the Access PCT assay. Samples exceeding the analytical measurement range of any analyzer (>100 μg/L) were excluded from the study.

The PCT values from the two analyzers were classified into four risk categories based on medical decision points: low risk, group 1 (<0.5 μg/L); intermediate risk, group 2 (≥0.5 to <2.0 μg/L); high risk, group 3 (≥2.0 to <10 μg/L); and very high risk of sepsis, group 4 (≥10 μg/L) [18]. Data comparison was performed using Passing-Bablok regression, correlation coefficients, and Bland-Altman plots. In addition, an agreement test was conducted to calculate the weighted kappa (κ) to assess concordance.

Results

1. Precision assessment of Access PCT assay

The repeatability CV%s and the within-laboratory CVs for low (0.53 μg/L), intermediate (3.68 μg/L), and high (29.20 μg/L) concentration QC materials in the Access PCT assay were 4.41% and 5.45%, 2.34% and 2.68%, and 2.24% and 3.13%, respectively (Table 1). All measured CV% values were below the manufacturer's precision threshold of 6%.

2. Detection capability

The LoB, LoD, and LoQ were successfully verified, meeting the manufacturer's limits of <0.005, <0.01, and <0.02 μg/L, respectively.

3. Linearity validation

In the linear regression analysis, the assay demonstrated robust linearity ranging 0.00–93.92 μg/L. In the linearity analysis, deviations from linearity for all the prepared materials were within the allowable limits of deviation (Fig. 1).

4. Reference range verification

The PCT levels of all 20 participants were below the proposed reference interval, allowing the adoption of the manufacturer's reference range.

5. Carry-over evaluation

The carry-over was evaluated by testing four high-concentration samples measuring at 67.05, 66.06, 66.88, and 64.60 μg/L, respectively. The low-concentration samples were measured at 0.97, 1.09, 1.05, and 0.97 μg/L, respectively. The calculated carry-over rate was –0.06%, thus confirming that the carry-over falls within the acceptable range.

Table 1. Imprecision of Access PCT

Analyte	Level	Mean (μg/L)	Repeatability CV (%)	Within-laboratory CV (%)
QC material	QC 1	0.53	4.41	5.45
	QC 2	3.68	2.34	2.68
	QC 3	29.20	2.24	3.13

PCT, procalcitonin; CV, coefficient of variation; QC, quality control.

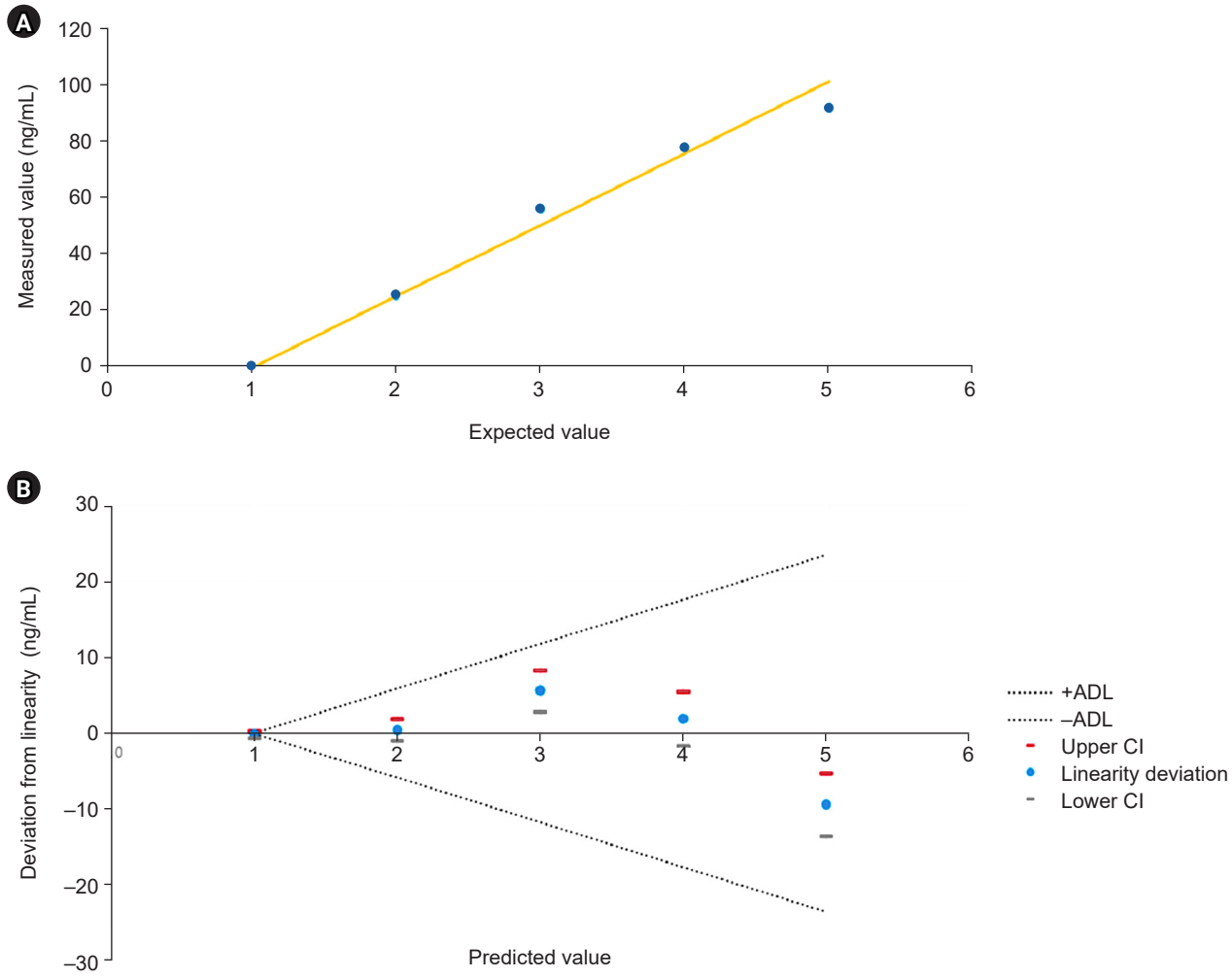

Fig. 1. Linearity analysis of PCT. (A) Linearity data versus linearity fit. (B) Comparison of ADL to the deviation from linearity. PCT, procalcitonin; ADL, allowable deviation from linearity; CI, confidence interval.

6. Comparative analysis of Access PCT and Elecsys BRAHMS PCT assays

Eight samples that exceeded the analytical measurement range were excluded, resulting in 182 samples used for the analysis. According to the Bland-Altman plot (Fig. 2), Access PCT displayed values that were 14.36% higher on mean than Elecsys BRAHMS PCT, with a 95% confidence interval (CI) ranging, 29.56%–58.24%. Despite this notable bias, the correlation was deemed excellent, as evidenced by the Passing-Bablok regression analysis, which showed a correlation coefficient (r) of 0.996.

To further explore bias within subgroups, samples were categorized based on the Elecsys BRAHMS PCT results, which served as a reference. The subgroup sample sizes were 75, 43, 37, and 27 for groups 1–4, respectively. The derivative results from the Bland-Altman plot and Passing-Bablok analysis are shown in Fig. 3. The mean bias was lowest in group 1 (bias, –3.14%; 95% CI, –40.11% to 33.83%) and increased in groups 2–4, with biases of 24.02% (95% CI, –2.35% to 50.40%), 34.40% (95% CI, 0.02% to 68.79%), and 20.10% (95% CI, –1.33% to 41.54%), respectively. Excellent correlations were maintained across all subgroups, with correlation coefficients ranging 0.958–0.993.

The agreement analysis results are detailed in Table 2, with the sample values assigned to the cells based on their measurements using Access PCT (rows) and Elecsys BRAHMS PCT (columns). Approximately 85.2% of the samples were classified into the same subgroup by both

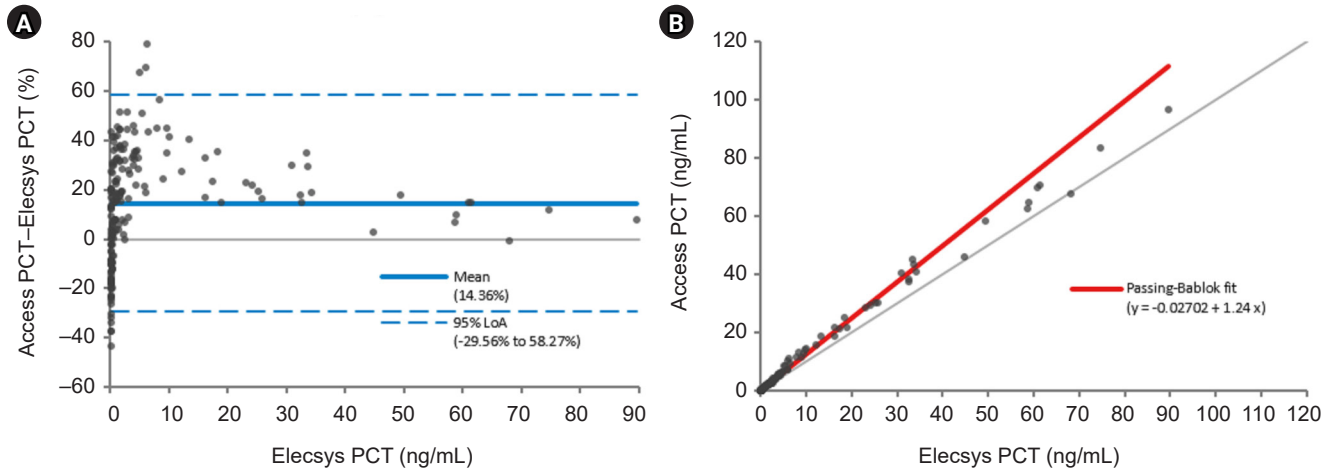

Fig. 2. Comparative analysis of the Access PCT and Elecsys PCT assays. (A) Bland-Altman plot assessing agreement. (B) Passing-Bablok regression for correlation. PCT, procalcitonin; LoA, limits of agreement.

analyzers, and the weighted kappa value was 0.941, indicating high agreement. Discrepancies tended to show Access PCT, thus classifying samples into one subgroup higher than the Elecsys BRAHMS PCT. This tendency is consistent with the observed mean bias of 14.36% between the two assays. Fig. 3A shows that the Access PCT consistently reported higher values than the Elecsys BRAHMS PCT, starting at approximately 0.35 μg/L.

Discussion

The Elecsys BRAHMS PCT assay is widely used in South Korea and is well documented in the literature [19,20]. In contrast, Beckman Coulter's Access PCT assay was introduced more recently to the South Korean market, resulting in a comparative dearth of analyses, especially between these two assays [21]. In the present study, the analytical performance of the Beckman Coulter Access PCT assay met the manufacturer's specifications for precision, detection capacity, linearity, reference interval, and carry-over, indicating reliable performance within the specified parameters. These findings are broadly consistent with those reported in previous studies [3,21].

Both Elecsys BRAHMS PCT and Access PCT assays have previously shown satisfactory concordance with the BRAHMS KRYPTOR assay developed by BRAHMS GmbH (now part of Thermo Fisher Scientific), which is considered the reference method. However, despite these strong correlations, variations in bias have been observed across different concentration intervals among various testing kits [22]. The mean bias was influenced by the distribution of elements across groups. In our study, the results from group 1 showed a 3.14% lower bias in Access PCT than in Elecsys BRAHMS PCT, whereas the differences in other groups ranged from +20.10% to +34.40%. The sizes of group 1 and the other groups were 75 and 107, respectively. Increasing the proportion of patients in group 1 could potentially reduce the overall observed bias. Previous studies have reported varying biases when different analyzers assessed the same methods. For instance, the bias between Access PCT and Elecsys BRAHMS PCT was reported to be 32.10% [21], which was significantly higher than that in our findings. This discrepancy can be attributed to differences in sample size distribution; in the cited study, there were only 26 samples with levels of <0.5 μg/L, compared to 134 samples with levels above this threshold.

As variability in biases across studies has been observed even when the same assays were evaluated, the authors noted that comparing all methods directly is challenging because of the differing biases across concentration ranges. The clinical cutoff values have decreased from the initial values of 0.5 and 2.0 when PCT was first introduced [23]. However, the commonly used PCT decision points were adjusted to 0.1, 0.25, 0.5, and 1.0 [24]. Biases below 2.0, particularly at 0.5, were considered critical for decision-making. In our study, for group 1 (<0.5), the absolute bias was

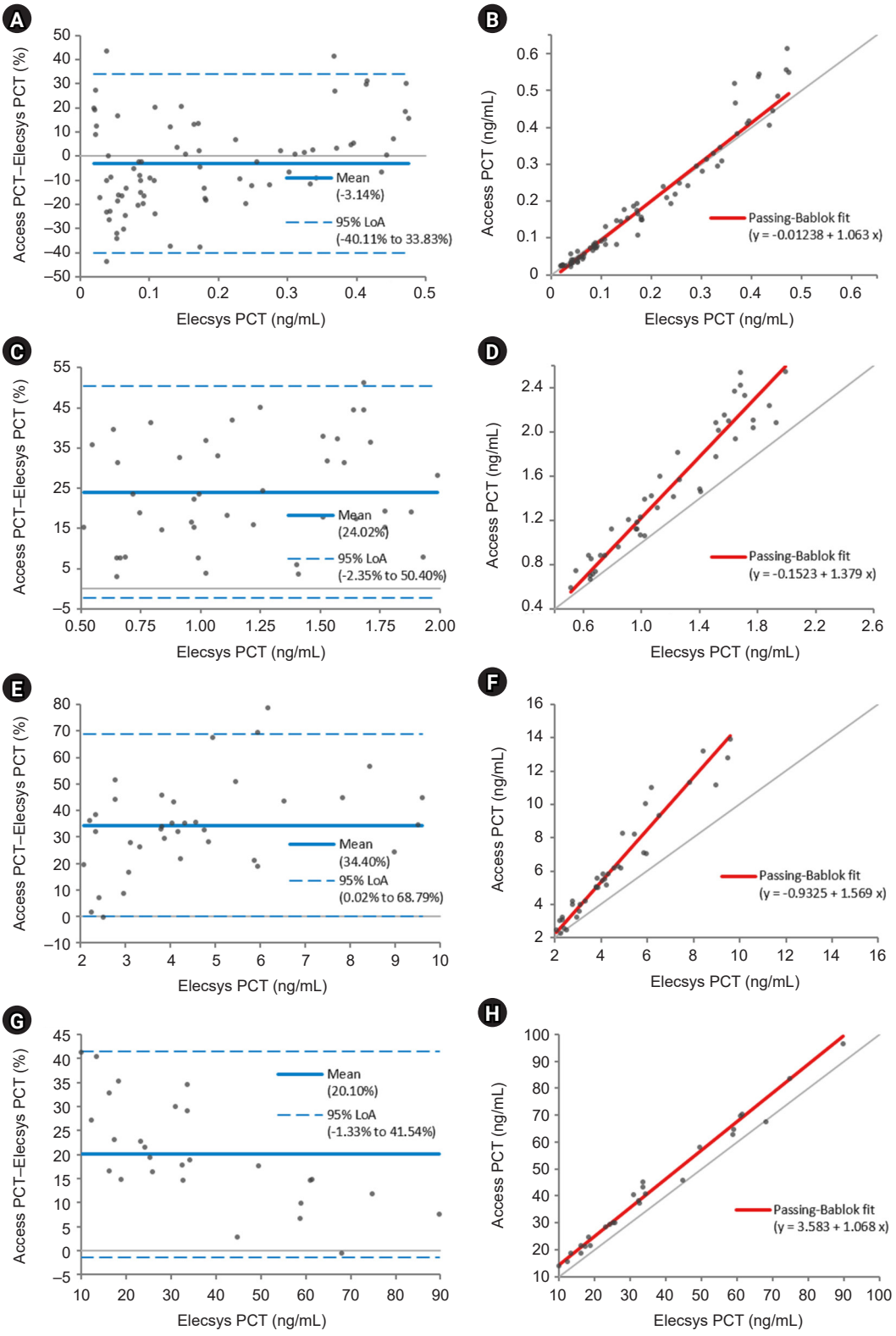

Fig. 3. Comparison of Bland-Altman plots (blue line) and Passing-Bablok (red line) regression of the Elecsys PCT and Access PCT assays. (A, B) Group 1, <0.5 μg/L; (C, D) group 2, ≥0.5 to <2.0 μg/L; (E, F) group 3, 2.0 ≥ to <10 μg/L; and (G, H) group 4, ≥10 μg/L. PCT, procalcitonin; LoA, limits of agreement.

Table 2. Classification of PCT results based on clinical decision points presented in the two assays

Elecsys PCT	Access PCT				Total
	Group 1	Group 2	Group 3	Group 4	
Group 1	69	6	0	0	75
Group 2	0	30	13	0	43
Group 3	0	0	30	8	38
Group 4	0	0	0	26	26
Total	69	36	43	34	182

Each sample was categorized based on the procalcitonin (PCT) results as follows: group 1 (PCT values <0.5 μg/L), group 2 (0.5≤ PCT values <2.0 μg/L), group 3 (2.0≤ PCT values <10.0 μg/L), and group 4 (PCT values ≥10.0 μg/L).

3.14. At these pragmatic clinical decision points, the performance of the Access PCT was observed to be reasonably comparable to that of the Elecsys BRAHMS PCT.

Owing to changing analytical methods is a common issue in clinical laboratories, it is advisable to segment bias analysis by decision-point groups to better understand the variations affecting clinical outcomes. Moreover, when reviewing prior studies, it is crucial to consider the bias at each level or group and its distribution, along with the total assay bias. Notably, the mean bias can vary substantially, which may obscure significant analytical performance issues depending on the proportion of each component used in the calculation.

Recent discussions have raised concerns about whether clinical thresholds established from one assay can be accurately applied to subsequent assays [24,25]. Similar to the bias, the reliability of the agreement tests can be significantly influenced by the sample distribution. In a previous study, analysis of clinical decision points revealed that despite reasonable analytical agreement among all methods evaluated, several samples were categorized differently [7]. In agreement analysis, the concordance rate was 85.2%. These discrepancies were primarily attributed to instances in which Access PCT reported higher PCT levels than Elecsys BRAHMS PCT, consistent with the observed biases. Similar discrepancies were observed when the same assays were compared with a previous study. Such variations are commonly noted in comparisons between assays. While these discrepancies or biases were previously accepted, the increasing emphasis on patient safety and evidence-based medicine necessitates reassessment of the biases between assays and cutoff points for medical decisions [26,27]. Notably, there is a growing demand for a common reference calibrator, and the International Federation of Clinical Chemistry and Laboratory Medicine working group has initiated efforts to produce commutable reference materials [28].

Our study had several limitations. First, the BRAHMS PCT LIA and BRAHMS KRYPTOR assays are considered traceable surrogate reference methods. Although comparability with the BRAHMS PCT KRYPTOR has been reported in previous studies, including evaluations using these reference assays is desirable. However, our study only compared the results of the Access PCT with the Elecsys BRAHMS PCT, which utilizes original materials from BRAHMS. Second, we aimed to subdivide the PCT values to include a cutoff of 0.1, but this was not feasible due to sample shortage. Lastly, clinical information such as patient diagnoses or laboratory tests was not collected, precluding a comprehensive clinical analysis in cases of discrepancy.

Despite these limitations, this study has several strengths. Unlike previous studies that have often analyzed total biases, we analyzed biases based on subdivided values. This approach should be particularly useful for laboratories interested in understanding detailed bias of the Access PCT assay.

In conclusion, although the Access PCT and Elecsys BRAHMS PCT assays both provide reliable and consistent PCT measurements, differences in bias across concentration ranges highlight the need for careful calibration and potentially uniform reference materials to ensure that clinical decisions are based on precise and comparable PCT values. These findings support the requirement for ongoing evaluation and standardization efforts to measure PCT across different assay platforms.

Article information

Conflicts of interest

This research was supported by Beckman Coulter company in 2019.

Hyunyong Hwang 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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Author contributions

Conceptualization: HH. Data curation; Formal analysis: HC, SSL, HH. Funding acquisition: HH. Investigation; Methodology; Resources: HC, SSL, HH. Supervision: HH. Validation; Visualization: HC, SSL, HH. Writing - original draft: HC, SSL. Writing -review & editing: HC, SSL, HH. All authors read and approved the final manuscript.

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Intracranial aneurysms in autosomal dominant polycystic kidney disease

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Background: The incidence of intracranial aneurysms (ICA) is high in patients with autosomal dominant polycystic kidney disease (ADPKD). However, little is known regarding the optimal screening and treatment methods for ICA.
Methods: This study investigated the characteristics of ADPKD patients with ICA, analyzing each variable according to whether the ICA ruptured, and examined the outcomes according to the treatment method. Specifically, a retrospective study was conducted on the treatment of ICA patients with ADPKD at a single institution for 10 years, from 2013 to 2022.
Results: The mean age of the 17 enrolled ADPKD patients with ICA was 57.4 years. Surgical and endovascular treatment methods were used in four and 13 patients. Eleven patients had unruptured ICAs, and the remaining six patients had suffered subarachnoid hemorrhage (SAH). Two patients experienced neurological deficits after discharge. All patients with unruptured ICAs were discharged without any complications, although one of them underwent additional treatment 5 years later. Four patients with SAH had known ADPKD at the time of diagnosis (67%). As for the treatment method, 13 patients were treated with coiling. In a comparison of variables between unruptured ICA and SAH patients, the location of the ICA showed a statistically significant difference ($p<0.05$).
Conclusions: In ADPKD patients, diagnostic screening for the detection of ICA is essential, and with appropriate management, interventional endovascular treatment may be a good treatment option.

Keywords: Autosomal dominant polycystic kidney; Intracranial aneurysm; Subarachnoid hemorrhage

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the relatively common genetic diseases affecting approximately one in 400 to 1,000 people worldwide. It is a genetic disease that invades the kidney parenchyma with multiple cysts and reduces kidney function [1]. It is known that mutations in the *PKD1* and *PKD2* genes are the cause of ADPKD [2]. The number and size of renal cysts increase as the disease progresses, and end-stage renal disease gradually progresses around age 60 [1,3]. It causes cystic formation in other organs, such as the pancreas and liver, and it is associated with arterial hypertension, which is clinically critical intracranial aneurysms (ICA). ICA is found in approximately 10% of ADPKD patients [1,2]. ICA is one of the most important diseases associated with ADPKD. The rupture of ICA and the occurrence of subarachnoid hemorrhage (SAH) are fatal to ADPKD patients [2]. According to a paper, it was announced that about 12% of patients with ADPKD had ICA when they received a diagnostic screening [3]. There is also a higher incidence rate of cerebral aneurysm rupture in younger patients than in patients

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with normal cerebral aneurysms, showing risk of serious complications and high mortality rate [4-6]. Compared to healthy patients, the prevalence of ICA is reported to be approximately three to four times higher in ADPKD patients. It is also reported that compared to healthy patients, ADPKD patients are five times more likely to develop SAH due to ICA rupture [5,6]. Thus, screening for rapid diagnosis is crucial for ADPKD patients. There are no clear guidelines regarding the natural history, risk factors, appropriate diagnosis, and treatment of ADPKD patients with ICA. The current American Heart Association/American Stroke Association guidelines recommend a noninvasive screening for all patients with ADPKD. The Kidney Disease Improving Global Outcomes conference also recommends a selective screening for patients with other risk factors [7,8]. According to the study by Butler et al. [9], diagnostic screening in ADPKD patients with ICA had a positive impact on the prognosis of patients and was also cost-effective. However, no specific guideline has been presented for the clear natural course, prognosis, and treatment strategy of ICA patients with ADPKD. This study is a retrospective study conducted for 10 years at a single institution on the ADPKD patients with ICA. It investigated the prognosis and characteristics of the treated and untreated groups among ICA patients with ADPKD. In addition, ICA patients who received treatment were divided into a ruptured group and a non-ruptured group to examine their characteristics and prognosis.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kosin Medical Center (IRB No. KUGH IRB 2024-04-018-002). Written informed consent was waived.

The patient research was conducted by first selecting ADPKD patients and cross-checking the diagnostic codes of unruptured cerebral aneurysm, SAH, and ruptured aneurysm. This study conducted a survey for 10 years, from January 2013 to December 2022, and 33 patients were enrolled in the study. Of the 33 patients, 16 of them who did not receive treatment were excluded from this study, and all patients had unruptured cerebral aneurysms. Basic information included the age and sex of the patients, location and size of the cerebral aneurysm, and data on smoking, family history, and aneurysm treatment method.

Seventeen patients received either a conventional surgical treatment (clipping, trapping) or an endovascular interventional treatment (coiling, stent assisted coiling), and they were treated in the neurological intensive care unit. As the patient was an ADPKD patient with existing kidney lesions, special care was taken in the treatment. During the conventional surgery, all medications which may involve a strain on the kidneys were excluded, and special care was taken during the endovascular treatment. When performing transfemoral cerebral angiography (TFCA) and interventional cerebrovascular treatment (coiling) for the diagnosis of the ICA in patients, the following protocol was implemented before and after the procedure. In cases of TFCA or coiling that require the use of contrast medium, overnight hydration was performed using 2 L of normal saline fluid, and the same was performed after the procedure. In addition, N-acetylcysteine was taken before the procedure to minimize the kidney damage. In cases of patients with SAH caused by ICA rupture, sufficient hydration was performed using normal saline during the procedure or after the surgery since such a protocol was not able to be performed before the procedure.

The patient group was divided into two subgroups. The first group consisted of patients with SAH caused by ruptured ICA, and the second group consisted of patients with unruptured ICA. After dividing into two subgroups, data research was conducted on patient characteristics, treatment methods, and prognosis for each group. Then, statistical comparison tests were also conducted between the two groups. All patients included in the study were diagnosed with ADPKD prior to ICA diagnosis. In addition, in the group of patients who received a surgical treatment for SAH due to a ruptured aneurysm (six patients), no one previously had a diagnostic screening for cerebral blood vessels. In cases of patients with unruptured cerebral aneurysms, the patients were diagnosed by using computed tomography (CT) or magnetic resonance angiography (MRA), and all patients underwent TFCA. All patients with SAH were initially diagnosed with CT, and they also received TFCA additionally. Imaging follow-up of patients who received treatment was performed for 6 months to 1 year, and CT angiography or MRA were adopted as the diagnostic methods for follow-up observation. The prognosis of the patients who performed the study was confirmed 6 months after

discharge.

The data used in this study were analyzed using SPSS 25.0 for windows (IBM Corp.). The mean values expressed as continuous variables were analyzed using Student *t*-test, and dichotomous variables were analyzed using Fisher exact test. All results with a probability value of less than 0.05 were considered statistically significant.

Results

Data was collected on patients at a single institution for a total of 10 years from January 2013 to December 2022. Among 33 ADPKD patients with ICA, 17 of them underwent conventional surgery or interventional endovascular procedures. According to data collection results, the mean age of ADPKD patients with ICA was 57.4 years, and 12 of them were females, accounting for 70.6% of the total patients. Three of the 17 patients had a smoking history. The mean size of cerebral aneurysm was 5.34±3.32 mm, and 64.7% of patients were aware of ADPKD at the time of first diagnosis of ICA. Among them, one patient had multiple ICAs, and two patients had a family history, which is one of the important past histories. Four patients received a clipping surgery, a conventional craniotomy, while the remaining 13 patients took an interventional endovascular treatment (coiling or stent assist coiling) (Table 1). A research was conducted by dividing patients into two subtypes: those in which SAH occurred due to ruptured cerebral aneurysm and those in which SAH did not occur. To examine the characteristics of each group, the location of the ICA was first examined (Table 2). Characteristically, bifurcation of middle cerebral artery was the most common location in both groups, and treatment of ICA located in the para-clinoid segment of the internal cerebral artery was found only in the non-ruptured group.

The results of the investigation into the characteristics of the SAH group are summarized in Table 3. Six patients were diagnosed with SAH and all patients received an emergency treatment within 24 hours and received an intensive care in the neurological intensive care unit. Four out of six patients with SAH had known ADPKD at the time of diagnosis. The locations of cerebral aneurysms were anterior circulation in four patients and posterior circulation (superior cerebellar artery, basilar artery) in two patients. The existence of ICA was unknown because all patients had not been screened previously. Two patients had a family history of cerebral aneurysm. Five patients were treated with the interventional endovascular method, and the remaining one patient underwent open surgery (clipping and decompressive craniectomy) case of a large amount of SAH and high intracranial pressure. Four of the treated patients were discharged without neurological deficits, and two of them remained with neurologic deficits. It was not a problem due to complications of surgery and treatment, but the level of consciousness was poor at the time of SAH diagnosis. Two patients were discharged with a Hunt-Hess grade (grade 4) which was the same as when they visited the emergency room at the institution, and there was no difference in their modified ranking scale scores during follow-up.

A total of 11 patients were enrolled, and all ICA locations were anterior circulation. Seven patients were aware of ADPKD at the time of diagnosis (63.6%). Eight patients were treated with an interventional endovascular method,

Table 1. Characteristics of ICA patients with ADPKD

Characteristic	Variable (n=17)
Age (yr)	57.4±11.0
Female sex	12 (70.6)
Smoking	3 (17.6)
Size of aneurysm (mm)	5.34±3.32
Known ADPKD at first diagnosis	11 (64.7)
Multiple aneurysms	1 (5.9)
Familial history of ICA	2 (11.8)
Treatment methods	
Clipping	4 (23.5)
Coiling	13 (76.5)

Values are presented as mean±standard deviation or number (%).
ICA, intracranial aneurysm; ADPKD, autosomal dominant polycystic kidney disease.

Table 2. Location of cerebral aneurysms in patients with and without rupture

Location of aneurysm	Unruptured aneurysm	Ruptured aneurysm
MCA bifurcation	4	2
Paraclinoid ICA	4	0
P-com	1	2
A-com	2	1
SCA	0	1

MCA, middle cerebral artery; ICA, internal cerebral artery; P-com, posterior communicating artery; A-com, anterior communicating artery; SCA, superior cerebellar artery.

Table 3. Characteristics of patients with ruptured cerebral aneurysms

Sex	Age (yr)	Smoking	Familial history of aneurysm	Hunt-Hess grade[a]	CT Fisher grade[b]	Location of aneurysm	Previous diagnosis of aneurysm	Size of aneurysm (mm)	Methods of surgery	Prognosis
Female	58	×	○	2	1	Rt. MCAb	×	3.59	Coil	Discharged at home
Female	60	×	×	4	4	Rt. SCA	×	3.42	Coil	Neurological deficit/ tracheostomy state
Female	68	×	×	2	3	Rt. P-com	×	8.33	Coil	Discharged at home
Male	43	○	○	4	4	Rt. MCAb	×	3.84	Clip	Hemiparesis/living dependently
Male	47	×	×	2	3	A-com	×	4.10	Coil	Discharged at home
Female	53	×	×	2	3	BA	×	3.18	Coil	Discharged at home

CT, computed tomography; Rt., right; MCAb, middle cerebral artery bifurcation; SCA, superior cerebellar artery; P-com, posterior communicating artery; A-com, anterior communicating artery; BA, top of basilar artery.
[a]Hunt and Hess grade: grade 1: asymptomatic, mild headache, slight nuchal rigidity; grade 2: moderate to severe headache, nuchal rigidity; grade 3: drowsiness, confusion, mild focal neurological deficit; grade 4: stupor, moderate to severe hemiparesis; grade 5: deep coma, decerebrate posturing, moribund appearance [22]; [b]CT Fisher grade: grade 1: no hemorrhage; grade 2: diffused thin film of subarachnoid bleeding (vertical film ≤1 mm); grade 3: localized clot or thick film of subarachnoid bleeding (vertical layer ≥1 mm); grade 4: intracerebral hemorrhage or intraventricular hemorrhage with diffuse or subarachnoid bleed [23].

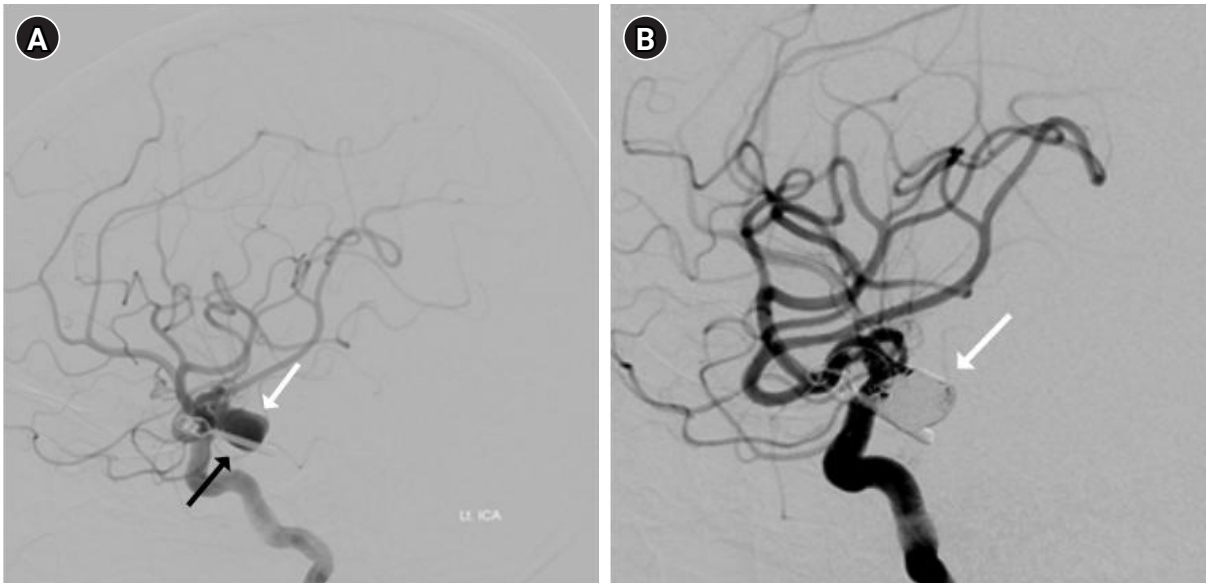

Fig. 1. Coil embolization performed in patients with recurrence after clipping surgery. (A) On transfemoral cerebral angiography, an intracranial aneurysm (ICA) was observed in the left posterior communicating artery (white arrow). A clip, a trace of previous surgery, is also observed (black arrow). (B) After the stent-assist coiling operation was completed, the ICA was no longer filled with contrast medium, and total occlusion was observed (white arrow).

and three patients underwent a conventional open surgery (72.7%). One of the patients who underwent open surgery was additionally treated with the endovascular method 5 years later due to regrowth of the aneurysm (Fig. 1). The difference from other patients was the size of the cerebral aneurysm. It was a large aneurysm (18 mm in size), and aneurysm clipping was selected as a treatment method due to concerns about recurrence caused by regrowth and coil compaction when treated with an endovascular treatment. Open surgery was performed for ICA of the left posterior communicating artery, surgical ligation was performed using a 20 mm straight clip. Meanwhile, TFCA was performed 5 years later as a follow-up. As a result, an ICA of about 15 mm regrew and was treated with stent-assist coiling (Table

4). In cases where SAH occurred due to ICA rupture, surgical clipping and decompressive craniotomy were required occasionally due to increased intracranial pressure. In these cases, even if the shape of the aneurysm is suitable for endovascular treatment, conventional surgical treatment is necessary (Fig. 2). In the other 10 patients, no recurrence of the treated aneurysm or new aneurysm was found elsewhere during the follow-up examination.

Of the 17 patients, 11 of them were unruptured patients, and the remaining six patients were ruptured patients with SAH (Table 5). The mean age values for unruptured and ruptured ICA were 58.8 years and 54.8 years, respectively (p=0.475). The mean size of the aneurysm was 5.8 mm in the unruptured cerebral aneurysm patient group and 4.4 mm in the SAH patient group, slightly larger in the former patient group, but not statistically significant (p=0.410). The remaining variables, including smoking, awareness of ADPKD at the time of aneurysm diagnosis, and family history of ICA, did not show statistically significant values. The location of the aneurysm (anterior circulation vs. posterior circulation) obtained a statistically significant value in the comparison between the two groups (p=0.041).

Discussion

The incidence of ICA in ADPKD patients has been reported to be approximately 10% to 12%, which is three times higher than that of the healthy population [4,5,8,9]. Rupture of the ICA is the cause of approximately 80% of spontaneous SAH. In ADPKD patients, ICA is the most common vascular-related complication. However, due to the lack of accurate and large studies of ADPKD patients with ICA, information regarding the incidence rate, natural history, and prognosis is lacking [1,3,5,6]. The ICA patients with ADPKD ruptured aneurysms at a younger age than other groups. Rupture of cerebral aneurysms has a lethal mortality rate and involves permanent neurological deficits [4-7]. The annual incidence rate of spontaneous SAH in the world population is approximately 0.01%. However, among patients with ADPKD, the incidence rate of SAH is about four times higher than that of the general population. As mentioned above, the probability of aneurysm rupture is higher at a younger age, and it is reported that rupture occurs in smaller aneurysms [10]. Therefore, appropriate diagnostic screening and surgical treatment are crucial.

The expression of cerebral aneurysms in ADPKD patients is related to mutations in the *PKD1* and *PKD2* genes [11]. It is known that mutations in these genes increase smooth muscle cell apoptosis, contributing to aneurysm formation, especially in patients with hypertension [12,13]. Conventionally, early screening of ICA patients with ADPKD has been limited [14]. Selective diagnostic screening is recommended only for high-risk patients, such as those with a previous history of ICA, family history of SAH, or a history of hypertension [15-17]. The reason for this selective screening was that a contrast agent was used for the diagnosis of ICA or an invasive TFCA test required. However, with the recent development of contrast-free MRI scans

Table 4. Characteristics of patients with ruptured cerebral aneurysms

Sex	Age (yr)	Smoking	Familial history of aneurysm	Location of aneurysm	Size of aneurysm (mm)	Methods of surgery
Male	64	×	×	Lt. paraclinoid ICA	4.58	Coil
Male	42	○	×	Lt. ophthalmic ICA	10.92	Clip
Female	79	×	○	Lt. MCAb	2.89	Clip
Female	56	×	×	Rt. paraclinoid ICA	3.60	Coil
Female	65	×	×	A-com	3.75	Coil
Female	58	×	×	Lt. MCAb	3.31	Coil
Male	41	×	×	Lt. MCAb	3.01	Coil
Female	63	×	○	A-com	4.52	Coil
Female	45	×	×	Rt. paraclinoid ICA	7.80	Coil
Female	71	×	○	Lt. P-com	15.00	Clip/coil
Female	63	○	×	Lt. MCAb	5.00	Coil

Lt., left; Rt., right; ICA, internal cerebral artery; MCAb, middle cerebral artery bifurcation; A-com, anterior communicating artery; P-com, posterior communicating artery.

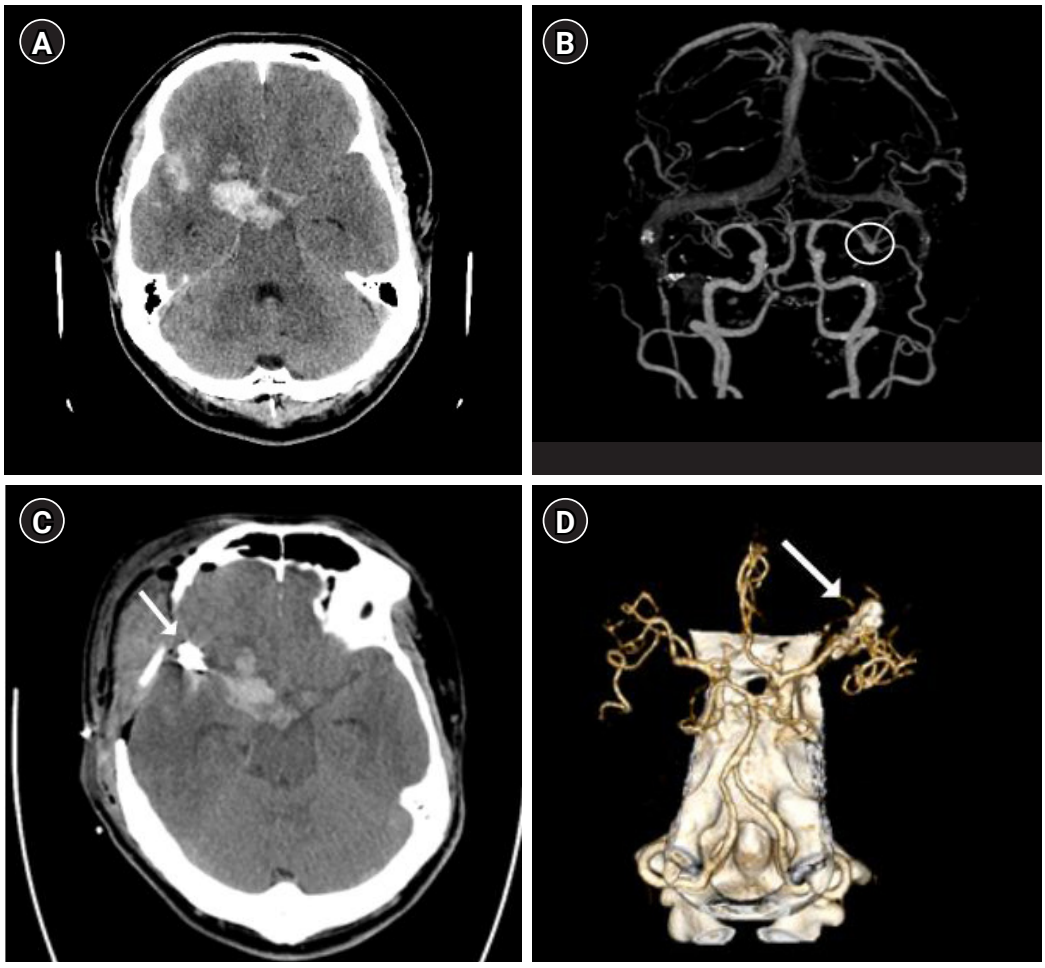

Fig. 2. Decompressive craniotomy and clip surgery performed in patients with elevated intracranial pressure. (A) Subarachnoid hemorrhage and intracerebral hemorrhage are observed predominantly in the right cerebral hemisphere on brain computed tomography (CT). (B) A cerebral aneurysm was observed at the bifurcation of the right middle cerebral artery on CT angiography (white circle). (C) After surgery, clip shadows were observed on brain CT, and bone flaps were removed to reduce intracranial pressure (white arrow). (D) In postoperative CT angiography, a clip is observed in the ruptured cerebral aneurysm (white arrow).

Table 5. Presentation according to whether the aneurysm ruptured in ICA patients with ADPKD

Characteristic	Unruptured ICA (n=11)	Ruptured ICA (n=6)	*p*-value[a]
Age (yr)	58.8±12	54.8±9	0.475
Female sex	8 (72.7)	4 (66.7)	0.793
Smoking	2 (18.2)	1 (16.7)	0.938
Size of aneurysm (mm)	5.8±4	4.4±2	0.410
ADPKD known at diagnosis	7 (63.6)	4 (66.7)	0.901
Familial history of aneurysm	3 (27.3)	2 (33.3)	0.793
Anterior circulation	11 (100)	4 (66.7)	0.041

Values are presented as mean±standard deviation or number (%).
ICA, intracranial aneurysm; ADPKD, autosomal dominant polycystic kidney disease.
[a]Statistical methods: Student *t*-test or Fisher exact test.

and the reduced risk of TFCA, early regular ICA testing is recommended [18,19]. As a result of this study, a total of 17 patients were treated for ICA, six of them who were treated after SAH had not been previously diagnosed with ADPKD. On the other hand, all but four out of 11 unruptured ICA treated patients were found through early screening. SAH due to rupture of a cerebral aneurysm may be fatal even if treated in the early stage. About one-third of SAH patients die, another one-third remain severely disabled, and only the remaining patients recover from the hemorrhage [20]. Furthermore, since rupture occurs in ICA at a younger age and at a smaller size than other general populations, early screening is considered necessary.

The treatment of ICA patients with ADPKD was mostly open surgery, that is, clipping. This is because there is a concern about renal toxicity as the endovascular treatment method itself uses an amount of contrast agent. However, the recent development of treatment methods for renal toxicity of contrast media, endovascular methods have become a good treatment option [21-23]. This study treated a total of 17 patients, 13 of whom were treated with endovascular methods. In the data, the clipping method was used when a decompressive craniotomy was required due to a large amount of SAH or when an additional stent was required in addition to the coiling in endovascular methods due to a wide neck of the aneurysm (Fig. 2). Endovascular treatment clearly has several advantages over the conventional clipping surgery. First, the treatment time is relatively short. In cases of end stage renal function state in ADPKD patients, if surgery is performed for a long time, there is a high possibility of problems occurring in other organs such as the lungs or heart of the patients [24,25]. Second, in cases of conventional clipping surgery, the level of difficulty varies depending on the location of the cerebral aneurysm. In cases of aneurysms located proximal to the intracerebral artery, the difficulty of clipping is high, which not only prolongs the surgical running time but also increases the risk of complications caused by the surgery [25,26]. Even in cases of aneurysms located in the posterior location, endovascular treatment is more advantageous [10,27,28].

Among all 17 patients included in this study, 13 patients treated with ICA using interventional endovascular methods did not show deterioration of their renal function. Sufficient hydration for at least 12 hours overnight was performed using normal saline, and after the procedure, hydration was performed similarly and N-acetylcysteine was taken. Immediately after surgery, the patients were monitored in the intensive care unit and consulted with the nephrology department. As a result, all 11 patients with unruptured ICA were discharged without any complications, and two out of six patients with SAH were discharged with neurological deficits. In these two patients, the prognosis did not worsen due to complications during surgery or during treatment. As shown in Table 3, the two patients with neurological deficits were in a poor state of consciousness at the time of diagnosis due to a large amount of SAH and increased intracranial pressure. For ADPKD patients, a treatment method tailored to the situation may be better than an unconditional clipping. As in this study, when surgical decompression is required due to high intracranial pressure or when an aneurysmal endovascular stenting is not absolutely necessary due to the wide neck of the aneurysm, interventional endovascular methods may also be a good treatment method. It is the most important to quickly detect ICA before renal failure progresses seriously, and screening the aneurysm through CT angiography or MRA may be remarkably helpful in the treatment of ADPKD patients.

This study has limitations in that it is a retrospective study conducted at a single institution with a small sample size. There were no studies of ICA patients with untreated ADPKD.

ADPKD patients showed a three to four times higher incidence rate of ICA compared to healthy people. Additionally, SAH due to rupture of the ICA also occurs at a young age and when the size of the aneurysm is smaller. Therefore, appropriate screening for early detection of ICA is essential. A careful approach through sufficient hydration, medication for kidney protection, collaboration with nephrologists, and intensive care is important, and through this protocol, endovascular treatment is also one of the treatment options for patients with ADPKD with ICA.

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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Sonozaki syndrome (pustulotic arthro-osteitis) causing anterior chest pain: a case report

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Sonozaki syndrome is an exceptionally rare chronic rheumatic disorder characterized by pustulosis on the palms and soles, as well as arthritis and osteitis. This syndrome belongs to the category of spondyloarthritis, which includes psoriatic arthritis. Pustules are concentrated on the palms and soles, whereas arthro-osteitis predominantly affects the sternoclavicular and costochondral joints. This report presents the case of a 32-year-old man with a 2-month history of worsening anterior chest wall pain and pustular eruptions on the palms and soles.

Keywords: Arthritis; Case reports; Chest pain; Osteitis

Introduction

Pustulosis of palms and soles (PPP) is also known as "pustulosis palmaris et plantaris" or "palmoplantaris pustulosis." PPP is a chronic and recurring pustular skin lesion which is confined to the palms and soles [1]. Due to its similarity, it is often regarded as a subtype of psoriasis, but it only affects the palms and soles [2,3]. It typically occurs in patients aged 30 to 60 years and is equally common in males and females. It is common in Japan and the Scandinavian Peninsula, with a prevalence of 0.05% [4]. Inflammatory osteitis occurs in 10% to 30% of patients with PPP and is then called pustulotic arthro-osteitis or Sonozaki syndrome. This disease can induce chest pain and tenderness, especially in the costosternal joint, and it is often important to distinguish it from rib fractures and coronary artery disease. In this paper, we describe the diagnosis and treatment of a patient with Sonozaki syndrome, which has been treated in several hospitals due to chest pain, but successful resolution was not achieved.

Case

Ethical statements: This report was approved by the Institutional Review Board (IRB) of Kosin Gospel Hospital (IRB No. 2024-06-008). The IRB waived the requirement for informed consent.

A 32-year-old male presented to our hospital with a 2-month history of lower chest wall pain and skin pustules. The chest wall pain was pleuritic and initially began in the left anterior chest wall, gradually spreading to the right anterior and posterior chest wall areas. He experienced temporary relief when he was treated at a local clinic, but the symp-

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toms returned soon after. The pustules were localized to the palms and soles without pain or irritation. No relevant past or family history was noted. On physical examination, vital signs were as follows: blood pressure of 110/70 mmHg, heart rate of 78 beats/min, respiratory rate of 20 breaths/min, and body temperature of 36.7 °C. The electrocardiogram was normal. No abnormal findings were observed in the head and neck areas, but severe tenderness was palpated around the sternum. Multiple pustules with erythematous eruption were observed on the palms and soles (Fig. 1A, 1B), but no other skin lesions were found. Peripheral blood tests showed white blood cell count 13,700/mm^3 (neutrophil 64.3%, lymphocyte 25.0%, monocyte 7.9%, eosinophil 2.3%, and basophil 0.5%), hemoglobin 14.1 g/dL, hematocrit 41.1%, and platelets 415,000/mm^3. The urinalysis result was normal. Other pertinent results included elevated C-reactive protein level at 3.5 mg/dL, elevated erythrocyte sedimentation rate at 73 mm/hr, rheumatoid factor, anti-cyclic citrullinated peptide antibody, anti-nuclear antibody, and *HLA-B27* gene results were all negative. Biopsies were conducted to obtain specimens from the palms and soles. It showed superficial perivascular dermatitis and subcorneal pustules (Fig. 2). No specific findings were observed in the radiologic tests. Bone scans, however, revealed isotope uptake at multiple levels of the costochondral junctions on both parasternal areas (Fig. 1C).

After a comprehensive history, physical examination, and relevant laboratory tests, trauma and other inflammatory diseases were ruled out, leading to a diagnosis of Sonozaki syndrome. Medications, such as prednisolone (5 mg/day), aceclofenac (200 mg/day), and esomeprazole (20 mg/day), were administered. After 2 weeks, the symptoms of the patient were completely resolved. Two months later, the patient returned with recurring chest wall pain and skin symptoms. The sulfasalazine (1,000 mg/day) was added to the same medication regimen as before. The symptoms subsequently improved, and he is currently scheduled for a follow-up without any medications.

Discussion

There are many conditions that can cause chest pain. When patients visit the department of thoracic and cardiovascular surgery with chest pain or discomfort, trauma, cardiovascular diseases, and pleural diseases are differentiated. Treatment becomes straightforward when there are clear causes such as fractures of bony thorax, pneumothorax, hydrothorax, and ischemic heart diseases. However, un-

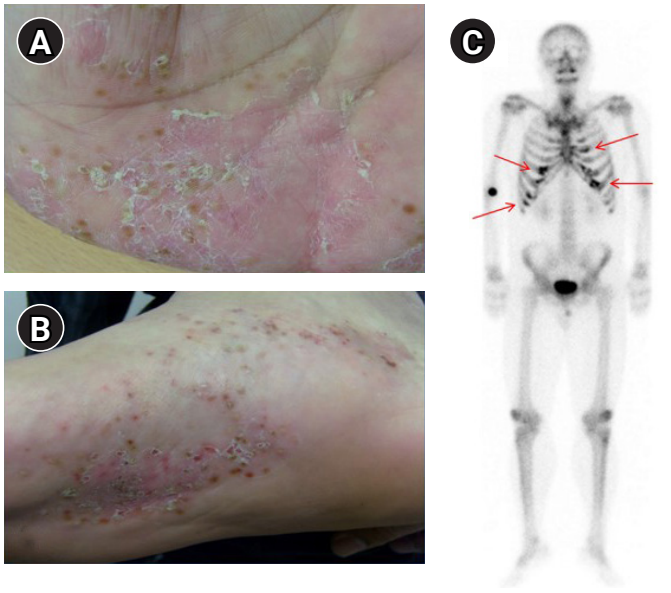

Fig. 1. Numerous erythematous lesions with pustules, blisters, and thick yellow scales are evident on the palm (A) and sole (B). Bone scan with ^{99m}TC shows increased uptake in the affected ribs (red arrows) (C).

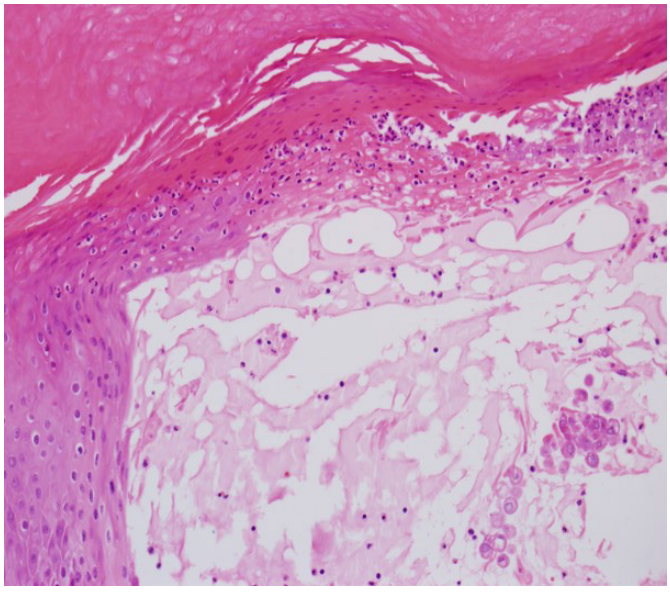

Fig. 2. Skin biopsy shows superficial perivascular dermatitis with subcorneal pustules (hematoxylin and eosin stain, ×200).

fortunately, many patients do not know the exact cause of chest pain even after various tests. In such cases, most patients receive symptomatic treatment such as pain control and sometimes undergo psychiatric counseling. Symptomatic treatment may bring temporary improvement in symptoms. However, without addressing the underlying causes, the symptoms eventually recur. Patients who experience symptom recurrence or worsening often transfer to other hospitals, wasting time and sometimes missing the optimum timing for treatment. Specifically, as conditions like Sonozaki syndrome are rarely considered as a cause of chest pain, sharing of clinical experiences and reviews of the literature are important.

The possible etiologies of PPP include infection, trauma, smoking, and environmental factors. However, the exact causes are not known. According to a recent study, PPP patients have elevated levels of cytokines such as interleukin-17 and interleukin-22 in their serum and tissues, elevated T helper 17 cell counts, and depressed regulatory T cell counts, implying that an immunological imbalance could be an etiology of PPP, as well as psoriasis [5,6]. PPP may have a wide range of clinical manifestations, including pustules with surrounding erythema, pruritus, stabbing pain, and musculoskeletal symptoms [7-9]. When PPP is accompanied by arthro-osteitis, it is called pustulotic arthro-osteitis or Sonozaki syndrome, first reported by Sonozaki in 1981 [7,10]. Like psoriatic arthritis, Sonozaki syndrome is currently regarded as a type of seronegative spondyloarthritis [11].

Arthro-osteitis changes are localized to the sternum, clavicle, rib, spine, and pelvis and develop most frequently in claviculomanubrial joint [12]. However, this patient exhibited an unusual presentation with widespread pain at the bilateral costochondral junctions. In the case of PPP, arthritis is characteristically transient and non-erosive. Approximately 70% of arthro-osteitis patients experience skin lesions, and it usually takes 2 years after skin lesions occur before arthro-osteitis develops.

In our case, Sonozaki syndrome was diagnosed by finding chest tenderness on palpation, costochondritis on bone scan, and characteristic skin lesions on the palms and soles, as well as through excluding other diseases on the differential diagnosis.

Sonozaki syndrome typically follows a chronic, relapsing-remitting course, with treatments mainly focused on symptomatic management. Analgesics and nonsteroidal anti-inflammatory drugs are frequently used. When patients do not respond to these medications or experience a recurrence of symptoms, then glucocorticoid, colchicine, sulfasalazine, methotrexate, and cyclosporine can be used [10,11].

In our patient, sulfasalazine was added after a recurrence. The patient has been doing well without any further recurrences. If a recurrence occurs in the future, immunosuppressants may be considered. When a patient presents with unexplained chest pain, it is important not to focus solely on thoracic lesions. Instead, paying attention to various lesions, such as skin manifestations, can help in diagnosing and treating rare conditions like Sonozaki syndrome.

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

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Case report

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Idiopathic pneumoperitoneum diagnosed and treated differently in preterm infants: two case reports

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Pneumoperitoneum that develops in the absence of a perforated abdominal viscus and does not require laparotomy is considered to be idiopathic. Differentiating between idiopathic pneumoperitoneum and highly lethal perforation due to necrotizing enterocolitis in preterm infants is important. Herein, we report two cases of idiopathic pneumoperitoneum in preterm infants who underwent exploratory laparotomy and conservative treatment, respectively. The first patient was born at 32+5 weeks of gestation and developed pneumoperitoneum on day 7 of life. The patient underwent exploratory laparotomy and was diagnosed with idiopathic pneumoperitoneum after surgery. The second patient was born at 30 weeks of gestation. He developed pneumoperitoneum on the eighth day of life. Idiopathic pneumoperitoneum was suspected, and the patient was treated conservatively without laparotomy. Based on our awareness and experience of the first case of idiopathic pneumoperitoneum, we were able to treat the second patient conservatively. These cases will be helpful for diagnosing and treating pneumoperitoneum in preterm infants.

Keywords: Case reports; Infant, premature; Pneumoperitoneum

Introduction

Pneumoperitoneum is defined as the presence of free gas within the peritoneal cavity and is caused by perforation of the gastrointestinal tract in the majority of cases (>90%). However, approximately 10% of cases that result from a benign source and do not involve viscus perforation, do not require surgical intervention [1,2]. These cases of idiopathic pneumoperitoneum (IPP) develop in the absence of intestinal perforation and have been termed nonsurgical, spontaneous, asymptomatic, unexplained, or benign pneumoperitoneum in different reports [3,4]. IPP is a rare condition with only a few case reports [5,6]. The exact mechanism of air entry into the peritoneum remains unknown. However, the most likely mechanism is air tracking from the ruptured alveoli along the walls of the adjacent vessels into the mediastinum [4,7]. We present herein two cases of IPP in preterm infants who were successfully treated.

Case

Ethical statements: This report was approved by the Pusan National University School of Medicine Research Committee (IRB No. 2210-003-120). Written informed consent was obtained from the patients' parents to publish this case report.

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1. Case 1

A 2,310 g male baby was born at 32+5 weeks of gestation by vaginal delivery. His mother was a 27-year-old primigravida who was referred to our hospital at 28 weeks of gestation because of preterm labor. This patient was the first baby of a healthy Korean parent. The patient had no family history of congenital anomalies. The patient had Apgar scores of 6 and 8 at 1 and 5 minutes, respectively. On admission to neonatal intensive care unit, his vital signs showed a heart rate of 150 beats per minute and 95% of saturation of percutaneous oxygen (SpO_2). However, the infant experienced respiratory difficulties. The patient was intubated and mechanically ventilated. Owing to deterioration of his respiratory symptoms, he underwent surfactant replacement therapy. The patient was placed on synchronized intermittent mandatory ventilation with a peak inspiratory pressure of 16 cm H_2O, peak expiratory end pressure 5 cm H_2O, respiratory rate of 30 breaths per minute, and 30% fraction of inspired oxygen (FiO_2). Enteral feeding commenced on the first day of life and was gradually increased.

On day 7 of life, the abdominal distension worsened. Plain abdominal radiography revealed a pneumoperitoneum (Fig. 1). Chest radiography revealed no pneumothorax, pneumomediastinum, or interstitial emphysema. Vital signs including oxygen saturation and temperature were normal except for lower blood pressure than the previous days and the results of laboratory tests including white blood cell count and C-reactive protein (CRP) were normal. However, the patient often showed abdominal bowel loops and feeding intolerance. And the patient had umbilical catheters for the first 3 days of life. Therefore, necrotizing enterocolitis (NEC) could not be excluded. The patient underwent urgent bedside exploratory laparotomy to evaluate intestinal perforation due to NEC or spontaneous intestinal perforation. An exploratory laparotomy revealed no visceral perforation or meconium in the abdominal cavity. The patient was diagnosed with IPP. Two days after surgery, the patient was extubated and enteral feeding was recommended. On day 17, the enteral feeding was increased to 120 mL/kg/day. The remaining course of his hospital stay was uneventful, and he was discharged at 28 days of life (36+5 weeks of postmenstrual age).

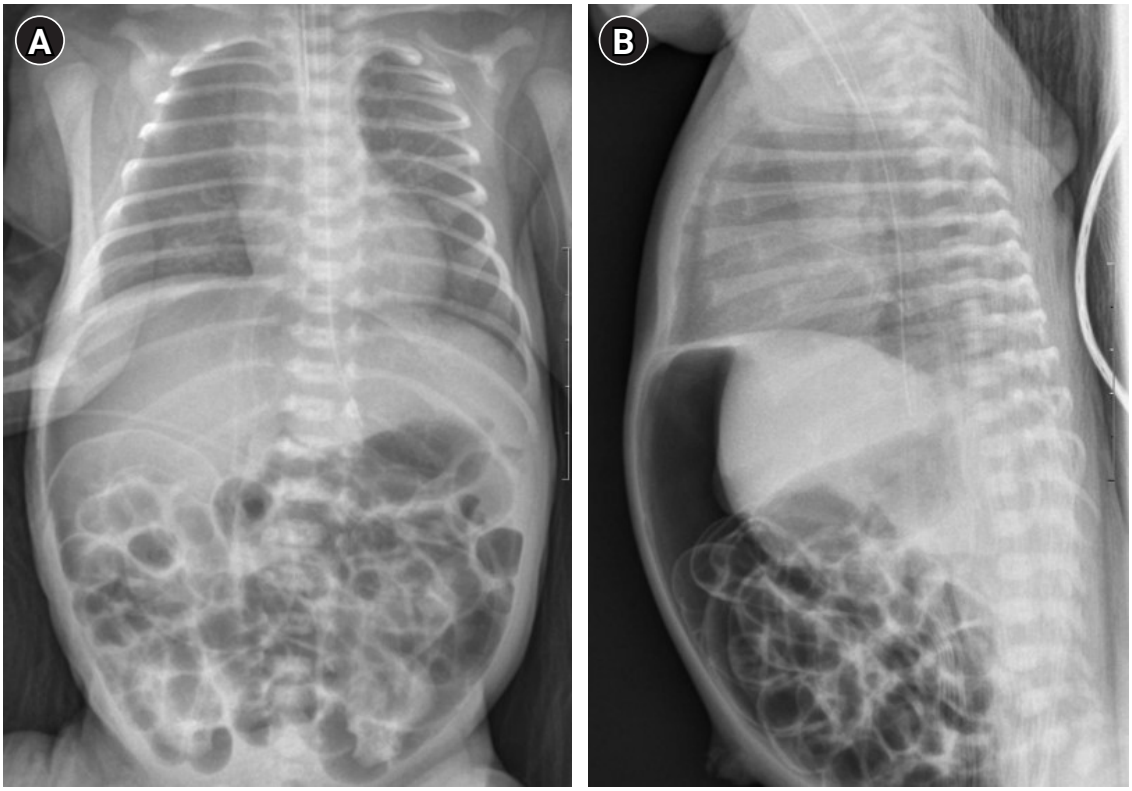

Fig. 1. Plain abdominal X-ray showing free peritoneal air occupying the entire abdomen in patient 1. (A) Supine view. (B) Lateral view.

2. Case 2

A 1,480 g male baby was born at 30 weeks of gestation by cesarean section. He was the 2nd of a set of twins born to a 35-year-old multigravida who was referred to our hospital at 28 weeks of gestation because of preterm labor. The patient had no family history of congenital anomalies. The patient had Apgar scores of 4 and 6 at 1 and 5 minutes, respectively. On admission to neonatal intensive care unit, his vital signs showed a heart rate of 120 beats per minute and 95% of SpO_2. After birth, the infant experienced respiratory difficulties. Although the patient underwent surfactant therapy for respiratory distress syndrome, his respiratory symptoms deteriorated. Eventually, he required high-frequency ventilatory support and inhaled nitric oxide. The ventilator settings were: amplitude 30, frequency 12 Hz, mean airway pressure 17 mmHg, and FiO_2 60%. Inhaled nitric oxide was administered at 20 ppm. On day 5 of life, inhaled nitric oxide was stopped, and the ventilator settings were gradually decreased. Subsequently, enteral feeding was commenced. One day later, the patient developed an abdominal distension. Plain abdominal radiography revealed ileus; therefore, enteral feeding was discontinued.

On day 8 of life, the abdominal distension worsened. Plain abdominal radiography revealed pneumoperitoneum (Fig. 2). Chest radiography revealed no features of air leak, except for right upper lobe atelectasis. However, his vital signs including oxygen saturation and blood pressure were normal and the results of laboratory tests including CRP were all normal. There was no any evidence of NEC including abdominal tenderness, gastrointestinal bleeding, and fever. We suspected him of IPP. Paracentesis was performed because of the severe abdominal distension. However, no liquid content suggestive of intestinal perforation was observed.

The patient was diagnosed with IPP. On day 11 of life, enteral feeding was recommended because of improved pneumoperitoneum; however, the pneumoperitoneum worsened again after feeding. Therefore, paracentesis was performed again, which showed no evidence of bowel perforation. Subsequently, pneumoperitoneum resolved slowly and disappeared on day 15. Enteral feeding was also recommended on the same day. On day 18, the patient was extubated. After initiation of enteral feeding, the patient did not show the abdominal distension, visible bowel loop and inflammation or infection evidences on the results of his laboratory tests. Enteral feeding was proceeded successfully, and reached to 120 mL/kg/day on 24 days of life. He was transferred because of progressive intraventricular hemorrhage and post-hemorrhagic hydrocephalus at 1 month of age. After ventriculoperitoneal shunt at that hospital, he reached full enteral feeding uneventfully. He was discharged home on demand bottle feeding at 2 months of age.

Discussion

NEC, which requires surgical treatment, is a leading cause of pneumoperitoneum in preterm infants. By contrast, IPP requires conservative treatment and resolves within several

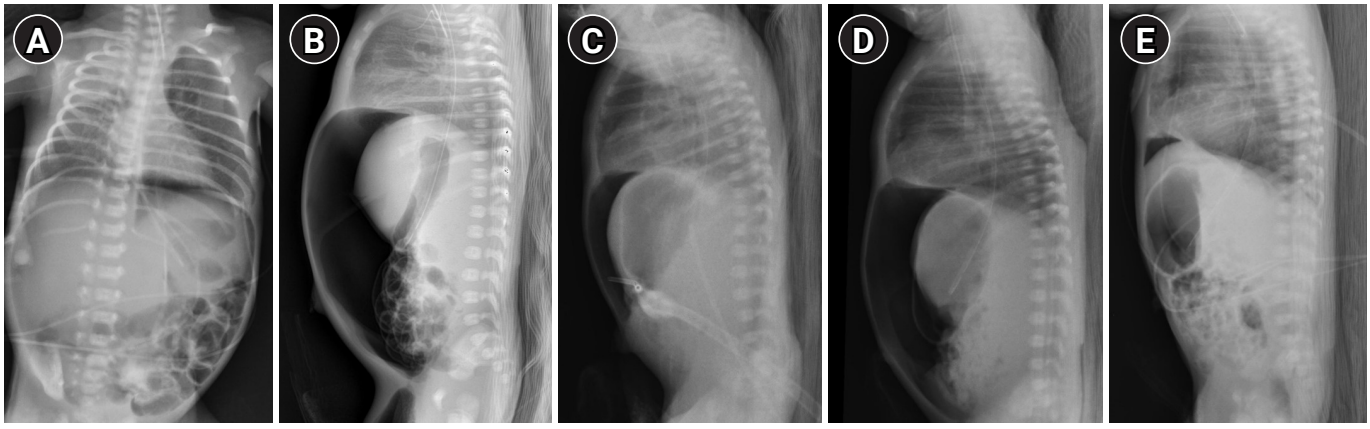

Fig. 2. Plain abdominal X-ray showing free air in patient 2. (A, B) Day of pneumoperitoneum onset. (C) Three days after onset, a lateral abdominal X-ray showed decreased pneumoperitoneum. (D) Four days after onset, pneumoperitoneum worsened after feeding. (E) Eight days after onset, the free air had nearly resolved.

days. Therefore, it is important to differentiate between IPP and highly lethal perforation caused by NEC in preterm infants [8]. Diagnosing IPP without exploratory laparotomy in preterm infants when a neonatologist encounters a case of pneumoperitoneum is difficult because of the high possibility of lethal perforation due to NEC. In fact, majority of reported Korean preterm cases of IPP involved exploratory laparotomies like our first case [9,10].

Our first patient showed ileus on X-ray, feeding intolerance and abdominal distension and had a history of umbilical catheterization. Therefore, we could not exclude NEC, although vital signs and laboratory tests were within normal range. Finally, he was diagnosed IPP after exploratory laparotomy. In our second case, we suspected IPP when the pneumoperitoneum appeared for the first time. Because there was no evidence of NEC and the patient showed stable vital signs including blood pressure. The patient had no history of umbilical catheterization contrary to our first case. Therefore, we decided to treat him conservatively.

However, conservative treatment is not easy because it is difficult to decide when enteral feeding should be commenced when the pneumoperitoneum persists for a long time. In our second patient, the pneumoperitoneum resolved within 8 days, which was the longest duration reported [3]. We attempted to feed the patient on day 3 of pneumoperitoneum but his condition worsened after feeding. Eventually, enteral feeding was recommended after resolution of pneumoperitoneum on day 8. Although enteral feeding was delayed, the second patient was successfully treated without general anesthesia or laparotomy.

Several reports have shown variations in the age of onset and duration of pneumoperitoneum among preterm infants treated conservatively [3,4]. Karaman et al. [4] reported a case of a preterm infant born at 30 weeks of gestation, in whom pneumoperitoneum developed on the third day of life and resolved within 2 days. Unfortunately, the patient died of sepsis at 33 days old. Duan et al. [3] reported six cases involving newborns, including one preterm infant, treated conservatively; they were aged between 4 and 25 days. The time to resolution of pneumoperitoneum was 3 to 8 days, which was longer than the 2 days reported by Karaman et al. More reports on feeding problems in cases of prolonged pneumoperitoneum are required for conservative treatment.

In the neonatal population, IPP occurs in 5.4% to 7.8% [11]. Although the cause of IPP remains unclear, the most likely cause of IPP is air tracking from the ruptured alveoli along the walls of the adjacent vessels into the mediastinum. However, there was no evidence of pneumothorax and pneumomediastinum in our two cases. Thus, mechanical ventilation and high intrathoracic pressure due to abdominal distension with concealed pulmonary interstitial emphysema were felt to be the cause. Majority of reported IPP cases were one of them, who was diagnosed after exploratory laparotomy or who had respiratory air leak syndrome [9,10]. Our second case is a rare case because the patient had no evidence of air leak syndrome and was very successfully treated conservatively. Based on our experience with the first case of IPP, we could treat the second patient conservatively.

In conclusion, we report two cases of IPP in preterm infants. One of them was misdiagnosed bowel perforation and performed exploratory laparotomy and the second one was successfully treated by conservative treatment. Our cases will help neonatologists diagnose and treat pneumoperitoneum in preterm infants. Neonatologists should be aware that IPP can occur in preterm infants on ventilator support. Furthermore, if a patient has mild clinical symptoms and stable vital signs and laboratory findings, IPP should be considered to avoid unnecessary surgery.

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Conflicts of interest

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

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Author contributions

Conceptualization: KHP. Funding acquisition: KHP. Writing - original draft: SJP. Writing-review & editing: KHP. All authors read and approved the final manuscript.

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Corrigendum

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Correction to "Traumatic neuroma of the right posterior hepatic duct with an anatomic variation masquerading as malignancy: a case report"

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A clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" should be registered with the primary registry prior to publication. The KMJ accepts registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (https://www.who.int/clinical-trials-registry-platform), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), ISRCTN Resister (www.ISRCTN.org), or the Clinical Research Information Service (CRIS), Korea CDC (https://cris.nih.go.kr/cris/index.jsp). The clinical trial registration number shall appear at the end of the abstract.

Data-sharing statement

The KMJ accepts the "ICMJE Recommendations for Data Sharing Statement Policy." All manuscripts reporting clinical trial results from July 1, 2018 should submit a data-sharing statement following the ICMJE guidelines. Authors can refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee

of Medical Journal Editors," in JKMS Vol. 32, No. 7:1051-1053 (http://crossmark.crossref.org/dialog/?doi=10.3346/jkms.2017.32.7.1051&domain=pdf&date_stamp=2017-06-05).

Statement of informed consent and IRB approval

Copies of written informed consent and institutional review board (IRB) approval for clinical research (original article and case report) should be kept. Authors should include the IRB approval number in the manuscript. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct. For studies involving human subjects, the method through which informed consent was obtained from the participants must be stated in the Methods section.

Statement on human and animal rights

Clinical research should be done in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in the Helsinki Declaration (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. For publication, the human subjects' identifiable information, such as the patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, the research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct, such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of the KMJ will discuss the suspected cases and reach a decision. The KMJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

Errata

Errata provide a means of correcting errors that occur during the writing, typing, editing, or publication (e.g., a misspelling, dropped word or line, or mislabeling of a figure) of a published article. Errata can be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), enter "Not Applicable" and upload the text of the proposed erratum. Please see a recent issue for correct formatting.

Author corrections

If the addition or deletion of authors or a change to the order of authorship is required, the corresponding author must complete the authorship change form and submit it through the KMJ online manuscript management portal with the signature of all existing authors and new authors. In the Abstract section of the submission form (a required field), enter "Not Applicable." The text of the proposed erratum should be uploaded as a Microsoft Word file. When there is a request for a change by the author, the editorial committee assembles an ethics committee to judge whether the change is appropriate. If a new author should be added or an author should be deleted after submission, it is the responsibility of the corresponding author to ensure that all authors are aware of and agree to the change in authorship. The KMJ assumes no responsibility for such changes. Please see a recent issue for correct formatting.

Retractions

Retractions are reserved for major errors or breaches of ethics that, for example, may call into question the source of the data or the validity of the results and conclusions of an article. Retractions should be submitted through the KMJ online manuscript management portal as a Microsoft Word file. In the Abstract section of the submission form (a required field), put "Not Applicable." Letters of agreement signed by all of the authors must be supplied as Miscellaneous Files Not for Publication (scanned PDF files). The retraction will be assigned to the journal's editor-in-chief, and the editor who handled the paper and the chair of the KMJ editorial board will be consulted. If all parties agree to the publication and content of the retraction, it will be sent

to the journals department for publication.

For the policies on research and publication ethics not stated in the Instructions, Guidelines on Good Publication (http://publicationethics.org) or Good Publication Practice Guidelines for Medical Journals (http://kamje.or.kr) can be applied.

V. MANUSCRIPT PREPARATION AND FORMAT

1. General requirements

- Every manuscript should be written in English.
- The main document, including manuscript text and tables, should be prepared in MS Word.
- The manuscript should be double-spaced on 21.6 × 27.9 cm (US letter) or 21.0 × 29.7 cm (A4) paper with top, bottom, right, and left margins of 3.0 cm.
- All manuscript pages are to be numbered consecutively, beginning with the abstract as page 1. Neither the authors' names nor their affiliations should appear on the manuscript pages.
- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. A spelled-out term followed by the abbreviation in parentheses should be used on first mention unless the abbreviation is widely recognized (e.g., UN for United Nations).
- The names of manufacturers of equipment and non-generic drugs should be given.
- When quoting from other sources, supply a reference number after the author's name or at the end of the quotation (see References section).
- Authors should express all measurements in conventional units, using the International System (SI) of units.
- To make papers more readable and informative, mark the followings in italics.
  - Biological names of organisms: *Saccharomyces cerevisiae*, *E. coli*
  - Restriction enzymes and some enzymes: *EcoRI, Taq polymerase*
  - Names of genes: *src, c-H-ras, myc*
  - Latin words: *in vivo, in vitro, in situ*
  - Centrifugal acceleration: *g* (e.g., 100,000 *g*)

2. Reporting guidelines for specific study designs

Research reports frequently omit important information. As such, reporting guidelines have been developed for a number of study designs, and some journals may ask authors to follow them. Authors are also encouraged to consult the reporting guidelines relevant to their specific research design. A good source for reporting guidelines is the EQUATOR Network (http://www.equator-network.org/home) and the United States National Library of Medicine (http://www.nlm.nih.gov/services/research_report_guide.html).

3. Original articles

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The manuscript should be prepared according to the "ICMJE Recommendations for the Conducts, Reporting, and Publication of Scholarly Work in Medical Journals" (2021) (http://www.icmje.org). In addition to the ICMJE recommendation, a number of reporting guidelines have been developed by experts to facilitate reporting of research studies or clinical trials (http://www.equator-network.org/library). For reporting of randomized controlled trials, the KMJ requires compliance with the CONSORT statement (http://www.consort-statement.org) and the ICMJE Statement on Data Sharing (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html).

Manuscript components

The manuscript, including tables and their footnotes and figure legends, should use the 12-point Times New Roman font and line spacing should be set to "double." The manuscript should be in the following sequence: title page, Conflicts of interest, Sources of funding, Author contributions, ORCID iDs, Abstract and Keywords, Introduction, Methods, Results, Discussion, Acknowledgments, References, Tables (each table complete with a title and footnotes), and Figure Legends (figures should be uploaded separately, not embedded in text). All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscript except for the first word of a sentence. Tables and figures should not be inserted in the main text. A combined table file can be uploaded separately from the main manuscript file. A combined figure file or individual figure files can be uploaded separately from the main manuscript.

File formats

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Title page

Include the following items on the title page: (1) the title of the manuscript (the title should be short, informative, contain the major keywords, and be no more than 200 characters in length, including spaces between words; acronyms and abbreviations should be avoided, and the species of any experimental animal must be indicated in the title; (2) an author list (include ORCID*); (3) the names of each author's institutional affiliation; (4) the name, address, telephone number, and email address of the corresponding author; (5) the source of any research funding, if any, and a list of where and when the study has been presented in part elsewhere; and (6) a running title of no more than 50 characters.

*ORCID: We recommend that the open researcher and contributor ID (ORCID) of all authors be provided. Authors can obtain an ORCID at http://orcid.org. Registration is free to every researcher in the world.

Conflict of interest

State any potential conflict of interest that could influence the authors' interpretation of the data, such as financial support from or connections to pharmaceutical companies, political pressure from interest groups, or academically related issues.

Author contributions

What authors have contributed to the study should be described in this section. To qualify for authorship, all contributors must meet at least one of the 12 core contributions defined by CRediT (conceptualization, methodology, software, validation, formal analysis, investigation, data curation, funding acquisition, project administration, resources, supervision, and visualization), as well as at least one writing contribution (original draft preparation, review, and editing). Authors may also satisfy the other remaining contributions; however, these alone will not qualify them for authorship.

Contributions will be published with the article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

An example:

Conceptualization: GDH. Data curation: YSJ, YC. Formal analysis: CSK. Methodology: YK, GDK.; Software: YK, YSJ. Validation:..... Investigation:..... Funding acquisition:..... Project administration:..... Resources:..... Supervision:..... Visualization:..... Writing - original draft: GDH, YSJ. Writing - review and editing: YC, YK, CSK.

Abstract and keywords

The abstract should briefly describe the content of the manuscript in a structured format within 250 words. The abstract should be structured as follows; Background, Methods, Results, and Conclusion. Initialisms, acronyms and informal abbreviations should be avoided where possible; if needed, they should be kept to an absolute minimum and accompanied by proper definitions. Three to five keywords should be listed below the Abstract on the Abstract page. For the selection of keywords, refer to Medical Subject Headings (MeSH) in PubMed, or http://www.nlm.nih.gov/mesh/MBrowser.html.

Main text

- Introduction

A brief background, references to the most pertinent papers general enough to inform readers, and the relevant findings of others should be included. It is recommended that the introduction include a "General and specific background," "Debating issue," and "Specific purpose of this study."

- Methods

The explanation of the experimental methods used should be concise and sufficient for repetition by other qualified investigators. Procedures that have been published previously should not be described in detail. However, new or significant modifications of previously published procedures require full descriptions. Clinical studies or

experiments using laboratory animals or pathogens should mention approval of the studies by relevant committees in this section. The sources of special chemicals or preparations should be supplied, along with their location (name of company, city and state, and country). The method of statistical analyses and the criteria for determining significance levels should be described. An ethics statement should be placed in this section when the studies are performed using clinical samples or data, and animals. Examples are provided below.

(For clinical study)

The present study protocol was reviewed and approved by the Institutional Review Board of xxx XXXXXX of the University College of Medicine (approval No. 2018001). Informed consent was submitted by all subjects when they were enrolled.

(For animal study)

The procedures used and the care of animals were approved by the Institutional Animal Care and Use Committee at xxxXXXXX University (approval No. 2018002).

(For clinical trials)

This was a randomized clinical trial at the second phase, registered at the Clinical Research Information Service (CRIS, http://cris.nih.go.kr), number KCT0002018.

Other international registration is acceptable. Manuscripts reporting interventional clinical trial should include a data-sharing plan following the ICMJE statement by referring to the ICMJE Statement on Data Sharing.

When describing participants, ensure correct use of the terms sex (for biological factors) and gender (identity, psychosocial, or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population, (e.g., only one sex), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should describe how they determined race or ethnicity and justify their relevance.

• Results

This section should be presented logically and in a manner consistent with the Methods section. Tables and figures are recommended when they can present data more succinctly and clearly. Do not duplicate the content of tables or figures in the Results section. Briefly describe the core results related to the conclusion in the text when data are provided in tables or in figures. In the Results section, audio or video files are also welcomed. Supplementary results can be placed in an Appendix.

• Discussion

The data should be interpreted concisely without repeating materials already presented in the Results section. A summary or conclusion should be included at the end of this section. We recommend authors describe the clinical or biomedical significance of the study. Speculation is permitted but must be clearly supported by the results or literature published.

Acknowledgments

The authors can list the names of persons who helped plan or conduct the study but are not eligible authors in this section. Funding sources, which are supplied on the title page, should not be duplicated in this section.

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References should be numbered in the order they appear in the text and should not exceed 40 in number. Citation of references in the text should be identified with Arabic numerals in square brackets (for example, ... the leading cause of death in Korea [1,2] and preceding any punctuation). References should be listed in the order they are cited in the text, with consecutive numbers in this section. The style for citing papers in periodicals is: last name and initials of all authors, full title of article, journal name abbreviated in accordance with the PubMed style, year, volume, issue number and first and last page numbers. The style for a chapter of a book is: author and title of the chapter, editor of the book, title of the book, edition, volume, publisher, year, and first and last page numbers. Up to six authors can be listed in a reference; the names of all authors after the first 6 should be abbreviated to "et al." The use of software to manage references (e.g., EndNote) is recommended.

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   Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.
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4. Conference
   Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsale, Ireland. Springer; 2002. p. 182-91.
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Tables: Tables are to be numbered in the order in which they are cited in the text. A table title should concisely describe the content of the table so that a reader can understand the table without referring to the text. Each table must be simple and provided on a separate page with its title. Explanatory matter is placed in the footnotes below the table and not in the title. All non-standard abbreviations should be explained in the footnotes. The symbols a), b), c), d), should be used (in that order) for footnotes. Statistical measures such as standard deviation (SD) or standard error (SE) should be identified. No vertical or horizontal rules should appear between table cells.

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Figures should be numbered, using Arabic numerals, in the order in which they are cited. In the case of multiple prints bearing the same number, use English letters immediately after the numerals to indicate the correct order. (e.g., Fig. 1A, Fig. 1B and C; Fig. 2A–D).

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Description of *p* value: p is always italicized and in lower case. When p values are statistically significant, the corresponding data should be marked with superscripted asterisks ($p<0.05$, $p<0.01$, $p<0.001$).

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Units of measurement: Laboratory values are expressed using conventional units of measure, with relevant System International (SI) conversion factors, if necessary expressed secondarily (in parentheses) only at first mention. Figures and tables should use conventional units, with conversion factors given in legends or footnotes. The metric system is

preferred for the expression of length, area, mass, and volume.

Names of drugs, devices, and other products: Generic names of pharmaceuticals should be used. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name in the Methods section.

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Authors can submit supplementary materials for online-only publication when there is insufficient space to include the materials in the main article. Supplementary materials should be original and important to the understanding and interpretation of the report. As supplementary materials will not be edited or formatted after publication, authors are responsible for the accuracy and presentation of this material.

Supplementary materials should be submitted in a single MS Word document or a single PDF file, which should include all materials (information, tables, figures, and references). Each element included in supplementary material should be cited in the text of the main manuscript (e.g., Supplementary Table 1, Supplementary Fig. 1, Supplementary Methods). The first page of the online-only document should list the number and title of each element included in the document.

4. Review articles

Reviews are comprehensive analyses of specific topics. They are typically solicited by the Editor, but we also consider unsolicited material. Please send us a Presubmission Inquiry before writing a review article. All review articles undergo the same review process as other types of articles prior to acceptance. Reviews are organized as follows: title page, abstract (a single unstructured paragraph of no more than 250 words) and three to five keywords (as in MeSH), introduction, main text, conclusion, acknowledgments, references, tables, and figure legends. Reviews have no restrictions on word count or the number of figures and tables. However, authors should eliminate redundancies, emphasize the central message, and provide only the data necessary to convey that message. A review article is limited to less than 6,000 words, with a maximum of 100 references, excluding tables or figure legends.

5. Case reports

Case reports will be published only in exceptional circumstances, if they illustrate a rare occurrence of clinical importance. The manuscript should be in the following sequence: title page, abstract (no more than 250 words) and three to five keywords (as in MeSH), introduction, case(s), discussion, acknowledgments, references (no more than 20), tables, and figure legends. The manuscript should have no more than six tables or figures in total. For case reports involving humans, whether informed consent for publication of clinical data was obtained from the study participants must be stated in the case description section.

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Editorials are invited by the Editor and should provide commentary on articles in the current issue. Editorial topics could include active areas of research, fresh insights, and debates in all fields of interest to KMJ readers. Editorials should not exceed 1,000 words, excluding references, tables, and figure legends. No more than 20 references should be cited. The manuscript should have no more than three tables or figures. Any article longer than these limits should be discussed with the editor.

Table 1. Specifications for publication types

Type of article	Original article	Review article	Case report	Editorial
Abstract (words)	250	250	250	NR
Text (words)[a]	NL	6,000	1,500	1,000
References	40[b]	100	20	20
Tables and Figures	NL	NL	6	3

NL, not limited; NR, not required.
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To prepare a revised version of your manuscript, authors should carefully follow the instructions given in the Editor's

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Changes referring to an Editor or reviewer query regarding moving or adding references, tables, or figures should be highlighted. Deletions should be marked with strikethrough (a line drawn through the selected text, using the ab button) and highlighted. Authors should submit a highlighted clean version without using the track changes function in MS Word.

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☐ **Formatting:** Double-spaced typing in A4 or letter-size paper using 12-point Times New Roman font in an electronic file made by Microsoft (MS) Word.

☐ **Sequence:** Title page, Conflict of interest, All sources of funding, Author contributions, Abstract and keywords, Main text, (Acknowledgments), References, Tables, and Figure legends. Numbered pages and lines (from Abstract page).

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☐ **Abstract and Keywords**

- Original article (structured—background, methods, results, and conclusion—within 250 words)
- Review article (unstructured, ≤250 words)
- Case report (unstructured, ≤250 words)

Three to five keywords as in MeSH

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- Original article (introduction, methods, results, discussion)

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Check that all references in the References section are cited in the text and vice versa.

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All table and figure numbers found in the text. No incorrectly numbered sections and mislabeled tables or figures must be found.

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Case report (no more than 6 tables or figures), Editorial (no more than 3 tables or figures)

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☐ **IRB/IACUC** approval must be stated in the Methods section.

☐ Authors should submit the **Author Statement Forms**, signed by all authors, simultaneously with the submission of their manuscript.

☐ A **covering letter** describing the scientific significance of the research, stating that the material has not been published previously and will not be submitted for publication elsewhere, and listing any conflicts of interest of all listed authors.

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☐ **Abstract and Keywords**

· Original article (structured—background, methods, results, and conclusion—within 250 words)
· Review article (unstructured, ≤250 words)
· Case report (unstructured, ≤250 words)
Three to five keywords as in MeSH

☐ **Main text**

· Original article (introduction, methods, results, discussion)
· Review article (≤6,000 words), Case report (≤1,500 words), Editorial (≤1,000 words)
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☐ **References**

Check that all references in the References section are cited in the text and vice versa.
· Original article (≤40 references)
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☐ **Tables and Figures**

All table and figure numbers found in the text. No incorrectly numbered sections and mislabeled tables or figures must be found.
Each figure as separate files, in JPEG, TIFF, PDF format, minimum 300 dpi.
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Case report (no more than 6 tables or figures), Editorial (no more than 3 tables or figures)

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- All authors have seen and approved the content of the submitted manuscript. The paper presents original work not previously published in similar form and is not currently under consideration by another journal.
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