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

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

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What is the effect of deferred laser treatment on reactivated retinopathy of prematurity after anti-VEGF injection?

Ji Hye Jang

Department of Ophthalmology, Keimyung University School of Medicine, Daegu, Korea

See “Revascularization of immature retinas with retinopathy of prematurity using combination therapy of deferred laser treatment after a single intravitreal bevacizumab injection” by Ju Seouk Lee, Ki Yup Nam, Ji Eun Lee, Joo Eun Lee, Sang Joon Lee

Retinal blood vessels of premature infants begin to form from the optic nerve head to the periphery according to the gestational age, and when the formation of retinal blood vessels is delayed or stopped, retinopathy of prematurity (ROP) occurs [1]. Angiogenesis is an important process in the development of ROP, and in particular, vascular endothelial growth factor (VEGF) is involved in regulating the development of retinal blood vessels [2]. When the concentration of VEGF in the retina is abnormally high, retinal neovascularization or plus disease appears [1,2].

Currently, laser ablation and anti-VEGF agent injection are available as an acute phase of ROP treatment to reduce the amount of VEGF. Laser ablation burns the avascular retina to reduce the number of VEGF-producing retinal cells, and has the effect of reducing the concentration of VEGF that will be formed later, rather than reducing the concentration of existing VEGF. On the other hand, intravitreal anti-VEGF injection is injected into the vitreous cavity and directly binds with VEGF, so it helps to normalize ROP by simply and quickly lowering VEGF concentration [3].

Currently, bevacizumab (Avastin), conbercept (Lumitin), and aflibercept (Eylea) are available off-label, and only ranibizumab (Lucentis) was first approved in Europe for the treatment of ROP [3]. The advantages and disadvantages of laser ablation versus anti-VEGF injection are summarized in Table 1.

The ophthalmologists decide whether to use laser ablation or anti-VEGF agent, but anti-VEGF treatment appears to be more beneficial than laser treatment for zone I ROP or aggressive ROP [4,5]. In a recent multicenter study on ROP conducted in Korea [6], anti-VEGF injection was preferentially selected for zone I ROP and posterior zone II (zone IIp) ROP, and laser ablation was selected for ROP located in zone II. This paper published in *Kosin Medical Journal* [7], evaluated a total of 40 consecutive infant eyes of 21 patients who received bevacizumab injection or laser ablation. Bevacizumab injection was performed in all cases of zone I ROP, and laser ablation was performed in all cases of zone II ROP. In addition, in the case of zone IIp ROP located between zone I and zone II, injection treatment was

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Table 1. The advantages and disadvantages of laser ablation versus anti-VEGF injection

	Laser ablation	Anti-VEGF injection
Treatment method	Laser ablation burns the peripheral retina to stop neovascularization.	Anti-VEGF agent immediately bind to the VEGF in the vitreous cavity and retina.
Administration	Laser treatment is not easy to learn and it can last for 60–90 minutes. Treatment should be performed in a neonatal intensive care unit or an operating room equipped with an intubation unit.	Intravitreal injections are performed aseptically under local anesthesia on awake infants at the bedside.
Treatment response	It may take one to 2 weeks for laser treatment to stop the progression of ROP.	It starts working right away. Usually, regression occurs as early as 1–3 days.
Follow-up periods	Since the avascular peripheral retina was ablated, follow-up up to 50–55 weeks of postmenstrual age may be recommended.	Long-term follow-up is required until retinal vascularization is complete.
Recurrence (=reactivation)	Reactivation after laser ablation is uncommon. Most cases of reactivation may be related to skip area.	Reactivation occurs more frequently after anti-VEGF injection. However, the degree of reactivation may vary depending on the severity of ROP, the type of anti-VEGF, and the injected dose.
Refractive error	Myopia progression is larger and more rapid in children with ROP who received laser treatment than injection treatment.	Two-year follow-up data from the BEAT-ROP study showed a significant decrease in the amount of myopia.
Visual fields	The wider the laser range, the more the peripheral visual field is disrupted.	It offers the potential to provide a wider visual field with anti-VEGF than with laser, by giving the peripheral retina an opportunity for blood vessels to grow.
Systemic effects	Anesthesia-related problems and mortality may occur.	VEGF is a necessary component for neural, vascular, and lung development. There is ongoing research to evaluate the long-term effects of VEGF suppression.
Complications related to procedure	Extensive laser ablation causes ocular inflammation and causes certain complications such as anterior segment ischemia or, rarely, laser-induced cataract formation.	Intravitreal injection-related procedures can cause conjunctival hemorrhage, increased intraocular pressure, hyphema, vitreous hemorrhage, cataract, and endophthalmitis.

VEGF, vascular endothelial growth factor; ROP, retinopathy of prematurity.

selected in 71.43% (10/14) and rapid laser treatment was selected in 28.57% (4/14).

Reactivation of ROP commonly occurs after anti-VEGF injection compared to laser therapy and is accompanied by complete or incomplete regression of the original lesion [8,9]. After anti-VEGF treatment, the rate of retinal vessel formation is unprecedentedly slow. Reactivated ROP occurs when plus disease reappears or when neovascularization develops at the ridge lesions or advanced edge of vascular-avascular retina [10,11]. As a phenomenon different from the natural course of ROP, reactivation of ROP is an important issue in the era of current anti-VEGF therapy and should not be viewed as something like acute ROP [3,10]. However, there are no major clinical trial data on treatment guidelines for reactivation of ROP. Additionally, all forms of reactivation ROP do not require retreatment.

Martinez-Castellanos et al. [12] proposed a treatment algorithm for treatment failure and reactivation after injection of bevacizumab in type 1 ROP. They recommend that

repeat anti-VEGF injection should be considered in the presence of flat neovascularization, and vitrectomy be performed in the case of fibrovascular proliferation or vitreous traction. Garcia Gonzalez et al. [13] reported that the treatment failure rate was low when prophylactic laser treatment was performed on the peripheral persistent avascular retina after injection of bevacizumab in ROP.

This paper in *Kosin Medical Journal* [7] mentions how much the retina is rescued by deferred laser when ROP reactivated after bevacizumab injection. In 42.86% (12/28 eyes) of the bevacizumab injection group, retinal blood vessels were successfully formed to the periphery, and in 57.14% (16/28 eyes) of them, deferred laser treatment was performed due to reactivation of ROP. In the deferred laser treatment group, 1/3 of cases of zone I ROP and all cases of zone IIp ROP. It took an average of 7.9 weeks to receive deferred laser treatment after bevacizumab treatment. In the deferred laser group, during the window period, retinal vessels in zone I were formed up to zone IIp, and retinal

vessels in zone IIp were formed to zone II, showing that laser treatment was possible in an area similar to that of the prompt laser.

This study is a retrospective study with a small number of infants and a short follow-up. Nonetheless, this study showed that if deferred laser was administered in reactivated ROP after anti-VEGF injection, the risk of systemic exposure from repeated injections and the risk of extensive retinal destruction by prompt laser could be reduced. Also, deferred laser therapy is another option for second-line treatment when reactivation occurs after injection, which could help provide new guidelines for reactivation ROP treatment. Additionally, in the future, large-scale studies are needed to determine the timing of treatment for reactivation and the long-term effects of various treatments.

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All the work was done by JHJ.

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Faculty development: the need to ensure educational excellence and health care quality

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The definition of faculty development has been refined and expanded over the past few decades, and various definitions have been used in higher education. Initially, faculty development was defined as activities that help teachers improve teaching skills, design better curricula, and improve the organizational environment for education. Since then, as the focus of faculty development has shifted from individual professors to institutional needs, faculty development is now defined as the personal and professional development of professors, clinicians, researchers, and managers to meet institutional goals, visions, and missions in social terms and moral responsibility to the community. Faculty development in medical education is universally needed to recognize and cope with widespread changes in education, including the traditional role of professors, advances in pedagogical theory, changes in learning styles, innovative curriculum models, and evaluation philosophy. However, critics have pointed out that most universities could not actively implement faculty development or accept professors' various demands. In this paper, various reports related to faculty development are reviewed to summarize how faculty development has progressed and present future directions for accepting various opinions to improve educational excellence and the quality of health care.

Keywords: Educational excellence; Faculty; Medical education; Quality of health care

Introduction

Faculty development refers to a variety of activities and initiatives designed to support and enhance the skills, knowledge, and effectiveness of faculty members' roles as teachers, researchers, and members of academia. Bergquist and Phillips [1] define faculty development as a process that includes personal development, to enhance faculty competence and attitudes toward research and education; class development, to enhance teaching techniques to improve the quality of education; and organizational development. This is defined as an organized activity.

Professors' competencies are largely divided into basic and lecture competencies [2]. Basic competencies refer to work ethics, moral values, self-development, and the global mind. Lecture competencies include educational philosophy, pedagogical theory, knowledge in the field of specialization, development and operation of class, facilitation, communication, evaluation and feedback, diagnosis, and reflection. In the early studies of faculty development, most studies have defined the important competency of a professor as teaching competency and designed instructional development programs focusing on the teaching role in the class. At the 1988 World Federation for Medical Edu-

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cation (WFME) meeting, participants vowed to pursue an agenda designed to improve medical education worldwide [3]. The Edinburgh Declaration made 12 recommendations, the fifth had an educator's focus: "training teachers as educators rather than content experts, and rewarding excellence in this area as well as excellence in biomedical research or clinical practice." Irby and O'Sullivan [4], citing the Edinburgh Declaration, asserts the need for a policy to ensure that all medical professors receive the knowledge and skills necessary to teach. The Edinburgh Declaration recommended that professors develop their skills and careers as educators beyond simply improving the content knowledge of their specialties. Since content knowledge in specialized fields is essential but insufficient for excellence in education, professors need knowledge of various educational roles, professional practice skills, and identity formation beyond teaching professional knowledge; therefore, faculty development is necessary. Cantillon et al. [5] also suggest that faculty development should strive to increase cooperation regarding environmental factors that form the identity of professors, beliefs, and practices. They emphasize the importance of establishing perceptible professor profiles within educational institutions to support the maintenance and development of clinical professors' identities.

As the new millennium began, education experts criticized the limitations of the program and called for various changes to foster faculty members. They emphasized that faculty development programs should aim for various goals and that the fields should become more diverse, especially supporting research capabilities, leadership, and career development requirements. This change can be said to reflect the evolving needs of faculty in response to the changing medical environment; it also means that, as the demand for faculty development programs at each stage of life increases, the contents and levels of the program should be diversified [6]. Steinert [7] suggested that the following tasks should be pursued by fostering faculty members in the future: broadening the scope of faculty development from teaching to academic development, expanding approaches to faculty development, utilizing a competency-based framework for faculty development, supporting teachers' professional identities, focusing on organizational development and change, and promoting research and scholarship in faculty development.

This study aims to determine how faculty development has progressed so far and propose directions for future development.

Faculty development: past and present

Generally, university professors are appointed in recognition of their outstanding research results in their major fields, and they are expected to be able to educate students through extensive knowledge in their specialized fields. Kim [8] argues that all professors in medical schools have adequate and sufficient education and training backgrounds in their fields of expertise and are researching steadily while separately making efforts to maintain and improve their research and patient care capabilities. However, regarding student education (which is the essential mission of the university), he expresses concern about a situation in which they are appointed as professors without additional education or research about education and teaching students without weight.

There is a saying that "the quality of education cannot exceed that of professors." The recent curriculum emphasizes a student-centered approach and students' active participation. Some may think that professors' teaching capabilities are less important than those of lecture-oriented classes, but in situations where team-based learning, problem-based learning, and task-based learning are frequent, professors must participate in various educational roles such as facilitators, role models, and resource developers. Medical school professors have the considerable burden of using new educational methods that they never experienced, while efforts to improve their class capabilities are insufficient. Many universities have introduced a professor evaluation system that allows professors to receive evaluation and feedback, but it is evaluated by students' preferences rather than actual evaluation and feedback. Son [9] indicated the reasons why university professors' efforts to improve their teaching capabilities—unlike those of elementary and secondary education teachers—were insufficient. First, in most universities, educational activities are considered less valuable than research activities. Second, professors generally think that students should work harder on their own rather than being well taught and guided. Third, while pursuing the excellence of education, evaluation of the educational field was considered less im-

portant in various university evaluations. Fourth, research achievements are a much more important factor than educational achievements in the promotion and evaluation of professors. In his review of educational situations in medical schools, professor Kang [10] argues that teaching methods have not improved because professors do not receive formal education or training related to teaching; professors and university authorities prioritize research and patient care over educational activities, and professors are not open to evaluating and providing feedback on their own educational activities. He claims it is important to develop various teaching and development programs to improve professors' interest in these areas.

In 1968, the World Health Organization (WHO) agreed on the need for in-service educational education for medical school professors to improve medical education and established Regional Teacher Training Centers (RTTC) in six WHO regions. In Western countries, such as Japan and Australia, some medical schools have established departments related to medical education to operate faculty development programs. While Korea founded the Korea Medical Education Association in 1970 and sought various directions to improve medical education, it agreed that Korea also needed an institution dedicated to medical education. The National Teacher Training Center for Health Personnel opened in 1975 with professors who completed their training at an RTTC overseas and has been striving for the development of professors through medical education seminars and workshops. Individual universities have also held faculty development programs with departments for teaching and development, such as teaching and learning centers and educational development centers.

Faculty development in medical education has been found to be effective in enhancing the teaching skills and knowledge of medical educators, ultimately improving the quality of medical education. Steinert et al. [11] investigated the effectiveness of faculty developments through a systematic literature review and found that, in most studies, professors showed favorable changes in their development and views on faculty. Professors' teaching skills and knowledge of teaching principles showed notable improvement and consistently reported changes in their teaching behavior, which had also been observed by students. It is also known that the effectiveness of faculty development is influenced by a variety of key characteristics, such as

empirical learning, provision of feedback, strong peer relationships, interventions guided by well-designed teaching and learning principles, and integration of multiple teaching methods in a single intervention. Skeff et al. [12] state that professors share their perceptions of the merits and usefulness of faculty development, but their participation is low; their attitudes, misunderstandings, lack of institutional support, and relatively insufficient research on how to improve education are potential barriers. It was pointed out that the tendency to underestimate the need or the potential benefits of the programs, the lack of faith in the usefulness of educational technology, and the belief that teacher training is not related to teaching excellence are the reasons for low participation. To determine what kind of faculty development program medical school professors need, Na et al. [13] investigated the level of awareness of medical school professors' educational preparation, implementation, and evaluation and studied the contents that should be strengthened. In this study, professors recognized the importance of class preparation, execution, and evaluation, but the actual degree of performance was low. In particular, the frequency and performance of educational implementation and evaluation were found to be lower than the frequency of performance of educational preparation, and the professors emphasized the need for a steady teaching development program as they thought that their teaching lacked quality.

Steinert [14] summarized the overall characteristics of faculty development through a systematic literature review published in 2020, particularly recent trends. First, research on faculty development is becoming increasingly active in the field of medical education. Second, the field covered by faculty development is still limited to teaching development, and programs such as research capacity or leadership development are lacking. In addition, as programs for teaching improvement also concentrate on teaching and learning methods, it was recommended to develop programs related to evaluation and assessment. It was pointed out that the teaching and learning methods used in faculty development are limited to workshops and seminars, and more diverse methods such as simulation-based learning, interactive theater, peer observation, mentoring, and non-face-to-face online learning must be used. Third, Steinert found that research on various topics is being conducted in different countries: recommendations for more programs

and perspectives, as well as reflections on the role and importance of faculty development, frameworks for teaching and learning and document reviews are among the research topics.

Faculty development: in the future

Steinert points out that he has focused on improving teaching skills for faculty development and has urged in favor of various changes [7,14], on the following six topics: (1) broadening the scope of faculty development from teaching to academic development; (2) expanding approaches to faculty development; (3) utilizing a competency-based framework for faculty development; (4) supporting professors' professional identities; (5) focusing on organizational development and change; and (6) promoting research and scholarship in faculty development.

1. From teaching to academic development

While many authors have highlighted the role that faculty development can play in academic and career advancement, research, and leadership development [15-17], most faculty development efforts still tend to focus on strengthening the role of faculty as teachers and educators. Faculty focuses on personal and career development and can explore different ways to foster academic development, considering partnerships with other units and organizations. Song et al. [18] classify professors' competencies into basic competencies, management competencies, and teaching competencies and emphasize that university teachers' duties are not limited to lectures and teaching activities. They also recommend that professors play various roles related to education, research, and services according to their ranks and positions, and faculty development should support them. Park et al. [6] define the role of a professor as a professional educator, an expert in the relevant field, and a community leader and suggest faculty development programs for research and projects and programs related to continuous self-development in specialized fields to strengthen the necessary competencies according to their roles. Chun and Park [19] developed and operated a faculty development program based on the characteristics of medical school teachers and then published the results of investigating professors' responses. They argue that faculty development programs must go beyond education, such as

instructional design or teaching methods, to improve simple teaching ability, strengthen various competencies required according to the teaching profession, and approach them from the perspective of lifelong learning. In fact, Duke-National University of Singapore (NUS) develops, operates, and implements various faculty development programs [20]. A separate curriculum is under way for instructors, assistant professors, and senior professors. For example, the Associate Consultant Readiness Programme (ACRP) for newly appointed professors consists of various programs to promote a high level of professional development (such as exploring the healthcare system, roadmap for future career options, and approaches to managing healthcare legal issues and challenging patient issues), providing a platform for networking and interaction with colleagues in other fields of expertise as well as time for conversation with senior professors. The Academic Medicine Education Institute (AMEI) for competency development as an educator is also a systematic and continuous faculty development program that operates using various teaching and learning methods [20,21].

2. Expanding approaches to faculty development

Barab et al. [22] define community of practice (CoP) as a "persistent, sustaining, social network of individuals who share and develop an overlapping knowledge base, set of beliefs, values, history, and experiences focused on a common practice and/or mutual enterprise." Professors dedicated to education often feel isolated within educational institutions and are incapable of fighting for changes that they believe are necessary. The CoP is an efficient strategy to bring together faculty dedicated to teaching and learning activities, while creating a safe and reliable environment. Yoo [23] stresses that cooperation with fellow professors and support at the university level must be provided to properly develop teaching skills at the individual level and that teaching capabilities can be more effectively strengthened if each major forms a common learning body and develops accordingly. de Carvalho-Filho et al. [24] outline 12 "ips" for implementing a CoP for faculty development, which include the following: articulating the goals and value of a CoP; starting with a specific project or task that unites the members; keeping the CoP open and inviting members with both expertise (memory) and fresh ideas (innovation); working to ensure institutional support; and

promoting sustainability.

3. Competency-based framework for faculty development

Steinert argues that most teaching development programs should be developed based on performance as teaching development pursues and that most teaching development programs are being conducted at the request of professors or curriculum developers at any time without a curriculum [14]. The United Kingdom Academy of Medical Educators has developed professional standards for medical educators that are divided into core values and five domains [25]. Core values include professional integrity, educational scholarship, equality of opportunity and diversity, respect for the public, respect for patients, respect for learners, and respect for colleagues. The five domains of educational practice identified by the Academy are the design and planning of learning activities, teaching and supporting learners, assessment and feedback to learners, educational research and evidence-based practice, and educational management and leadership. Although this does not have to be the outcome of the faculty development programs of all medical educational institutions, it is necessary to develop a program that reflects the agency's mission or the needs of its members to achieve the best results.

4. Support professional identities

Professional identity refers to the way an individual perceives themselves within a professional context, including the values, beliefs, attitudes, skills, and behaviors related to their chosen profession [26]. It encompasses a sense of belonging and identification with a particular professional group and commitment to the values, standards, and ethics of the profession. Professional identity is shaped by a variety of factors, including education and training, work experience, relationships with colleagues and mentors, and societal and cultural influences. It can also evolve over time as individuals gain new experiences and perspectives. A strong professional identity can contribute to a sense of fulfillment and satisfaction in one's work as well as promote professionalism and ethical behavior. People often implicitly consider their understanding of who they are or who they want to be when they contemplate what they should do or what path they should take. Identity is inherently social, in that it is formed in relationships with others, and people constitute their identity in relation to

the communities in which they participate. Medical school professors play the role of clinicians, researchers, and educators. In a study where interviews were conducted with medical school professors, participants unanimously identified their primary identities as clinicians/scientists/researchers, with their identity as medical educators being seen as secondary without exception [27,28]. They felt significant temporal and physical pressures related to their prioritization of these identities and expressed confusion regarding the notion that their identity as a clinician/scientist was a prerequisite for fulfilling the role of an educator. For novice teachers, this can lead to difficulties in integrating their teacher role into their identity. Such difficulties or tensions can lead to identity dissonance involving negative emotions, such as low self-worth or frustration. Identity dissonance is problematic because it can prevent teachers from practicing with confidence. Crossed and fused identities are desirable because individuals with strong identities as teachers enjoy their roles more, are more likely to stay in health vocational education, and are willing to invest more in professional learning [27]. Through the existing faculty development program, one can explore one's identity and strengthen the value of the teaching role through questions, discussions, and reflections on identity. It was also said that the opportunity to continuously explore identity through a longitudinal program should be provided and that comparing oneself with others or sharing learning experiences with colleagues who are compatible through faculty development or mentoring programs and community building and networking will often provide important opportunities for professional identity and career development.

5. Focusing on organizational development and change

Medical schools have three missions, namely, education, research, and patient care. So far, university policies have been essential for their excellent achievements in conducting these missions. Faculty development can play an important role in promoting organizational change and development. As Swanwick [29] notes, faculty development should be "an institutional-level pursuit with the intention of specializing teachers' educational activities, strengthening their educational infrastructure, and building educational competence for the future." Faculty development should play various roles, such as promoting changes in

the educational curriculum in line with theoretical changes in education and establishing policies to improve professors' research achievements as well as medical school admission policies. To this end, it is possible to promote a culture of change by developing institutional policies that support and reward excellence, recognize innovation and scholarships, and provide learning opportunities. Resources should be available to junior and senior faculty members.

Faculty development not only provides an opportunity for professors to develop individual capabilities to run organizations and determine university policies, but it also creates an atmosphere of change in university policy and can help foster an environment that promotes critical exploration, adaptation, and growth. In other words, faculty development can help develop organizations, promote leadership and management, and support cultural change in the workplace.

6. Promoting research and scholarship

In 2018, Harden et al. [30] complimented the development of research and scholarships related to medical education in his contribution to the 40th-anniversary issue of *Medical Teacher*. However, research in the field of faculty development is limited. In Korea, many universities have departments for faculty development, such as teaching and learning centers and educational development centers. Regarding medical education, most medical schools, medical education societies, and medical education training centers operate various educational programs to improve the quality of education and students' learning achievements by supporting professors with the knowledge and skills necessary for education, such as teaching methods, educational skills, and learning psychology [31]. However, verification of the effectiveness of these teaching development programs is insufficient. Steinert et al. [32] make the following six recommendations for research in faculty development in their review of faculty development for medical teachers: (1) embed research in a theoretical or conceptual framework; (2) incorporate qualitative and mixed-method studies to conduct more rigorous research; (3) evaluate behavior and organizational outcomes using different methods and data sources; (4) evaluate changes over time; convert to practice; (5) analyze key functions of faculty development; and (6) explore the role of faculty de-

velopment within a larger organizational context.

In the future, we must expand our focus beyond individual educational effects, develop programs that expand over time, promote workplace learning and community development, and secure institutional support based on the achievements of faculty development. Research should also be included in the theoretical framework, and more qualitative and mixed-method studies should be conducted to evaluate behavioral and organizational changes, evaluate transitions to practice, analyze key functions, and explore the role of faculty development in a larger organizational context.

Conclusions

Faculty development is important to support faculty in developing and applying long-term proficiency, and many universities offer programs that strengthen and develop faculty in teaching, learning, and assessment methods, skills and tools, and research methodologies. Continuous changes and developments in learning methods and educational skills, as well as changes in student needs and expectations, require universities to continue developing and applying the professional knowledge and skills of faculty members to provide students with the best education.

The educational community has emphasized the importance of teaching and development for decades, but education is still subordinate to universities' responsibilities, such as education, research, service to the community, and patient care.

Likewise, educational experts have long suggested the direction of faculty development. Teaching development should be expanded not only to educate students by listening to the needs of professors but also to more diverse fields such as research capacity development and personal development. Most teaching and development should be conducted in various efficient ways away from the center of the lecture, especially examples such as mentoring by senior professors, peer tutoring, and community formation. A competency-based framework should be applied to develop continuous and goal-oriented teaching competencies, away from single-step educational content. And above all, it can be said that it is necessary to support professors to build their identity as educators. In addition, teaching development should be expanded to promote not only

individual professors but also organizational change and development, for which research and support for faculty development is needed. In addition, in the field of faculty development, important directions for the future include digital technology utilization and respect for diversity, flexibility, and adaptability.

Faculty development is one of the most important challenges faced by universities. If faculty development is promoted in this direction, students' learning achievements can be improved, and a higher level of quality improvement can be achieved in the field of education. In addition, it will play an important role in promoting the personal development of professors and developing the university's capacity to fulfill its social responsibilities.

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Future directions of online learning environment design at medical schools: a transition towards a post-pandemic context

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Coronavirus disease 2019 (COVID-19) has had an extremely large impact on methods of teaching and learning, and the need for online learning has grown enormously during the COVID-19 pandemic. Because most professors and students adjusted their mode of teaching and learning to this new context, online learning seemed to be going well. The problem is that distance learning was abruptly adopted as an alternative method of classroom instruction. To increase the effectiveness of online learning, more consideration is needed to explore future directions of creating learning environments. Therefore, this study suggests seven design guidelines for designing learning environments at medical schools based on a theoretical background and experiences from the pandemic. Constructivism and situated learning theory are introduced as the theoretical background for learning environment design, and the basic principles of learning environment design with the paradigm shift to learner-centered classrooms and experiences using EdTech, including HyFlex learning, flipped learning, learning management systems, and interactive learning tools, were used to develop the design guidelines. Each design guideline is strategically matched with the basic principles: learner-centeredness, real-world tasks and contexts, problem-solving, new roles of professors as facilitators or tutors, collaboration, and new perspectives of evaluation and assessment.

Keywords: Constructivism; EdTech; Learning environment design; Online learning; Situated learning theory

Introduction

Coronavirus disease 2019 (COVID-19) has extremely impacted current education systems all around the world, in particular, the method we teach and the way we learn. With the limitation of physical interactions, most schools temporarily closed their doors, and online learning has become the main means of teaching and learning. Although this kind of distance learning was already prepared theoretically through various research, it was difficult to

use practically in the field except for online-only classes [1]. However, the need for an online learning method has grown enormously through the COVID-19 pandemic situation. Most schools, including universities and colleges, were forced to change the way of teaching and learning, and educators and learners had to adjust their mode of teaching and learning to the recent phenomenon.

Medical schools were the same as other schools. Most curricula were delivered to students through pre-recorded lectures or real-time online classrooms with video confer-

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encing tools. Clinical clerkships and other clinical practices were postponed or suspended. The problem is that this remote learning was abruptly adapted as an alternative way of classroom instruction. There was no preparation for online learning, no discussion of the effectiveness of learning, and/or no agreement between professors and students. Distance learning was used not because it can be an effective way of learning activities but because it was urgent [2]. Numerous research on online learning in terms of the media used in online classes, the type of classes, and preferred online class methods to identify current experiences were also followed immediately after the change [3-6]. However, little attention has been given to research on the effectiveness of online learning and its future directions for learning environment design. The efforts for developing a better learning environment not only for online learning conditions but also for traditional learning situations based on the theoretical background to prepare after the COVID-19 or another pandemic situation are needed more at this point.

From the contemporary perspective on learning, building a digital learning environment where knowledge and information can be explored and acquired anytime and anywhere, and creating and utilizing integrated knowledge for real-world problem-solving are becoming normal. It goes beyond simply memorizing and utilizing a large amount of knowledge, and developing creative problem-solving skills and convergence thinking skills are becoming more important. With these perspectives on learning, the purpose of this study is to suggest how to design learning environments at medical schools after the COVID-19 situation based on the theoretical backgrounds and experiences from the past.

Theoretical backgrounds: constructivism and situated learning theory for basic principles of learning environment design

The constructivists' view of learning assumes that knowledge exists in the human mind that has its contents, and the knowledge can only be interpreted through personal and social experiences [7]. It provides more meaning to how knowledge is constructed than the knowledge itself, and learning is defined as a process in which the learner

constructs the inner meaning of knowledge anew in his or her own space. It is a personal interpretation uniquely developed by experiences [8]. Therefore, in order for this process to be transferred from the contents learned in school or classrooms to true knowledge, it is argued that learning must take place in complex and diverse situations that reflect real-world context [9,10]. Because this context is already integrated into the learned knowledge itself, it is impossible to learn knowledge in isolation from its actual context. Learning can be placed by situating cognitive experience in real situations [11].

According to the situated learning theory, students are failing to apply the knowledge they have learned in school because the experiences they are learning at school are very different from the experiences they face in real situations [12,13]. In particular, in the case of medical schools, students need to learn again and practice new things through internships and residency courses after graduation. The learning culture in Korea is characterized by students doing their best to follow teachers who organize the contents well during the class and passively acquiring knowledge [14]. As a result, the acquired knowledge does not transfer well into long-term memory, or the method of newly constructing and utilizing knowledge is inexperienced or focuses only on improving test-taking strategies to do well in tests by focusing only on test scores [15]. Although the clinical practice period at medical schools for third and fourth-year students provides opportunities to directly face actual clinical situations, mostly traditional lectures are provided in other learning periods. In order to prepare for situated learning, it is necessary to organize and provide a learning environment where students who go through the premedical period, basic medicine, and clinical medicine period can learn not only content knowledge but also situational and strategic knowledge in an integrated manner [16].

One of the recent major concerns for effective learning is what kind of learning environment should be organized to satisfy students' desire for intellectual inquiry. Another concern is whether it can enhance the problem-solving ability to recognize, investigate, analyze, and explore problems from a new perspective and develop the thinking ability to accept and integrate other disciplines beyond the framework of knowledge delivery as a traditional teaching method [8]. The World Economic Forum [17] presented

15 personal skills that will be important in 2025, including analytical thinking and innovation, active learning and learning strategy, complex problem-solving, critical thinking and analysis, creativity, and originality and initiative. The abilities to recognize problems and analyze situations are vital for medical students, and innovative thinking from these abilities is also needed. The abilities to creatively restructure the acquired knowledge through active learning and solve problems critically are important as well. Memorizing fragmentary knowledge or information itself is becoming meaningless, and a digital learning system has been established in which necessary knowledge and information can be searched for and obtained anytime and anywhere through the Internet or multimedia materials. In addition, as the development of knowledge accelerates, memorizing all knowledge and information is impossible, therefore the importance of using knowledge is being emphasized more than the importance of acquiring knowledge. Moreover, the ability to establish relationships in different communities through cooperation with others, including the ability to communicate with each other, is also being emphasized, which has a significant impact on the development of communication skills of medical students, which is considered important recently.

Based on the theoretical backgrounds, including constructivism and situated learning theory, mentioned above, the basic principles of learning environment design are as follows [8]. First, a learner-centered learning environment is essential. Learning is a process of constructing meaning through individual experiences, and it is important that the environment in which a learner as the subject of learning is the center. Meaningful learning is available when the learner actively participates in the learning process and constructs meaning from learning, rather than the knowledge imparted unilaterally by the instructor. Therefore, it is necessary to design a learning environment in which learning can occur, and learners should be able to engage in learning activities by themselves through active participation and evaluation. In addition, it should emphasize a learning environment in which various perspectives can be developed by providing complex and dynamic situations and problems.

Second, it is necessary to construct a learning environment that includes real-world contexts and tasks. Rather than delivering only objective and factual information

separated from the context, the context and process in which knowledge can be used should be emphasized, and this context and process should reflect the complex and ill-structured real-world situation. Unlike traditional classes, difficulties of knowledge transfer can be solved through contextual learning, such as case-based learning or problem-based learning, because the tasks to be performed by learners should also be authentic.

Third, creating a learning environment based on problem-solving is needed. By restructuring how thoughts and information in the knowledge domain are integrated and interrelated [18] and by providing problems through learning that knowledge can be directly or indirectly applied to, understanding of situations, ability to recall information, metacognitive sensing ability for processes of problem-solving, and thinking ability can be promoted [10]. In addition, it can induce learning motivation and provide learning experiences through the process of solving problems by identifying problems and acquiring related knowledge. Through problem-based learning or project-based learning, learning experiences including knowledge application and various decision-making processes can be provided.

Fourth, a different teacher's role is required. Instead of being a knowledge provider that delivers existing simple knowledge, professors should play the role of a tutor or facilitator who can create an environment in which learners construct meaning and help its process of the learning environment. This specific role can motivate learners and induce them to reflect on various perspectives through appropriate questions. And professors can play a role in helping learners solve problems on their own through immediate and continuous feedback. However, unlike the traditional method, this requires a lot of time and effort on the part of the professors, and it is necessary to participate in learning by considering the appropriate level of intervention. For this role, various support and compensation for professors are required, and also understanding of school administration is necessary.

Fifth, creating a learning environment that emphasizes cooperative learning is important. Since students' social interaction has an important influence on learning, it is necessary to construct an environment where learners can learn through peer-to-peer networking, such as group activities or project-based learning. When ideas are shared

and discussed within a learning community, various perspectives are encountered, and sometimes contradictions and inconsistencies are experienced and learned [19]. In addition, through interactions within the community, reflective thinking to look back on oneself is possible, and alternative perspectives compared to one's own point of view are analyzed and reviewed. This can help individuals' cognitive development and learning process, and it can also help learners improve their abilities.

Sixth, the concept and principle of evaluation should be changed. The role of assessment in the traditional view is focused on judging individual abilities and achievements, but the student assessment in the new learning environment should be done from time to time in the course of learning. The focus should be on the ability of the learner to recognize a problem in order to solve it, to transfer to a new situation based on the acquired knowledge and information, and to evaluate the ability to solve the problem. In other words, the focus of the new assessment should move from checking the acquisition of knowledge to confirming problem-solving ability.

Paradigm shift: from educating to learning

Teaching-learning paradigm in recent years is changing from educating to learning, from instructor-led classes to learner-led classes. Traditional lecture-oriented classes are shifting to inquiry-oriented and problem-solving classes, and collaborative learning and participatory learning through project-based learning or problem-based learning are more important than individual learning conducted by each student separately [8]. This paradigm shift is a simple message to every educator, however, the current learning in classes may be still traditional, teacher-centered.

Learner-centered paradigm includes several important goals for effective learning. First, it is important to clearly set competencies for students' performances and educational goals and to achieve them. Frank et al. [20] addressed that focusing on learning outcomes to be achieved, emphasizing abilities to be acquired, de-emphasizing time-based training, and promoting greater learner-centeredness to increase learners' participation are four rationales for competency-based medical education. Students should think in an integrated manner so that they can achieve outcomes

rather than just memorizing fragmentary knowledge, and medical school should help them acquire abilities according to the learning pace of each individual by providing clear learning goals to students in advance. This has benefits for cooperative learning among students and inducing intrinsic learning motivation, and this can be linked to personalized learning, which is ultimately pursued in competency-based learning.

In evaluation, a norm-referenced assessment that indicates relative rank or position based on the learner's evaluation results should be limited, and a criterion-referenced assessment that evaluates the performance level in specific knowledge or competence by indicating the score of the learner in consideration of the criterion, which is a pre-established mastery level, should be aimed. Focusing more on what individual learners know and don't know becomes a major concern to provide an opportunity for all learners to reach the given learning goal by proceeding with the evaluation with more emphasis on the reliability and validity of the evaluation. It is also possible to consider switching to absolute evaluation which evaluates the performance level of the learner, rather than evaluation information on relative positions.

Constructive feedback for students is also required in the learner-centered paradigm [21]. By providing immediate (just-in-time) feedback on the students' learning performance, it can serve as a reinforcement for task performance. Through the feedback, it is possible to determine whether students themselves have achieved their goals, enabling reflective thinking to look back on areas in need of improvement. Utilizing formative assessment can also be a good example of a learner-centered classroom. It is necessary to check the learning gap between students, which has widened due to online classes, and to conduct formative assessments and provide feedback to improve individual learners' learning by focusing on the learning process of learners. Through formative assessment, students can find out information such as what they are lacking in and what they have not achieved in consideration of their learning goals, and by checking and reflecting on whether they have achieved their learning goals on their own, it is a new element of reinforcement in future learning. This can also be an opportunity to motivate learning. Moreover, formative evaluation provides an opportunity for professors to improve learning progress and teaching methods through

reflection. By pointing out the contents that students misunderstand, it is possible to immediately check the level of achievement at a certain point in time and apply it to the instructor's teaching-learning method.

As mentioned above, this requires more time and effort from professors than traditional lecture-based classes. Learning in a learner-centered paradigm requires not efficiency of teaching and learning but effectiveness of them. It may expect professors' ownership and service-oriented leadership to lead their students to better learning. Therefore, the paradigm shift in learning should be applied as an important concept to construct all learning environments including online classes, and in particular, the online learning environment should be configured in a way that avoids online classes as a simple digital conversion of traditional face-to-face lectures as much as possible.

Enormous possibilities of EdTech taught from experiences with COVID-19

While face-to-face classes at educational institutions were reduced, almost 100% of non-face-to-face classes were implemented through the pandemic. As such, online learning activities caused by COVID-19 were another new normal in our society [2]. After online learning was settled by professors and students, other types of online learning activities were also introduced and implemented. Hybrid or blended learning refers to classes in which face-to-face classes, online discussions, and online lectures are operated in a mixed form using flipped learning or a learning management system [22]. A model that an instructor conducts classes with students participating in face-to-face classes in the classroom and transmits the classroom activities in an online environment for other students in real-time to provide a higher quality online class experience is called a HyFlex learning [14,23]. Beatty [23] introduced four characteristics of HyFlex classes: learner choice, equivalence, reusability, and accessibility, and through this, better learning outcomes can be achieved and flexible academic management can be coped with.

Recently, it has become possible to utilize various technologies that are rapidly developing to provide effective learning and to build a learning environment, called ubiquitous learning or U-learning, that allows learners and instructors to participate in classes anytime and anywhere

[24]. Medical schools are also utilizing various interactive learning tools that can help learners to focus on learning and expand mutual communication, along with support for online classes, to overcome this pandemic situation [25]. It also has been used to guarantee students' right to class and to improve effectiveness in learning. To minimize learning gaps in current pandemic situations, online classes using multimedia materials such as e-anatomy were also utilized for anatomy practices, case analyses, attending online conferences, and journal clubs online for clinical practice were employed. The important thing in configuring an online learning environment is not simply to transfer a lecture type of method from face-to-face classes to online but to enable effective learning to occur through online classes by utilizing various learning methods with theoretical backgrounds and technical methods that can be implemented online.

Despite the importance of EdTech, some medical schools have provided traditional lectures through pre-recorded classes without deep consideration of learning effectiveness in this COVID-19 situation. With current limitations, there are not that many ways that can apply various learning methods based on theoretical backgrounds. Since there is still a lack of research on the effectiveness of online classes, it is also necessary to utilize various methods and evaluate them.

Conclusions: design guidelines for HyFlex learning environment

In order to effectively provide essential learning to students, certain design guidelines are needed to implement active learning to provide opportunities for students to explore and apply knowledge on their own, away from passive learning of a simple knowledge transfer. Seven design guidelines based on the basic principles from the theoretical and practical backgrounds of the HyFlex learning environment are suggested in this section. Each design guideline is strategically matched with the basic principles and provided with the initial of the principles: learner-centeredness (L), real-world tasks and contexts (A), problem-solving (P), new roles of professors as facilitator or tutor (F), collaboration (C), and new perspectives of evaluation and assessment (E).

First, a real-time system is required for online learning (L,

C). Asynchronous learning, such as providing lecture videos to students, has been utilized for traditional e-learning systems. In the case of asynchronous learning, the focus is on learning for knowledge transfer and understanding. It will be passive learning centered on the instructor, and it is difficult to expect the effectiveness of learning through interaction between professors and students. In addition, in the case of classes using pre-recorded content, it is difficult to find a qualitatively better part compared to professionally filmed video content or education-related broadcasting, which is the expectation is too high of the current generation who has grown up with technology and video media since childhood. Even from the student's point of view, students have to take several classes online at the same time, therefore the concentration on the class may decrease differently from face-to-face lectures. For example, in the case of some students, they made lecture notes close to transcription through repeated playback several times and shared them with other students [3]. It was also found that parents or others instead of students participated in the class to help students or do assignments for them. Therefore, it is necessary to convey the image of teachers and learners creating a learning environment through interaction with students in the same way as the face-to-face class conducted in the classroom. Real-time classes should be also prioritized to ensure students' right to learn. In addition, it is necessary to prepare for a negative impact on the entire class if there is a technical problem. It is also necessary to actively operate small group activities because it is difficult to grasp the level of class participation at a glance when online learning is targeting all students. However, in the case of medical schools, there is a need to consider asynchronous learning due to the fact that the amount of knowledge medical students have to learn in the basic and clinical medicine periods is relatively heavy, and most of the classes are based on knowledge transfer. Asynchronous learning has some advantages of being able to search for knowledge from textbooks or the Internet after a pause in class [3], or to understand the contents of the class better through the opportunity to listen to the lecture repeatedly as needed on a self-directed basis.

Second, HyFlex learning can be an alternative method for online learning (L, C). In the case of some teaching methods, such as activity-based classes or clinical practice classes, excluding lectures, there are limitations in

conducting all classes online. For student assessment or evaluation, a face-to-face examination is more appropriate because taking the test online can cause fairness issues [25]. In addition, all students should be given the same opportunity for fairness of assessment, and learning outcomes should not be different due to additional information or data. In the case of an online assessment, it is impossible to prevent an environment in which students can gather together to solve problems, search for data, or directly check the contents of textbooks. It is necessary to conduct the assessment in small groups or prepare for a problem-solving type of test in which the content knowledge itself does not affect the result. Therefore, face-to-face classes or meetings can be added to achieve the learning outcomes of online classes, and the basic instructional model can be modified to choose both face-to-face and asynchronous instruction at the same time, providing equal opportunities to both professors and students. For example, online classes can be provided for all students, then small group meetings can be divided into breakout sessions through face-to-face meetings after the classes. Another example is that during lecture-style classes, 50% of students can participate in face-to-face classes, and the remaining 50% of students can participate in real-time online classes.

Third, Small group learning activities should be emphasized (L, C). In the case of general classroom classes, students must adjust their progress to the structured curriculum, and their learning proceeds according to the schedule without considering individual abilities and circumstances. Because the lecture method is mainly used to promote knowledge or information acquisition, many students lose their interest in learning or experience "learned helplessness" that is normalized to monotonous [26]. To this end, it is necessary to restructure learning activities that allow students to construct and develop knowledge by themselves, and to help them interact with the learning environment and construct meaning on their own. It is also necessary to change the composition of the online class environment so that learners who passively accept knowledge become learners who actively accept knowledge, learners who use acquired knowledge as creative producers, and learners who learn through cooperative thinking. In addition, some problems, including communication breakdowns with students, lack of student response, and difficulty in providing feedback, which is common in large-scale lectures, are dis-

advantages that can appear more easily in online classes. Therefore, the learning environment should be structured so that students can increase interaction between students, share and adjust various perspectives, experience contradictions and inconsistencies of multiple opinions, and experience reflective thinking that can be seen from the perspective of others through small group activities during online classes.

Fourth, authentic learning experiences should be embedded in learning environments (A, P, C). The knowledge provided by schools is abstracted, decontextualized, and highly structured, separate from the context or situations in which the knowledge is used [27,28]. Because of this, incomplete knowledge or immature knowledge that does not support complete understanding is transmitted to students, and they experience inert knowledge that is not applicable to solving real-world problems. Therefore, it is necessary to provide authentic learning experiences that require problem-solving logic similar to real-world problem-solving, have real-world complexity, and have problem types that can be faced in real life. Learning that can be easily transferred to real-world situations should occur with problem-oriented characteristics that require problem-solving rather than learning through simple knowledge acquisition so that teaching and learning methods, including problem-based learning, project-based learning, or case-based learning can be utilized. Through ill-structured authentic experience, students can indirectly learn to solve real-world problems, grow cognitively, reinterpret and transform their point of view, and make efforts to have a shared meaning.

Fifth, interactive learning tools can be utilized for better learning (L, F, E). It is necessary to actively utilize online interactive learning tools to expand communication and interaction between professors and students. For better classes, creating appropriate interactions between teachers and learners is essential. In particular, due to the nature of medical schools, communication between professors and students is more important because the relationship starts with the professor and continues as a senior doctor or fellow medical staff after graduation [3]. By using online interactive tools, such as Mentimeter, Kahoot, Socrative, and Padlet, which enable real-time student participation during classes, quizzes, opinion listening, and formative evaluation can be provided [25,29]. Because these tools

mainly use mobile devices, they can also bring a better class atmosphere and increase students' learning motivation.

Sixth, utilizing a learning management system is required (L, F, C). It improves learners' self-directed learning ability and provides class-related information and materials, feedback on assignments, the interaction between students, formative assessment, case-based learning, project-based learning, and student opinion exchanges through bulletin boards or forums to enhance two-way communication. In particular, in the case of medical schools, team teaching is being conducted in most of the courses, and since many instructors are in charge of different classes, it is difficult to provide a big picture of the entire learning courses to students. Because students are requesting a roadmap or systematic composition for the entire course, a large direction for the entire course should be presented through a learning management system to solve this problem. In addition, text-oriented communication is possible without exposing individual student's opinions during class, and it is possible to easily share multimedia learning materials or other materials by creating another online virtual classroom. For example, when cases need to be presented step-by-step, the individual problem-solving process or group problem-solving process corresponding to each stage can be recorded through a learning management system, and all information can be exchanged and viewed later again. Through the use of this learning management system, HyFlex learning, including real-time online classes, students' opinions and information exchanges, and learning assignments, can be conducted. For this system to be available, administrative support is also essential. In terms of administrative and technical issues, it is not easy for individual instructors to manage the system.

Seventh, qualitative improvement of multimedia learning materials is required (L, A, F). Current medical students are generation Z, who have been exposed to the digital environment and are familiar with the Internet and information communication, and are more accustomed to learning through visualized or imaged content than acquiring information through text. It is important to develop authentic learning materials to draw educational interest from students who are accustomed to well-organized online lectures or high-quality videos. It is also necessary to provide opportunities to develop and share multimedia learning

materials through learning assignments or project-based learning to students who are not afraid to actively share their interests and produce content. To this end, it is necessary to support multimedia equipment to develop learning materials or provide faculty development workshops, and discuss on which each college of medicine shares developed materials.

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Remote health monitoring services in nursing homes

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Aged people are challenged by serious complications from chronic diseases, such as mood disorder, diabetes, heart disease, and infectious diseases, which are also the most common causes of death in older people. Therefore, elderly care facilities are more important than ever. The most common causes of death in elderly care facilities were reported to be diabetes, cardiovascular disease, and pneumonia. Recently, the coronavirus disease 2019 (COVID-19) pandemic have a great impact on blind spots of safety where aged people were isolated from society. Elderly care facilities were one of the blind spots in the midst of the pandemic, where major casualties were reported from COVID-19 complications because most people had one or two mortality risk factors, such as diabetes or cardiovascular disease. Therefore, medical governance of public health center and hospital, and elderly care facility is becoming important issue of priority. Thus, remote health monitoring service by the Internet of Medical Things (IoMT) sensors is more important than ever. Recently, technological breakthroughs have enabled healthcare professionals to have easy access to patients in medical blind spots through the use of IoT sensors. These sensors can detect medically urgent situations in a timely fashion and make medical decisions for aged people in elderly care facilities. Real-time electrocardiogram and blood sugar monitoring sensors are approved by the medical insurance service. Real-time monitoring services in medical blind spots, such as elderly care facilities, has been suggested. Heart rhythm monitoring could play a role in detecting early cardiovascular disease events and monitoring blood glucose levels in the management of chronic diseases, such as diabetes, in aged people in elderly care facilities. This review presents the potential usefulness of remote monitoring with IoMT sensors in medical blind spots and clinical suggestions for applications.

Keywords: Nursing homes; Remote health monitoring service; Super-aged society

Introduction

The entering of a super-aged society and health-related quality of life is becoming more important than ever [1]. The Ministry of Health and Welfare reported a growing su-

per-aged society from 15.7% to 17.3% of the proportion of the population aged 65 and above (Fig. 1). With the rapid entry into a super-aged society, growing socioeconomic problems, which cause sharp increases in chronic disease-related complications, have been reported [1].

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The number of aged patients with severe illness or death from coronavirus disease 2019 (COVID-19) infections in Korea is significantly high compared to younger patients (Fig. 2) [2]. The recent COVID-19 pandemic caused serious problems in residents in elderly care facilities in Korea, including nursing homes and elderly daycare centers.

1. Increasing issue of medical blind spots: elderly care facilities

The main users of elderly care facilities are aged peo-

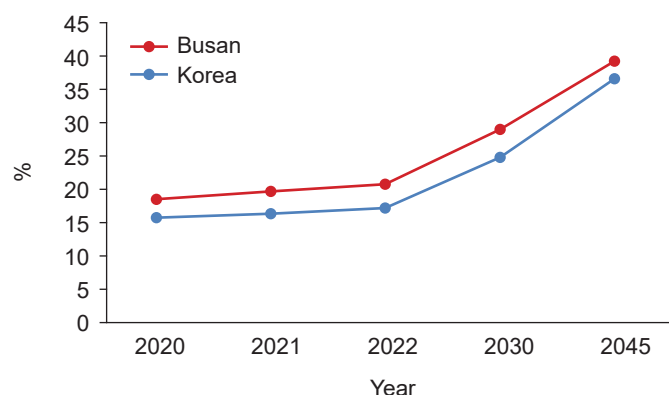


Fig. 1. Demographics of a super-aged society. Proportion of aged population.

ple with underlying diseases, and the rate of death from COVID-19 infections is very high. Among the total cumulative deaths from COVID-19 in Korea, the number of deaths due to infections in elderly care facilities is high [3,4]. Another outbreak of a COVID-19 strain variant is inevitable, and medical solutions to prepare for infections in elderly care facilities should be considered from a public governance perspective.

2. Governance of public health, private health, and care facilities

The main reason for such great casualties in elderly care facilities in the midst of the pandemic was the lack of communication between hospital professionals and medical staff in elderly care facilities. The medical staff of quarantined care facilities were isolated not only spatially but also medically, so no guidance from secondary advisory consultants could be provided [5]. Therefore, the medical governance of public health centers, hospitals, and elderly care facilities is becoming an important issue (Fig. 3).

3. Alternative solution for communication between care facilities and general hospitals

Based on the above situation, healthcare professionals are greatly challenged to develop new healthcare services to

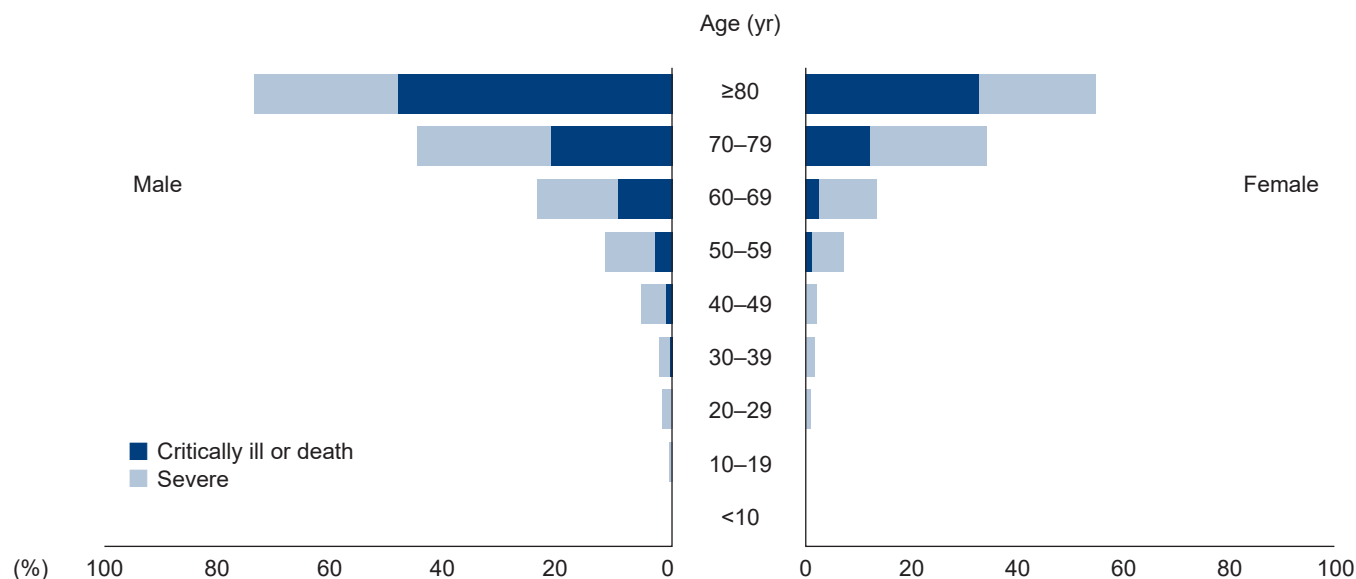


Fig. 2. Age and sex relationships with clinical severity during hospitalization or isolation from coronavirus disease 2019 (COVID-19).

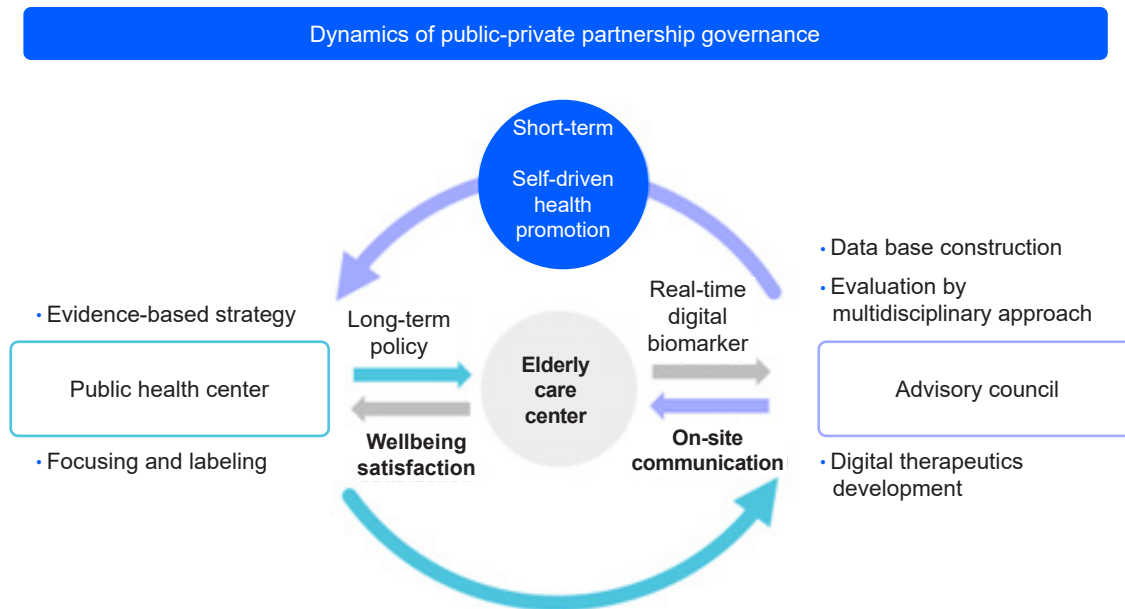


Fig. 3. Diagram of governance of public and private partnerships.



Fig. 4. Illustration of a remote health monitoring service for an elderly care center.

overcome the increasing service burden. The recent development of information, communications, technology technologies has enabled healthcare providers to investigate how to enhance healthcare services in response to the aging population issue [6-8]. Based on smart healthcare and recent innovations, home care technology, such as remote-monitoring services, is becoming a new complementary solution to transform the healthcare industry (Fig. 4).

4. Recent breakthrough in remote health monitoring services

Internet of Medical Things (IoMT)-based remote health monitoring services have been demonstrated as a challenging modality for communicating with elderly care facilities [9,10]. IoMT-based devices, such as real-time electrocardiogram (EKG) monitoring and continuous glucose monitoring sensors, gather digital data using a cloud server [11-14]. The visualization of digital biomarkers from EKG and blood glucose monitoring with a phone gateway helps patients achieve motivation for self-driven lifestyle modifications based on biofeedback from digital data from IoMT sensors (Fig. 5).

Clinically application of IoMT devices in elderly care facilities

1. Early detection of subclinical cardiovascular and infectious diseases

Real-time EKG monitoring is clinically useful in the detection of abnormal heart rhythms, such as arrhythmias and coronary diseases [15]. If the real-time EKG monitoring of high-risk patients in care facilities were possible, abnormalities could be detected early and proper medical precautions could be taken. As mentioned above, reports

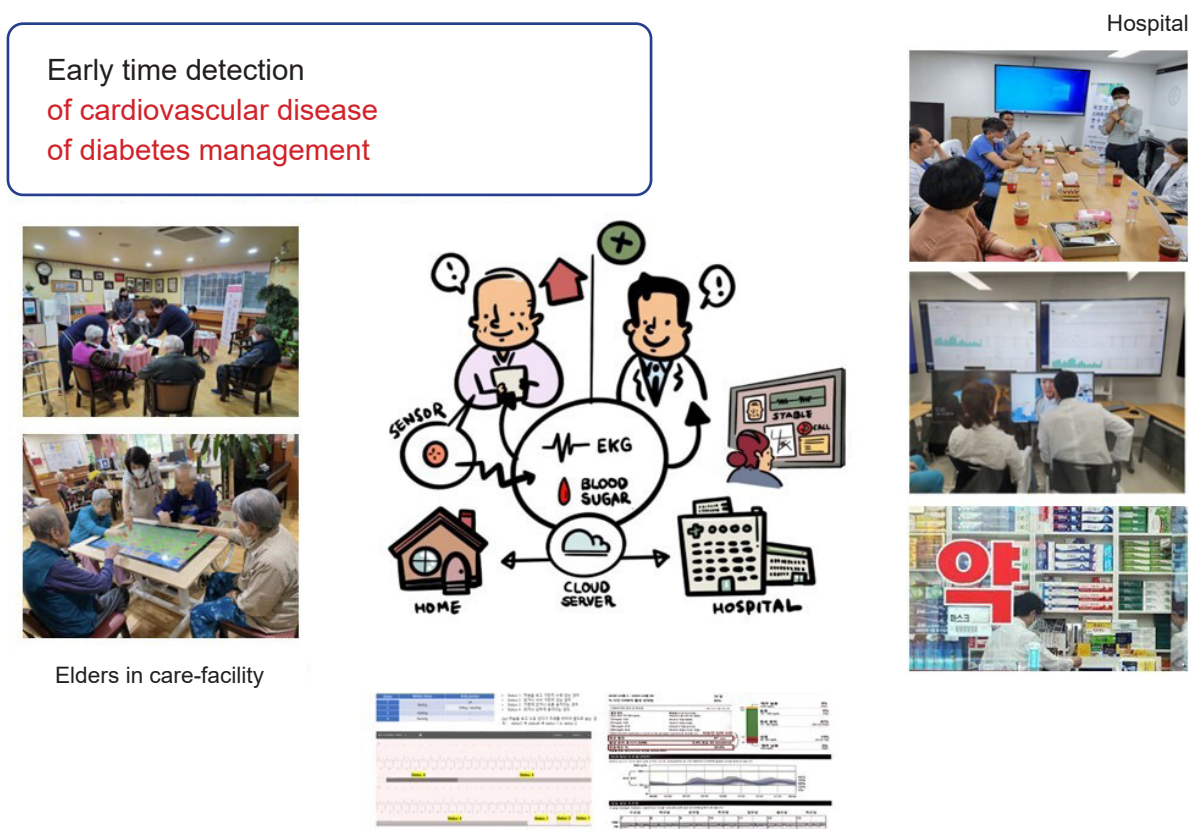


Fig. 5. Remote-monitoring care services from an elderly care center to a general hospital. EKG, electrocardiograms.

have demonstrated that the real-time EKG monitoring of higher-risk patients with cardiovascular diseases achieved early diagnoses and timely treatment [16]. Therefore, this medical evidence should be extended to applications in care facilities.

In the field of home care diagnostics, the use of artificial intelligence (AI)-powered diagnostic technologies, such as portable X-ray and ultrasound imaging, for patients in inaccessible areas at home or isolated facilities, is challenging [17-20]. Therefore, AI-powered digital imaging technology connected to real-time EKG monitoring is specifically promising for early detection, and intelligent platforms can assist in decision support and help recognize acute conditions in patients with fatal infectious diseases like COVID-19.

2. Evaluation and management of chronic diseases like diabetes

Well-thought-out blood glucose self-monitoring can mon-

itor a patient's glycemic status [21-23]. IoMT sensors can easily visualize and continuously record blood glucose monitoring data. This can be done mainly by a nurse or medical assistant in care facilities. These data are registered in a cloud server and reviewed by medical professionals, as well as care providers in care facilities, with the consent of the patient (Fig. 6). The patient and caregiver can use the analysis by advisory consultants for timely decision-support messages about the management of chronic diseases, i.e., lifestyle modification or supporting medication [24,25]. This collaboration between care facilities and hospitals may facilitate customized care services to improve the quality of life of patients with chronic diseases.

3. Digital literacy of aged people and evaluation of care services

IoMT-based healthcare services may improve the quality of life for people in care facilities. However, the main obstacle to applying IoMT technology is digital illiteracy. Caregivers



Fig. 6. Remote-monitoring care system for aged people for rapid responses to infection, cardiovascular disease, and poor sugar control.

must consider the role of medical assistants and nurses in care facilities. Their experiences and motivation for aged people with chronic diseases are essential for achieving remote health monitoring services in care facilities. Therefore, it is vital to establish the digital phenotyping of aged people in regard to simplicity and functionality. Aged people could suffer from a lack of digital experiences, resulting in the impairment of cognitive function [26,27].

Conclusion

IoMT-based smart healthcare services, especially remote health monitoring services, have become more acceptable. These technologies may provide useful opportunities for preparing safe medical solutions in the midst of the COVID-19 pandemic using real-time patient monitoring resources and services. Real-time EKG monitoring services are used to make early diagnoses of patients with infectious

and cardiovascular diseases. Continuous glucose monitoring services have significant potential to achieve the modification of chronic diseases, such as diabetes. Therefore, IoMT sensors may be used to collect useful data from care facilities so that rapid advisory consulting and timely decision-making could be possible for elderly patients.

Author contributions

Conflicts of interest

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Revascularization of immature retinas with retinopathy of prematurity using combination therapy of deferred laser treatment after a single intravitreal bevacizumab injection

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Background: This study aimed to observe the extent of retinal vascularization in patients with retinopathy of prematurity (ROP) who underwent deferred laser treatment (LT) after a single intravitreal bevacizumab injection (IVB).

Methods: This study retrospectively evaluated 40 consecutive eyes in 21 infants who received a single IVB or LT. Deferred LT was performed in cases of ROP recurrence after a single IVB. To assess the amount of retinal vascularization between the initial IVB and deferred LT, the cases were divided into three groups based on treatment: single IVB, deferred LT after a single IVB, and prompt LT. The growth and associated complications were compared between groups.

Results: There were 12, 16, and 12 eyes in the single IVB, deferred LT, and prompt LT groups, respectively. Deferred LT was performed at an average of 7.9 weeks after a single IVB. In the single IVB group, retinal vascularization proceeded to zone III, whereas the prompt LT group did not show any growth of vascularization beyond the laser scars. In the deferred LT group, during the window period before LT, retinal vascularization progressed from zone I to zone II posterior and from zone II posterior to zone II anterior, respectively, without further ROP recurrence.

Conclusions: Retinal vascularization progressed during the deferred window period, thereby reducing the area of the retina ablated by LT. A single IVB followed by deferred LT can be an alternative treatment option to prevent ablation of zone I or multiple IVBs.

Keywords: Bevacizumab; Laser therapy; Retinopathy of prematurity; Vascular endothelial growth factor

Introduction

Retinopathy of prematurity (ROP) is a major cause of childhood blindness. As the survival rate of premature infants

increases, the number of patients with severe ROP is increasing [1]. Laser treatment (LT) remains the main treatment for ROP.

In the early treatment for ROP (ET-ROP) trial, 9.1% of pa-

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tients had unfavorable structural outcomes [2]. After a large area of the retina is demolished by LT or cryotherapy, the normal retinal vascularization process does not proceed, and high myopia and visual field defect occur as they grow.

Recently, intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) have been developed and widely used for ROP. The injection has several advantages compared to LT, such as its simple and less time-consuming procedure; however, anti-VEGF injection can be complicated by late recurrence and is more likely to require retreatment than LT [3,4]. It can also reduce myopic progression and visual field defects caused by peripheral retinal ablation and allow for the growth of the neurovascular retina into the peripheral area [3-6].

Despite the low recurrence rate, there remains concern regarding the timing of recurrence and appropriate follow-up period after anti-VEGF intravitreal injection. Since the interval between anti-VEGF injection and recurrence is relatively long and varies from several weeks to months, careful follow-up is required until vascularization extends to the peripheral area to prevent unexpected recurrences [4,7,8]. Although it is widely used in clinical practice, there is no protocol for proper management after anti-VEGF injection. In addition to the long-term follow-up to observe ROP recurrence, another issue is the safety of multiple anti-VEGF injections in preterm infants. A single anti-VEGF injection was found to lower blood VEGF for a minimum of 7 to 8 weeks in a human study [9,10]. Because VEGF is an essential factor for the development of several organs, including the retina and brain, a decrease in blood VEGF levels affects infant growth.

Given the need for long-term follow-up and the risk of systemic side effects caused by multiple anti-VEGF injections, administering more than one anti-VEGF injection may carry increased clinical load and potential dangers. To avoid multiple injections, combination therapy with LT and anti-VEGF injection can be performed [11]. However, LT in zone I ROP can cause refractive errors and constriction of the visual field [12,13]. In such a case, deferred LT after an anti-VEGF injection can be an option to prevent the risks of multiple anti-VEGF injections or prompt LT in zone I [14,15]. Despite these points, to the best of our knowledge, the extent of retinal vascularization during the deferred window period has not been specifically studied. Thus, the present study evaluated the growth of vascularized retina

after a single intravitreal bevacizumab injection (IVB) until deferred LT.

Methods

Ethical statements: This protocol was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. KUGH 11-21). The study adhered to the tenets of the Declaration of Helsinki, and the informed consent was waived because this study design is a retrospective chart review.

The medical records of consecutive patients with ROP who received a single IVB or LT at three institutions in Busan, South Korea, between 2009 and 2016 were reviewed. Forty eyes of 21 patients who were followed for at least 6 months after receiving a single IVB or LT treatment were included. The eyes were divided into three groups based on the type of treatment: single IVB, deferred LT after single IVB, and prompt LT. Deferred LT was performed when the disease recurred or new vessels regrown and reached stage 3 after a single IVB. Three researchers from each center participated in the study, and each investigator was able to treat each eye differently in the treatment of each infant. Sex, gestational age, birth weight, postmenstrual age at IVB or LT, follow-up duration, surgical intervention, stage, and zone of ROP were investigated.

Routine fundus examinations for ROP screening were based on the ET-ROP guidelines. It was performed using indirect ophthalmoscopy with scleral depression under local anesthesia by three retinal specialists from each institution [16]. ROP zones and stages were classified according to the guidelines of the Revised International Classification for ROP [17]. The anteroposterior location of the ROP was described by retinal specialists at each center according to the aforementioned guidelines. Zone I was defined as a circle whose radius is twice the distance between the center of the optic disc and center of the macula [17]. For the purpose of this study, we divided zone II into posterior and anterior following the definition used by Mintz-Hittner and Kuffel [18]. Zone II posterior was defined as a circle whose radius is three times the distance between the center of the optic disc and center of the macula. Meanwhile, the zone of disease was determined based on the most posteriorly located neovascularization, regardless of extension. Two

ophthalmologists identified the zones and stages based on the same criteria as ROP recurrence.

The principle of treatment was applied according to the ET-ROP guidelines, and the method of treatment was independently selected at the discretion of the doctor at each center [16,17]. Infants with any stage of ROP with plus disease in zone I, stage 3 without plus disease in zone I, stage 2 or 3 with plus disease in zone II, or aggressive posterior ROP underwent treatment. Follow-up examinations were performed once or twice a week after the treatment to confirm ROP regression. In case of recurrent ROP, deferred LT was performed after a single IVB and IVB was performed after prompt LT. Recurrence was defined as the reappearance of the plus disease or development of a new demarcation line or above stages. The deferred window period was defined as the period between the first and second treatments. All LT procedures were performed using a diode laser with an 810-nm wavelength instrument under general anesthesia and applied to the avascular retina up to the ora serrata, with half-burn spacing between the laser spots.

IVB was performed under general anesthesia in the operating room. After preparing the eyelids and conjunctiva with 5% povidone iodine, 0.625 mg (0.025 mL) of bevacizumab (Avastin; Genentech Inc.) was intravitreally injected into the 1.5-mm intravitreal cavity in the nasal cavity or temporal limbus. Injection was performed under a surgical microscope using a 30-gauge needle. After the injection, topical antibiotics were administered.

T-tests for independent means, Mann-Whitney rank-sum test, chi-square test, and Fisher exact test were used for statistical analysis with significance ($p < 0.05$). Means and standard deviations are presented as mean (standard deviation).

GraphPad Prism version 6.03. (GraphPad Software, Inc.) was used for data analysis.

Results

1. Demographic characteristics

The single IVB, deferred LT after single IVB, and prompt LT groups included 12, 16, and 12 eyes, respectively (Table 1, Fig. 1). The mean birth weights in the single IVB, deferred LT after single IVB, and prompt LT groups were $1,052.3 \pm 374.5$, 622.2 ± 134.5 , and 822.1 ± 187.2 g, respectively ($p < 0.0001$) (Fig. 2A), and the gestational ages of the patients

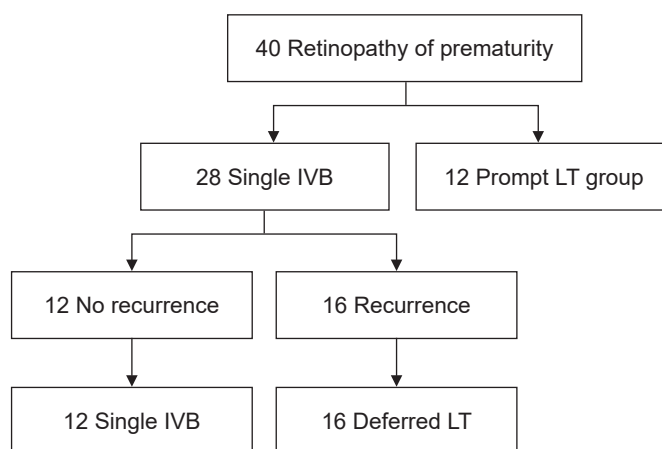


Fig. 1. Classification of patients (40 eyes) who received intravitreal bevacizumab injection (IVB) or laser treatment (LT) as an initial treatment for retinopathy of prematurity. The single IVB, deferred LT after single IVB, and prompt LT groups included 12, 16, and 12 eyes, respectively.

Table 1. Basic characteristics of the single IVB, deferred LT after single IVB, and prompt LT groups

Characteristic	Single IVB	Deferred LT	Prompt LT
No. of eyes (%)	12 (30.0)	16 (40.0)	12 (30.0)
Sex (male:female)	6:6	6:10	9:3
Gestational age (wk), mean \pm SD ^{a)}	27.8 \pm 2.9	24.3 \pm 0.7	25.2 \pm 1.1
Birth weight (g), mean \pm SD ^{a)}	1,052.3 \pm 374.5	622.2 \pm 134.5	822.1 \pm 187.2
Zone			
Zone I	12	6	0
Zone IIp	0	10	4
Zone IIa	0	0	8

IVB, intravitreal bevacizumab injection; LT, laser treatment; SD, standard deviation; Zone IIp, posterior half of zone II; Zone IIa, anterior half of zone II.

^{a)}Significance ($p < 0.0001$), Kruskal-Wallis test.

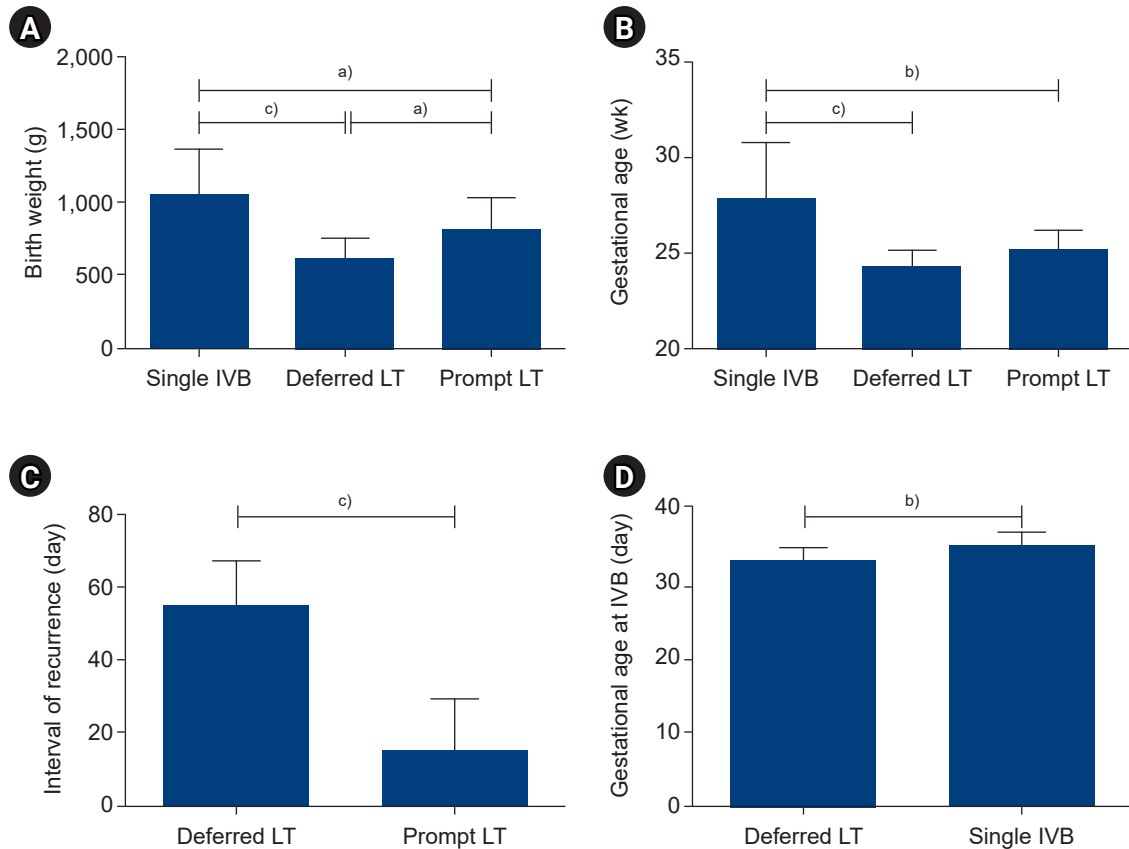


Fig. 2. Comparison of birth weight, gestational age, recurrence intervals, and gestational age at the time of intravitreal bevacizumab injection (IVB) in the single IVB, deferred laser treatment (LT) after single IVB, and prompt LT groups. (A) The mean birth weight was significantly different among the groups, and (B) the gestational ages of the single IVB group was significantly higher than that of the other groups ($p=0.016$). (C) The interval of recurrence between initial treatment and retreatment was significantly longer in the deferred LT after single IVB group than in the prompt LT group ($p=0.0001$). (D) Gestational age at IVB was significantly more in Single IVB than in deferred LT. Significance: ^a $p<0.05$, ^b $p<0.005$, ^c $p<0.0001$, Kruskal-Wallis test.

were 27.8 ± 2.9 , 24.3 ± 0.7 , and 25.2 ± 1.1 weeks, respectively ($p<0.0001$) (Fig. 2B). The single IVB group had a significantly higher gestational age than the deferred LT group. The recurrence interval between the initial and subsequent treatment was 55.0 ± 11.4 days and 17.0 ± 14.4 days in the deferred LT after single IVB and prompt LT groups, respectively, which showed a significant difference ($p=0.0001$) (Fig. 2C). ROP recurrence occurred in 10 of 12 patients in the prompt LT group, and all of them underwent IVB. The timing of IVB was 34.7 ± 0.9 weeks in the single IVB group and 32.3 ± 1.7 weeks in the deferred LT group ($p=0.0483$) (Fig. 2D).

2. ROP stage and zone

All 18 eyes with zone I ROP received a single IVB, and 12 eyes had revascularization of the retina and reached zone III without additional treatment (Table 2). The remaining six patients required deferred LT, and retinal vascularization progressed from zone I to zone IIp during the deferred window period. Zone IIp ROP and IIa ROP were noted in 14 and 8 eyes, respectively. Zone IIp ROP was observed in all 14 eyes. Of these, 10 eyes required deferred LT after IVB, and only prompt LT was performed in four eyes. Ten eyes with zone IIp ROP underwent retinal revascularization to zone IIa during the deferred window period, and retinal vascularization did not proceed until the final examination in four eyes with prompt LT only. All eight eyes with zone

Table 2. Comparison of the initial and final retinal vascularization in retinopathy of prematurity of the single IVB, deferred LT after single IVB, and prompt LT groups

Zone	Single IVB (n=12)		Deferred LT (n=16)		Prompt LT (n=12)	
	Initial exam	Final exam	Initial exam	Final exam	Initial exam	Final exam
Zone I	12	0	6	0	0	0
Zone IIp	0	0	10	6	4	4
Zone IIa	0	0	0	10	8	8
Zone III	0	12	0	0	0	0

IVB, intravitreal bevacizumab injection; LT, laser treatment; Zone IIp, posterior half of zone II; Zone IIa, anterior half of zone II.

IIa ROP underwent prompt LT, and retinal vascularization did not progress until the final examination. The average duration from single IVB until deferred LT was 7.9 ± 1.6 weeks. During this deferred window period, retinal vascularization progressed from zone I to zone IIp and from zone IIp to zone IIa.

In all eyes that received bevacizumab injection, the plus sign regressed within 2 to 6 days. In cases where pupillary stiffness and meningeal vessels were observed, neovascularization regressed within 2 to 3 weeks of the injection.

3. Adverse effects

In 40 eyes, short-term adverse effects of IVB within 2 weeks after injection included intraocular pressure elevation (n=1), subconjunctival hemorrhage (n=4), and retinal hemorrhage (n=1). There were no occurrences of infectious endophthalmitis or retinal detachment during the follow-up period, and no systemic complications were observed based on the opinions of the pediatric doctors. All patients showed fixation reflexes and were able to follow the object during the final vision examination. Only one patient in the IVB with deferred LT group showed exotropia due to macular dragging.

Discussion

This study confirmed that when LT was delayed after a single IVB, vascularization of the immature retina was re-established during this deferred window period and zone I ROP retinal vascularization progressed to zone II and zone IIa ROP to zone IIp. Additionally, deferred LT following a single IVB may minimize the potential systemic side effects of multiple IVBs.

The standard treatment for ROP is LT of the avascular peripheral retina. The ET-ROP trial reported that early LT for

high-risk or pre-threshold diseases resulted in better visual and structural outcomes than conventional LT for threshold disease; thus, LT is recommended for the treatment of type I ROP [2]. However, studies have shown that the more the peripheral retina is destroyed, the higher the risk of myopia changes and visual field defects [3,5,9]. Previous studies have reported that the average refractive error of the peripheral retina at 5 to 7 years after LT is -2.3 to -6.7 diopters (D), higher than that in the control group [13,19-22]. Hwang et al. [5] also reported that the myopic change was more severe in zone I ROP than in zone II ROP and that the mean spherical equivalent values were -10.1 ± 10.5 D and -4.7 ± 4.6 D, respectively. These findings were consistent with those of the BEAT ROP (Bevacizumab Eliminates the Angiogenic Threat of ROP) follow-up study [13]. Geloneck et al. [13] showed that, in addition to the myopic shift, visual fields were better preserved with IVB than with LT since IVB could lead to further growth of the peripheral retinal vessels. Considering the benefits of further growth of the vascularized retina, choosing a treatment method that can further revascularize an immature retina will have a significant impact on the patient's condition in terms of myopic progression and visual field preservation. Additionally, it would be advantageous if the laser could be avoided in zone I when possible. In this study, during the delay period, the location of retinal vascular growth changed from zone I to zone IIp and from zone IIp to zone IIa, avoiding LT in zone I and zone IIp.

Apart from the advantages of IVB, there are concerns regarding the fact that the timing of recurrence after IVB is not constant, the follow-up period is relatively long, and there are systemic side effects. The BEAT ROP study reported that the rates of recurrence of zone I ROP in the IVB and LT groups were 6% and 27%, respectively [4]. Despite the low recurrence rate of IVB, the researchers of the BEAT

ROP study had to wait for up to 20 weeks for relapse, and the intervals between IVB and recurrence in the BEAT ROP study were 19.2 ± 8.6 weeks and 14.4 ± 0.8 weeks in zone I and zone II ROP, respectively. Several case reports have described ROP recurrence after IVB. Hoang et al. [7] and Kong et al. [8] reported that ROP recurred 2 months and 11 months after the initial IVB, respectively. The intervals from initial IVB to recurrence were relatively long and variable, which can be affected by multiple factors, such as the systemic condition of the infant, population origin, and type of anti-VEGF agent used [7,8]. In the present study, the interval of ROP recurrence after initial treatment was significantly longer with IVB than with LT. Owing to the recurrence of such unexpected ROP, long-term follow-up is required, but this is impossible in actual clinical settings. For example, a complete examination of the peripheral retina of a baby aged >50 to 60 weeks may require general anesthesia, and there is no clear protocol for this follow-up.

Interestingly, the recurrence interval in this study was shorter than those reported in other studies. In the case of BEAT ROP, after IVB, zone I ROP is 19.2 ± 8.6 weeks and zone II ROP is 14.4 ± 0.8 weeks [4]. The recurrence interval after IVB injection was 8.8 ± 3.9 weeks in the study of Ling et al. [23] and 9.0 ± 7.1 weeks in the study of Tandon et al. [15]. In the study of Hu et al. [24], it was 14.4 weeks. The interval between recurrences after IVB varies considerably between investigators. Although the reason for this difference is unclear, it is assumed that the criteria for retreatment are slightly different among researchers. In this study, we also found that IVB reduced systemic VEGF in infants for nearly 2 months [10]. In that regard, we believe that vitreous VEGF increases again about 8 weeks after IVB and ROP may recur during this period.

To prevent these problems, several clinicians have suggested a combination therapy of IVB and LT [11,25]. Several studies have shown that LT can interfere with the further growth of the ROP vascularized retina [4,19], and deferred LT rather than prompt LT following initial IVB may increase the risk of the progression of retinal vascularization. Recently, studies on deferred LT after IVB have shown good anatomical results with less myopic shift [14,15]. However, no data were presented on the extent to which retinal vascularization progressed while waiting for deferred LT after IVB. The mean durations between IVB and LT were 9.0 and 8.7 weeks, respectively [14,15]. In this study, the

average duration was 7.9 weeks; during this period, retinal vascularization resumed, developing zone I into zone IIp and zone IIp into zone IIa. Deferred LT was performed when the plus sign recurred or new vessels regressed after a single IVB regrown and reached stage 3 in this study. However, if the drug used for intraocular injection was not bevacizumab, different results would be expected owing to the different vitreous body clearance rates.

If IVB is performed multiple times, it is possible that vascularization of the retina will progress to zone III; however, prior to this, systemic side effects of multiple IVBs must be considered. Several studies have shown that, from day 1, a proportional amount of IVB is absorbed systemically and can decrease VEGF levels in the blood for up to 7–8 weeks [9,10,26,27]. Systemic VEGF plays an important role in angiogenesis and development of various vital organs in infants [28]. Studies on the effects of systemic VEGF inhibitors in mice have shown the loss of fenestration in organs secondary to VEGF suppression, such as the pancreatic islets, thyroid, adrenal cortex, pituitary, villi of the small intestine, kidney, and choroid plexus [29,30]. In particular, patients with zone I ROP that require IVB are more likely to be affected by systemic side effects due to decreased maturity. In this study, infants who received deferred LT following IVB had a lower average gestational age than those who received a single IVB.

Despite these findings, this study had several limitations. First, it was a multicenter, retrospective study, and there were no randomized controls. This can lead to selection bias. The follow-up period was approximately 6 months, which was relatively short. First, the number of children included in this study was small. Additionally, our study did not compare the systemic effects of IVB and LT.

Therefore, deferred LT following a single IVB promoted revascularization of immature retinas during the deferred window period. Moreover, combination therapy may decrease the number of injections required and follow-up visits.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: SJL. Data curation: KYN, JSL. Formal analysis: SJL. Methodology: Ji Eun Lee, Joo Eun Lee, HWK. Project administration: SJL. Supervision: SJL. Validation: SJL. Visualization: KYN, JSL. Writing - original draft: SJL, KYN. Writing - review and editing: Ji Eun Lee, SJL. Approval of final manuscript: all authors.

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Comparison of circuit patency and exchange rates between the original and generic versions of nafamostat mesylate in critically ill adults receiving continuous renal replacement therapy

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Background: Nafamostat mesylate is widely used as an anticoagulant in continuous renal replacement therapy (CRRT). The generic versions of nafamostat mesylate have identical main components to the original product. However, it is questionable whether the generic versions have the same efficacy as the original. Therefore, we compared the circuit patency and exchange rates of the original nafamostat mesylate and a generic version to determine which is more efficient as an anticoagulant in CRRT.

Methods: This retrospective study enrolled 1,255 patients hospitalized to receive CRRT who received the original version of nafamostat mesylate or a generic version between January 2010 and July 2018. We evaluated the filter lifespan, number of filters used per day, mean blood flow, and transmembrane pressure (TMP).

Results: The mean filter lifespan was 36.3±15.1 hours in the original product group and 22.2±16.2 hours in the generic product group, which was not a statistically significant difference ($p=0.060$). The mean TMP was 62.2±47.3 mmHg in the original product group and 74.5±45.6 mmHg in the generic product group ($p=0.045$).

Conclusions: This retrospective study suggests no meaningful difference in filter lifespan between the original and generic versions of nafamostat mesylate. However, TMP was lower in the original product group than in the generic product group.

Keywords: Anticoagulant; Continuous renal replacement therapy; Nafamostat mesylate

Introduction

Continuous renal replacement therapy (CRRT) is an effective kidney replacement treatment in patients with hemodynamically unstable acute kidney injury (AKI) [1]. Over the years, CRRT has become easier and safer to adopt

because of advances in science and technology [2]. One of the advanced techniques is to minimize coagulation of the circuit filter, often through use of anticoagulants. Among them, heparin has been widely used for CRRT [3]. Heparin in CRRT produces some adverse effects, including bleeding events and heparin-induced thrombocytopenia [4]. There-

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fore, several studies have explored other anticoagulants to minimize the risk of bleeding and compared them with heparin (e.g., regional citrate anticoagulation, thrombin antagonists, prostacyclin anticoagulants) [1,3,5-7].

Nafamostat mesylate (6-amino-2-naphthyl p-guanidino-benzoate dimethane sulfonate; Futhan, SK Chemicals) is a prostacyclin analog that inhibits serine proteases. The half-life of nafamostat mesylate is 8 minutes, and it is eliminated quickly from the blood. Therefore, nafamostat mesylate can be used for people at high risk of bleeding [6]. At least one generic version of nafamostat mesylate has been released and is in use. These generic versions have identical main components to those of the original product; however, due to differences in additives and impurities, it is unclear whether they have the same efficacy. In this study, we conducted a comparison of circuit patency and exchange rates between original and generic versions of nafamostat mesylate among AKI patients receiving CRRT.

Methods

Ethical statements: This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. KUGH 2018-10-021). The written informed consent requirement was waived.

1. Patients

We conducted a retrospective study to compare the original nafamostat mesylate with generic versions, focusing on CRRT procedure time. In this single-center, unblinded, non-randomized study, 1,255 patients (aged 18–80 years) hospitalized in the intensive care unit for CRRT who received the original version of nafamostat mesylate or a generic version were enrolled between January 2010 and July 2018 at one of three tertiary hospitals.

2. Criteria

Patients were included in this study if they were diagnosed with AKI, aged 18 to 80 years, and considered by the medical team to require CRRT. All patients met at least one of the following criteria: (1) increase in serum creatinine >1.5 times above baseline; (2) glomerular filtration rate decreased by >25%; or (3) urine volume decreased to <0.5 mL/kg/hr for >6 hours. Patients who met any of the fol-

lowing criteria were excluded: (1) CRRT performed for <24 hours; (2) weight <50 kg or >120 kg; (3) undergoing CRRT due to a non-kidney indication; (4) receiving dialysis under a diagnosis of end-stage renal disease; (5) CRRT started <24 hours after hospitalization.

We excluded patients identified within 24 hours of hospitalization because of the many changes in anticoagulant dosing during this time of CRRT.

3. Clinical data collection

Clinical data on patient demographics, CRRT operating characteristics, and CRRT daily performance were collected at the beginning of the procedure. Laboratory testing, including blood urea nitrogen and creatinine measurements, also was performed at initiation of CRRT.

4. Study outcomes

The primary outcome was filter lifespan and number of filters used per day in AKI patients on CRRT receiving original or generic versions of nafamostat mesylate. The secondary outcome was mean blood flow and transmembrane pressure (TMP).

5. CRRT modality

Patients who received CRRT in this study were treated in continuous venovenous hemodiafiltration mode. We used a Prisma dialysis machine (Gambro), and selected membrane dialyzers were ST100 (acrylonitrile + sodium methallyl sulfonate + polyethylene imine) or M100 (acrylonitrile + sodium methallyl sulfonate). A 12-French dual lumen catheter was used for central vein access and inserted into the internal jugular or femoral vein. Bicarbonate-buffered replacement solutions were used and delivered in post-dilution mode.

The starting dose of nafamostat mesylate was 20 mg/hr, which was adjusted as needed by 20–30 mg/hr to achieve an activated clotting time of 150 to 200 seconds. Filters were exchanged every 48 hours or when they failed due to clotting.

6. Statistics

All variables were analyzed using SPSS for Windows version 23.0 (IBM Corp.). Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequency and percentage (%). A *t*-test

was used for continuous variables, and the chi-square test was used for categorical variables. $p < 0.05$ was considered statistically significant. Continuous variables are summarized as mean \pm SD values.

Results

1. Enrollment

Between January 2010 and July 2018, a total of 1,255 patients received CRRT as defined above. After data collection, 146 patients were excluded from the original product group and 49 patients were excluded from the generic product group. In the final analysis, we included 732 patients in the original product group and 328 patients in the generic product group (Fig. 1).

2. Patient characteristics

The age of patients was 64.1 ± 14.9 years in the original product group compared to 62.5 ± 13.6 years in the generic product group. The proportion of patients with chronic kidney disease was 31.1% in the original product group versus 35% in the generic product group. The most common cause of death was multiple organ failure, which affected 60.1% of patients in the original product group and 52.2% of patients in the generic product group. Acute Physiology and Chronic Health Evaluation III scores were 83.3 ± 34.1

points in the original product group and 82.9 ± 37.1 points in the generic product group. There was no significant difference between product groups according to sex, age, chronic kidney disease, death, or oliguria at baseline.

In terms of CRRT modality, blood flow was 120 ± 25.3 mL/hr in the original product group and 125.0 ± 22.1 mL/hr in the generic product group. The CRRT dose was 32.0 ± 10.2 mL/kg/hr in the original group and 30.0 ± 9.5 mL/kg/hr in the generic group (Table 1).

3. Etiology of AKI

The cause of AKI varied in this study, though the most common was ischemia or shock, affecting 40.1% of patients in the original product group and 51.2% of patients in the generic product group. Other reasons included sepsis, nephrotoxin, rhabdomyolysis, urinary tract obstruction, multiple myeloma, and tumor lysis syndrome. A multifactorial cause was found in 13.8% of cases in the original product group and 8.2% of cases in the generic product group. There was no meaningful difference between the two groups in terms of the etiology of acute renal failure according to anticoagulant used (Table 2).

4. Reasons for starting CRRT

CRRT was initiated due to oliguria or anuria in 45.6% of patients in the original product group and 41% of patients

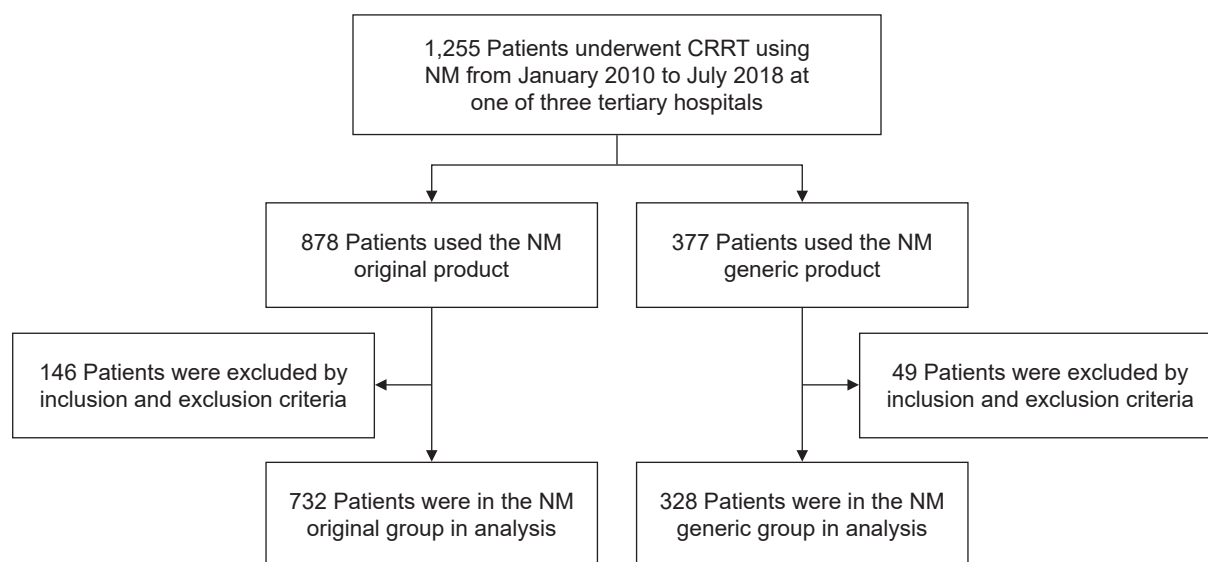


Fig. 1. Flowchart of the assessment of patients' eligibility and enrollment in this study. CRRT, continuous renal replacement therapy; NM, nafamostat mesylate.

Table 1. Characteristics of patients according to anticoagulant choice

Characteristic	NM original group (n=732)	NM generic group (n=328)	p-value
Sex (male/female)	424/308	160/168	0.558
Age (yr), mean±SD	64.1±14.9	62.5±13.6	0.309
CKD (%)	31.1	35.0	0.078
Death (%)	51.3	42.1	0.256
Cause of death (%)			0.416
MOF	60.1	52.2	
Cardiac	22.3	29.6	
Cerebral	6.5	5.0	
Respiratory	7.5	8.5	
Tumor recurrence	3.6	4.7	
Clinical setting (%)			0.732
Medical	72.3	73.2	
Surgical	27.7	26.8	
APACHE III score, mean±SD	83.3±34.1	82.9±37.1	0.823
Oliguria (%)	43.3	42.6	0.647
Mechanical ventilation (%)	58.6	61.3	0.259
Vasoactive drug (%)	55.1	56.3	0.725
Sepsis (%)	39.0	36.0	0.426
CRRT modality			0.636
Mode	CVVHDF	CVVHDF	
Blood flow (mL/hr), mean±SD	120.0±25.3	125.0±22.1	
Dosage (mL/kg/hr), mean±SD	32.0±10.2	30.0±9.5	

NM, nafamostat mesylate; CKD, chronic kidney disease; MOF, multiorgan failure; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal-replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; SD, standard deviation.

Table 2. Anticoagulant choice according to the etiology of acute kidney injury

Etiology	NM original group (n=732)	NM generic group (n=328)	p-value
Sepsis (%)	39.0	36.0	0.534
Ischemia or shock (%)	40.1	51.2	0.534
Nephrotoxin (%)	2.9	1.9	0.534
Rhabdomyolysis (%)	1.5	1.2	0.534
Urinary tract obstruction (%)	1.0	1.3	0.534
Multiple myeloma (%)	1.2	1.0	0.534
Tumor lysis syndrome (%)	0.5	0.2	0.534
Multifactorial cause (%)	13.8	8.2	0.534

NM, nafamostat mesylate.

in the generic product group. Fluid overload occurred in 28.9% of patients in the original product group and 26% of patients in the generic product group. Other, less common reasons included high blood urea nitrogen/creatinine levels, metabolic acidosis, and hyperkalemia (Table 3).

5. Filter characteristics

The mean (SD) filter lifespan was 36.3±15.1 hours in the

original product group compared to 22.2±16.2 hours in the generic product group, with no statistically significant difference. The mean number of filters per day was 0.9±0.6 in the original product group but 1.7±0.7 in the generic product group, also with no statistically significant difference. Finally, the mean TMP was 62.2±47.3 mmHg in the original product group versus 74.5±45.6 mmHg in the generic product group (Table 4).

Table 3. Reasons for starting continuous renal replacement therapy according to anticoagulant choice

Reason	NM original group (n=732)	NM generic group (n=328)	p-value
Oliguria/anuria (%)	45.6	41.1	0.458
High BUN/Cr (%)	11.2	18.2	0.458
Fluid overload (%)	28.9	26.2	0.458
Metabolic acidosis (%)	9.2	7.1	0.458
Hyperkalemia (%)	1.9	4.1	0.458
Others (%)	3.2	4.2	0.458

NM, nafamostat mesylate; BUN/Cr, blood urea nitrogen/creatinine.

Table 4. Filter characteristics during continuous renal replacement therapy according to anticoagulant choice

	NM original group (n=732)	NM generic group (n=328)	p-value
TMP (mmHg)	62.2±47.3	74.5±45.6	0.045
Filter lifespan (hr)	36.3±15.1	22.2±16.2	0.060
Number of filters (/day)	0.9±0.6	1.7±0.7	0.070
Mean blood flow (mL/min)	121.0±60.8	124.5±39.6	0.090

Values are presented as mean±standard deviation.

NM, nafamostat mesylate; TMP, transmembrane pressure.

Discussion

The results of this study showed no significant difference in filter lifetime of the original and generic versions of nafamostat mesylate. However, transmembrane potential (TMP), a parameter indicating intra-circuit obstruction as the pressure gradient on the two sides of the filter membrane, tended to be lower with the original version than with the generic version. An increase in TMP can be secondary to membrane clogging or some other form of clotting along the circuit [8,9]. Although there was no difference in filter lifetime between the formulations, use of the original version of nafamostat mesylate may be advantageous because it has a lower TMP than the generic version. The results of the present study showed no meaningful difference between the two groups in terms of patient characteristics, etiology of AKI, or reason for CRRT.

Nafamostat mesylate is a synthetic serine protease inhibitor that inhibits coagulation factors and platelet aggregation. Thus, nafamostat mesylate has been used as an anticoagulant in CRRT [6]. In Korea and Japan, when CRRT is performed in patients with a tendency to bleed significantly, anticoagulation is often performed using nafamostat mesylate. Therefore, several generic versions of nafamostat mesylate have been released, and research on each product has become necessary as the range of choices has

increased. In this study, we compared the circuit patency and exchange rates of the original nafamostat mesylate and a generic version to conclude which is more efficient as an anticoagulant in CRRT.

Although there was no meaningful difference in filter life between the two groups in this study, other such research has been published. In one study, the continuous hemodiafiltration run time of the generic product group was significantly shorter than that of the original product group (retrospective, n=24: generic 22.8±12.8 vs. original 36.3±10.3, $p<0.01$; prospective, n=7: generic 17.4±10.1 vs. original 32.3±13.3, $p<0.01$). Niwa et al. [10] used high-speed liquid chromatography to analyze the subcomponents in the original and a generic version of nafamostat mesylate. While about 0.2% of the original product comprised additives, that composition of the generic product was significantly higher at 0.3% to 0.5%, and unknown additives not detected in the original product were detected in the generic version. Such difference in additives could affect the filter lifespan. Even in the present study, the difference in filter lifespan with the original versus generic version may be due to variation in additives [10].

In this study, the mean filter lifespan was shortened to <24 hours in the generic product group. In general, dialysis filters used in CRRT in intensive care unit patients should be used for ≥1 day [2,11]. However, the use of generic

products that can cause intra-circuit obstruction within 24 hours should be decided in consideration of clinical situations.

Our study had several limitations. First, because this was a retrospective study, it is difficult to determine the cause-and-effect relationship. Second, although the difference was not statistically significant, it is necessary to analyze the mixtures of the original product and the generic product and conduct a prospective study in the future to confirm the filter lifespan in both groups. Third, it is necessary to assess platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen level in such patients. It is also necessary to check and compare the presence or absence of anticoagulation or antiplatelet drugs because it could affect circuit coagulation.

In conclusion, this retrospective study suggests no meaningful difference in filter lifespan between the original and generic versions of nafamostat mesylate. However, TMP was lower in the original product group than in the generic product group.

Article information

Conflicts of interest

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

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Author contributions

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Comparison of the prevalence and histology between primary benign bladder tumors and recurrent benign lesions after transurethral resection of malignant bladder tumors

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Background: Benign bladder tumors are rare disease entities, and insufficient studies have assessed their epidemiological characteristics. The authors investigated the prevalence of benign bladder tumors by retrospectively investigating pathology reports of transurethral resection of bladder tumor (TURBT) procedures over the past 20 years.

Methods: We analyzed 1,674 pathology reports of TURBT conducted in 1,160 patients from January 1, 2000, to April 30, 2022. The prevalence of benign tumors and histological classification according to the presence of primary (group 1) and recurrent (group 2) bladder lesions were retrospectively investigated.

Results: The mean age of patients was 65.2±11.5 years, and 1,284 cases (79.1%) were in men. Benign bladder tumors comprised 278 cases (248 patients) accounting for about 17.1% of the total TURBT cases (278/1,624). Furthermore, 184 patients (16.0%, 184/1,147) belonged to group 1 and 78 patients (27.4%, 78/285) belonged to group 2. Among all benign lesions that underwent TURBT, cystitis was the most common (41.0%, 114/278), and this rate was higher in group 2 (64/184 [34.8%] vs. 50/94 [53.2%], $p<0.001$). The prevalence of non-neoplastic lesions was higher in group 1 (44/184 [23.9%] vs. 11/94 [11.7%], $p<0.001$). There was no difference in the prevalence of noninvasive urothelial neoplasms between the two groups (22/184 [12.0%] vs. 8/94 [8.5%], $p=0.86$).

Conclusions: The probability of benign lesions in TURBT was 17.1%, among which cystitis was the most common. When TURBT was performed for recurrent lesions, the frequency of benign tumors was higher than that of primary benign bladder tumors.

Keywords: Prevalence; Transurethral resection of bladder; Urinary bladder neoplasms

Introduction

Benign bladder tumors are a rare disease entity [1,2]. Their types are diverse ranging from non-neoplastic lesions, such as Brunner's nest and inverted papilloma, to inflammatory

lesions, such as cystitis cystica and cystitis glandularis [3,4].

In some cases, a tumor is found to be benign after transurethral resection of bladder tumor (TURBT) is performed to remove tumors in relation to a papillary tumor or a granular lesion found on cystoscopy; in other cases, a tumor is

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found to be benign on an active biopsy performed when the tumor is thought to be a recurrent malignant tumor or an ambiguous lesion is found during regular follow-up with cystoscopy after bladder cancer surgery. As there is inadequate data on their incidence and frequent histological types, urologists actively perform TURBT for tissue confirmation. However, aggressive TURBT for all lesions suspected of recurrent bladder cancer may lead to over-treatment. Recently, the feasibility of active surveillance has increased due to the postponement of elective surgery and restricted access to hospitals caused by the coronavirus disease 2019 (COVID-19) pandemic [5]. In a study of the Bladder Cancer Italian Active Surveillance (BIAS) group, about one-third cases of lesions were diagnosed as benign lesions after TURBT, which progressed during active surveillance of low-grade-like bladder tumor, it could be seen that, in the case of low-risk appearance bladder lesion, the frequency of benign tumors is not low [6]. Therefore, the authors investigated the frequency and histological types of benign tumors by retrospectively comparing primary and recurrent benign bladder tumors diagnosed during the follow-up of primary benign bladder tumors and bladder cancers.

Methods

Ethical statements: This study was approved by the Institutional Review Board of the Kosin University Gospel Hospital (IRB No. KUGH 2022-08-030). The informed consent was waived because this design is a retrospective study.

Among a total of 1,624 cases in which 1,160 patients underwent TURBT from January 2000 to April 2022, the medical records of 1,624 cases and 1,140 patients were retrospectively investigated, after excluding 50 cases in which a second TURBT was performed for residual tumors in patients found to have a malignant tumor and repeat TURBT was performed for the purpose of identifying residual tumors after TURBT in another hospital. The basic principle of TURBT was removal of all possible visible lesions including the muscle layer. In the case of non-muscle invasive bladder cancer, cystoscopy was conducted at an interval of 3 months for 2 years and at an interval of 6 months for 5 years after TURBT, and in the case of benign bladder cancer,

although there was no follow-up consensus, cystoscopy was conducted once every 6 months for 2 years [7]. Benign bladder tumors were classified into a total of five groups; non-neoplastic lesions, cystitis, noninvasive urothelial neoplasm, mesenchymal and other tumors, and others based on the World Health Organization (WHO) 2004/2016 classification system [8]. Among them, the cystitis group was classified as a separate group since it includes all types of cystitis, such as polypoid-papillary cystitis and follicular cystitis, and it accounts for a considerable number among the total specimens, although it is not included in urothelial neoplasia. The patient groups were classified into primary bladder tumors (group 1) and recurrent benign bladder tumors found during regular follow-up after TURBT for a malignant or benign tumor (group 2), and the histological characteristics of the two groups were compared using the Student *t*-test. The data were analyzed using SPSS version 27.0 (IBM Corp.). If $p < 0.05$, it was considered statistically significant.

Results

The mean age of all patients was 65.2 ± 11.5 years, and males accounted for 1,284 cases (79.1%). The number of cases diagnosed with a benign bladder tumor was 278 (248 patients), accounting for about 17.1% of all TURBT cases. Among the 278 cases diagnosed with a benign bladder tumor, 184 patients (16.0%, 184/1,147) belonged to group 1 and 78 patients (27.4%, 78/285) belonged to group 2, showing that the percentage of benign bladder tumors was higher in group 2 ($p = 0.021$). The most common pathological outcome was cystitis (41.0%, 114/278). The total number of cases of papillary urothelial neoplasm of low malignant potential (PUNLMP) were 22 in group 1 and eight in group 2, accounting for 12.0% and 8.5%, respectively. PUNLMP was excluded from the incidence of benign tumors since these lesions fall under a borderline by a pathophysiologic taxonomy [8]. Non-neoplastic lesions were detected in 55 cases, noninvasive urothelial neoplasms in 30 cases, mesenchymal and other tissue lesions in nine cases, and others in 70 cases. A total of 55 cases of non-neoplastic lesions comprised 14 cases of Brunner's nest (25.5%), followed by nine cases of cystitis glandularis (16.4%), eight cases of squamous metaplasia (14.5%), and seven cases of urothelial hyperplasia (12.7%). A total of 30 cases of noninvasive urothe-

lial neoplasms comprised 15 cases of inverted papilloma (50.0%), followed by 10 cases of urothelial dysplasia (33.3%) and five cases of urothelial papilloma (16.7%). In the group of others, most tissues were not urothelial tissues, such as prostate tissues, necrotic tissues, and inflammatory tissue, or they could not be classified into the above categories. Except the groups of cystitis and others, the most common form of benign bladder tumor was inverted papilloma (14 cases, 18.7%) in group 1 and Brunn nest (5 cases, 26.3%) in group 2. With respect to the histological characteristics of group 1 and group 2, the incidence of cystitis was higher in group 2 (64/184 [34.8%] vs. 50/94 [53.2%], $p<0.001$) and the incidence of non-neoplastic lesion was higher in group 1 (44/184 [23.9%] vs. 11/94 [11.7%], $p<0.001$). In addition, there was no difference in the incidence of noninvasive urothelial neoplasm between the two groups (22/184 [12.0%] vs. 8/94 [8.5%], $p=0.86$) (Table 1). Among the 285 patients who underwent TURBT on two or more occasions, the number of patients who were diagnosed with a benign bladder tumor on both TURBT procedures was four, the number of patients who were diagnosed with a benign bladder tumor on the first TURBT but were diagnosed with a malignant tumor on surgery later was 16, and the number of patients who were diagnosed with bladder cancer on the first TURBT but were diagnosed with a benign bladder tumor later on surgery was 55.

Discussion

Various types of benign bladder tumors are already known, such as inverted papilloma, Brunn nest, and urothelial papilloma (Fig. 1) [8]. Many reports, such as case reports, focusing on pathological outcomes have documented each histological type in various ways (Fig. 2). However, there is a lack of adequate data on the prevalence of benign tumors found in all bladder tumors. In the present study, the frequency of benign bladder tumors after TURBT was 17.1%, and the incidence was higher in suspicious recurrent lesions than in primary bladder tumors by almost 2-fold (27.4% vs. 16.0%). The most common among all benign tumors in the present study was the cystitis group, which included polypoid-papillary cystitis and follicular cystitis. It may be difficult to distinguish such lesions from many papillary urothelial neoplasms and they account for a large proportion of cases in which TURBT is performed

Table 1. Prevalence of histological types in each group

Variable	Group 1	Group 2	p-value
Non-neoplastic lesions (n=55)			
Urothelial hyperplasia	7	4	
Brunn nest	14	5	
Cystitis cystica	5	2	
Cystitis glandularis	9	0	
Squamous metaplasia	8	0	
Malakoplakia	1	0	
Sum, No. (%)	44 (23.9)	11 (11.7)	<0.001
Cystitis (n=114)			
Acute/chronic cystitis	21	20	
Non-specific cystitis	22	16	
Eosinophilic cystitis	8	5	
Polypoid cystitis	4	3	
Florid proliferative cystitis	3	0	
Follicular cystitis	3	2	
Hemorrhagic cystitis	1	0	
Interstitial cystitis	1	0	
Denuding cystitis	1	0	
Granulomatous cystitis	0	4	
Sum, No. (%)	64 (34.8)	50 (53.2)	<0.001
Noninvasive urothelial neoplasms (n=63)			
Urothelial papilloma	1	4	
Urothelial dysplasia	7	3	
Inverted papilloma	14	1	
PUNLMP	26	7	
Sum, No. (%) ^{a)}	22 (12.0)	8 (8.5)	0.86
Mesenchymal and other tumors (n=9)			
Myofibroblastic lesion	3	0	
Paraganglioma	1	0	
Smooth muscle tumors	1	0	
Neurofibroma	1	0	
Vascular tumors	2	0	
Lymphoma	1	0	
Sum, No. (%)	9 (0.5)	0	-
Others (n=70)			
Sum, No. (%)	45 (24.5)	25 (26.6)	-
Total sum (n=278) ^{a)}	184	94	

Group 1: primary bladder tumors, Group 2: recurrent bladder tumors.

^{a)}Except papillary urothelial neoplasm of low malignant potential (PUNLMP).

and these lesions mimic a bladder tumor. If what a urologist has found on cystoscopy is close to an inflammatory lesion, pathologists should hesitate to diagnose the lesion as urothelial neoplasia [9]. Although it is difficult to histopathologically differentiate PUNLMP, urothelial dysplasia, and urothelial papilloma from each other, since their re-

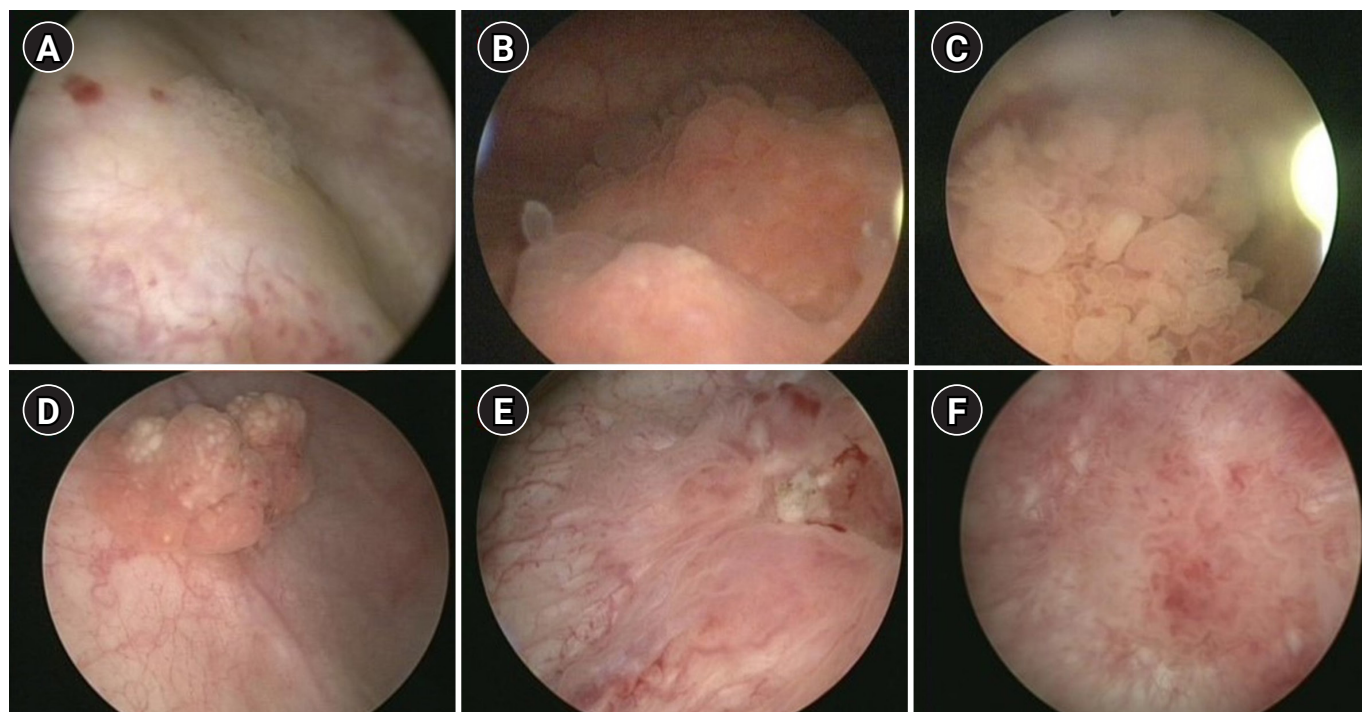


Fig. 1. Various cystoscopic findings of benign bladder tumors. (A) Brunn nest, (B) cystitis glandularis, (C) eosinophilic cystitis, (D) inverted papilloma, (E) urothelial dysplasia, and (E) urothelial hyperplasia.

currence and progression are different from each other, it is important to distinguish these lesions while diagnosing them [10,11]. In the present study, the rate of PUNLMP was reported to be 12.0% in group 1 and 8.5% in group 2. In the present study, PUNLMP was excluded from the investigation of the frequency of benign tumors since PUNLMP has the characteristics of a borderline tumor in light of the fact that Bobjer et al. [12] have reported that PUNLMP has a recurrence rate of 21%, Maxwell et al. [13] have also once reported a long-term recurrence rate of 20%, and Jones and Cheng [14,15] have argued that PUNLMP should be reclassified as low-grade carcinoma because its recurrence rate is high although its progression to invasive carcinoma is extremely rare. When a benign bladder tumor has an aspect of a papillary mass, it can be identified in an imaging study, such as ultrasonography or computed tomography, in which case TURBT is performed after checking the mass on cystoscopy. However, in the case of no visible mass in an imaging study, the cystoscopic finding is usually flat, edematous and inflammatory lesion. Thus, the cystoscopic finding is important to decide whether to perform TURBT or not. It can also depend on the urologist's experience.

The more the TURBT is performed actively, the further the incidence of benign lesions, such as cystitis, may increase, which may lead to unnecessary TURBT procedures causing an increase in the overall medical costs. In the present study, the percentage of cystitis was higher in recurrent lesions than in primary bladder tumors (34.8% vs. 53.2%). It will be possible to reduce unnecessary TURBT procedures when the indications for TURBT are well established in the lesions suspected of showing recurrence. In a study by Hernandez et al. [16], it was decided to perform interventions, such as TURBT, during active surveillance of low-grade bladder carcinoma, if there were tumor-related symptoms, hematuria, progressive suspicious lesions, malignant cells on urine cytology, or an increased number of tumors. With respect to the lesions suspected of showing recurrence, which are found during the follow-up of bladder carcinoma, since cystoscopic findings of recurrence can show discrepancy between urologists and may depend on the experience of the urologist, each urologist may have a different opinion on whether or not it is a case of suspected recurrence. Traditionally, bacillus Calmette-Guerin instillation is known to cause granuloma, but as the surgeon's

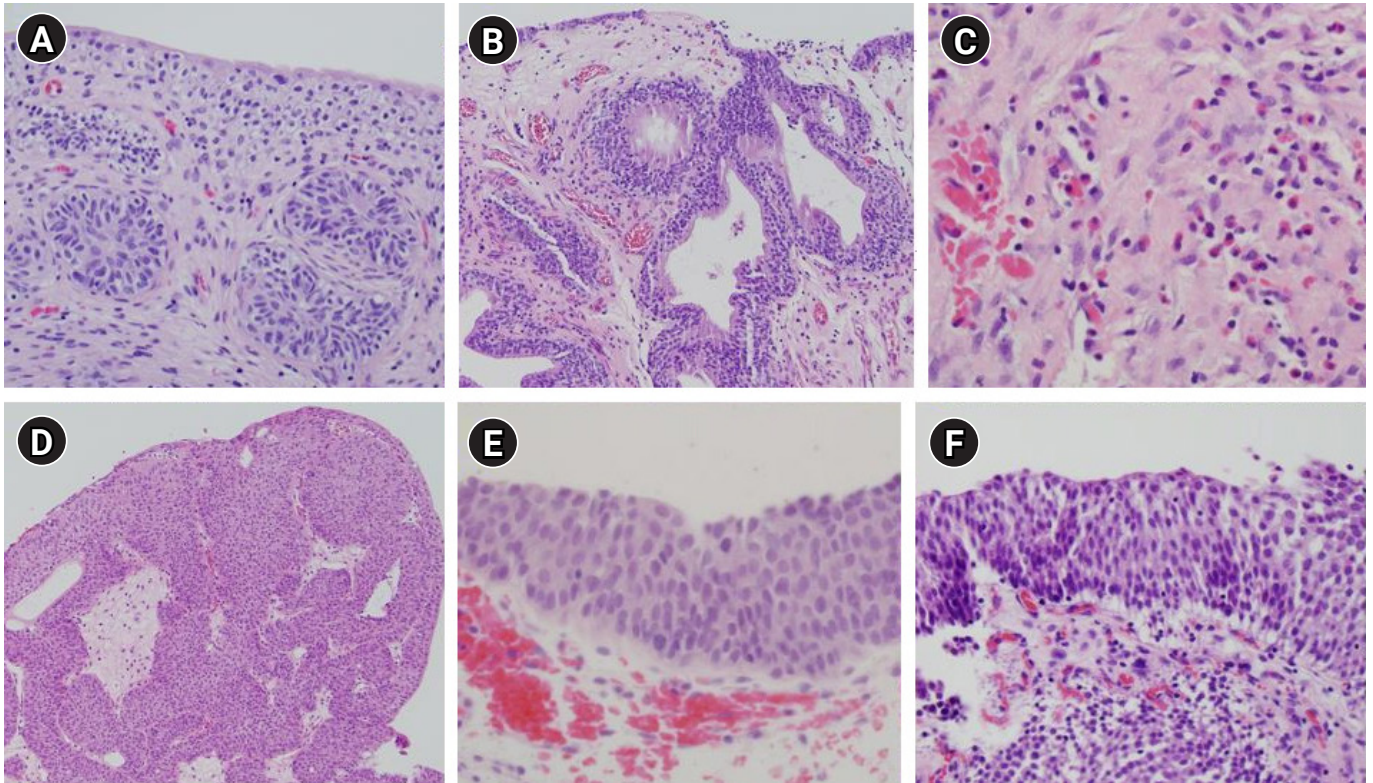


Fig. 2. Various pathologic findings of benign bladder tumors (hematoxylin and eosin stain). (A) Brunn nest ($\times 200$), (B) cystitis glandularis ($\times 100$), (C) eosinophilic cystitis ($\times 200$), (D) inverted papilloma ($\times 100$), (E) urothelial dysplasia ($\times 400$), and (F) urothelial hyperplasia ($\times 200$).

experience increases, it is not analyzed separately because it can be sufficiently distinguished cystoscopically. In the case of a urologist with accumulated experience, active surveillance of suspected lesions may reduce unnecessary TURBT procedures. In addition, if office fulguration is possible in an out-patient clinic, as reported by Soloway [17], it can reduce cumbersome anesthesia, hospitalization, and surgery; in which case, since TURBT for suspected lesions during follow-up can decrease, the frequency of benign bladder tumors that recur during follow-up can also be reduced. The authors have reported that the frequency of benign bladder tumors has increased after the introduction of a high-definition flexible cystoscopy system using narrow-band images. We believe that benign lesions were increased temporarily as suspected lesions could be found more easily because higher resolution images could be viewed using the technique [18]. However, as our experience increased, we have tried to reduce unnecessary TURBT procedures by active surveillance if there is no

change cystoscopically. In the present study, the data of three experienced surgeons were utilized and there was a limitation as standardization was not achieved for each surgeon since there was no agreement on the opinions on a recurrent lesion. However, in the study by the BIAS study group, they reported similar results; a considerable percentage of 32.8% in the case of a short-term follow-up and that 19.2% in the case of a long-term follow-up [6,19]. These results did not show many differences from those in the present study.

In conclusion, the probability of a benign lesion during TURBT surgery was 17.1%, among which cystitis was the most common. In the case of TURBT for recurrent lesions, the frequency of benign tumors was higher than that of primary benign bladder tumors, and the frequency of cystitis was significantly higher than that of primary benign tumors. In primary benign bladder tumors, although the frequency of non-neoplastic lesions was higher, there was no difference in the incidence of noninvasive urothelial

neoplasm between the two groups.

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Development of severe junctional bradycardia after dexmedetomidine infusion in a polypharmacy patient: a case report and literature review

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The authors report a case of newly manifested severe junctional bradycardia following dexmedetomidine administration during spinal anesthesia in a polypharmacy patient. A 77-year-old woman receiving multiple medications, including a beta-blocker and a calcium channel blocker, underwent right total knee arthroplasty. After spinal anesthesia, intravenous dexmedetomidine was initiated as a sedative; her heart rate decreased, followed by junctional bradycardia (heart rate, 37–41 beats/min). Dexmedetomidine was discontinued, and a dopamine infusion was initiated. Seven hours after surgery, junctional bradycardia persisted; a temporary transvenous pacemaker was inserted, and the beta-blocker and calcium channel blocker were discontinued. The patient was discharged on post-operative day 11 without any sequelae. Anesthesiologists should be aware of dexmedetomidine's inhibitory effects on the cardiac conduction system, especially in geriatric patients taking medications with negative chronotropic effects and in combination with neuraxial anesthesia.

Keywords: Anesthesia, spinal; Bradycardia; Case reports; Dexmedetomidine; Polypharmacy

Introduction

Dexmedetomidine, an alpha-2 adrenergic agonist [1], has generally been considered a relatively safe sedative agent, rarely resulting in hypotension and respiratory depression [2]. However, several previous studies have reported that dexmedetomidine has a negative chronotropic effect on the sinoatrial node, leading to severe bradycardia and even sinus pause or arrest [3,4]. Life-threatening bradyarrhyth-

mia is typically related to the co-administration of dexmedetomidine with other drugs rather than dexmedetomidine alone [3,4]. The global increase in aging populations corresponds with the gradual increase in the proportion of surgical patients with multimorbidities and polypharmacy [5]. In this context, it is necessary to consider the patients' pre-operative medication history in selecting the appropriate sedative agents and clinical applications. In this article, we report a case involving a polypharmacy patient with newly

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manifested severe junctional bradycardia following dexmedetomidine administration during spinal anesthesia.

Case

Ethical statements: This case report was approved by the Institutional Review Board of Pusan National University Hospital (IRB No. 2111-008-108). Written informed consent was obtained from the patient.

A 77-year-old woman (153 cm, 60 kg) was admitted for right total knee arthroplasty. The patient was diagnosed with chronic hepatitis C, asthma, hypertension, and intermediate coronary artery occlusive disease (stenosis diameter $\geq 40\%$ but $\leq 70\%$). Preoperative laboratory and chest radiography findings were unremarkable. However, an electrocardiogram (ECG) revealed sinus bradycardia (50 beats/min) (Fig. 1A). Preoperative transthoracic echocardiogram demonstrated normal left ventricular systolic function (ejection fraction 60%), and no evidence of regional wall motion abnormalities. The patient took medicines with furosemide (20 mg/day), bisoprolol (2.5 mg/day), fimasartan (120 mg/day), diltiazem (360 mg/day), isosorbide mononitrate (40 mg/day), rosuvastatin (5 mg/day), rabeprazole (10 mg/day), and umeclidinium bromide/vilanterol inhaler. The cardiologist advised taking all medications immediately before surgery.

The patient's baseline (preoperative) heart rate (HR), oxygen saturation (SpO_2), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were 47–56 beats/min, 96%–98% (room air), 100–140 mmHg, and 70–90 mmHg, respectively.

Vital signs and drugs used during surgery are reported in Fig. 2. For spinal anesthesia, 3 mL of 0.5% bupivacaine hydrochloride in dextrose was injected into the subarachnoid space using a 23-gauge spinal needle at the L3/4 level. After 10 minutes of spinal anesthesia, the sensory blockade level, as determined by cold sense with an alcohol swab, was up to T8; no further increase in the sensory blockade level was observed. Subsequently, ultrasound-guided femoral nerve catheterization was performed (Fig. 2). As per the standard regimen, dexmedetomidine was administered intravenously with a bolus loading dose of 1 $\mu\text{g}/\text{kg}$ for 10 minutes, followed by a maintenance dose of 0.8 $\mu\text{g}/\text{kg}/$

hr for 5 minutes. During the loading dose infusion of dexmedetomidine, a decrease in HR was observed (36 beats/min), and 500 μg of atropine was administered intravenously. The sedation level (Richmond Agitation Sedation Scale, -2; briefly awakens with eye contact to voice) and blood pressure (SBP: 100–107 mmHg, DBP: 50–50 mmHg) remained stable; however, junctional rhythm with hidden p waves was observed, and severe bradycardia (HR, 37–41 beats/min) persisted. Dexmedetomidine was discontinued. Subsequently, as there was no definitive finding of acute myocardial ischemia on electrocardiogram, intravenous dopamine infusion was initiated (5–10 $\mu\text{g}/\text{kg}/\text{min}$). Afterward, during surgery, the patient's vital signs remained stable, except for mild to moderate bradycardia (HR, 42–55 beats/min). At 30 minutes before the end of the operation, severe bradycardia and junctional rhythm (33 beats/min) recurred, and dobutamine infusion (5–10 $\mu\text{g}/\text{kg}/\text{min}$) was administered. However, HR reactivity to dobutamine was not observed, and dobutamine infusion was terminated.

In the recovery room, dopamine infusion and close monitoring continued. The patient's vital signs were as follows: HR, 28–51 beats/min; SpO_2 , 93%–97% (room air); SBP, 111–168 mmHg; DBP, 52–82 mmHg; and respiratory rate, 18–20 breaths/min. Seven hours after administration of spinal anesthetic, the patient was alert and the sensory blockade level dropped below S1, although junctional bradycardia with hidden p waves persisted (Fig. 1B). The levels of cardiac biomarkers were within the normal range. The patient was transferred to an intensive care unit, a cardiologist was consulted, and a transvenous temporary pacemaker via a left femoral vein (VVI mode) was inserted (Fig. 1C and D). Bisoprolol and diltiazem were discontinued. The patient was transferred to the general ward on a postoperative day (POD) 3. The patient's intrinsic sinus rhythm was restored on POD 3 (Fig. 1E), and the temporary pacemaker was removed on POD 4 (Fig. 1F). The patient was discharged on POD 11 without any sequelae.

Discussion

Although dexmedetomidine has been considered to have minimal effects on the circulatory and respiratory systems in clinical settings [2], cases of dexmedetomidine-induced severe bradycardia leading to cardiac arrest have also been reported [3,4]. These fatal complications are particularly

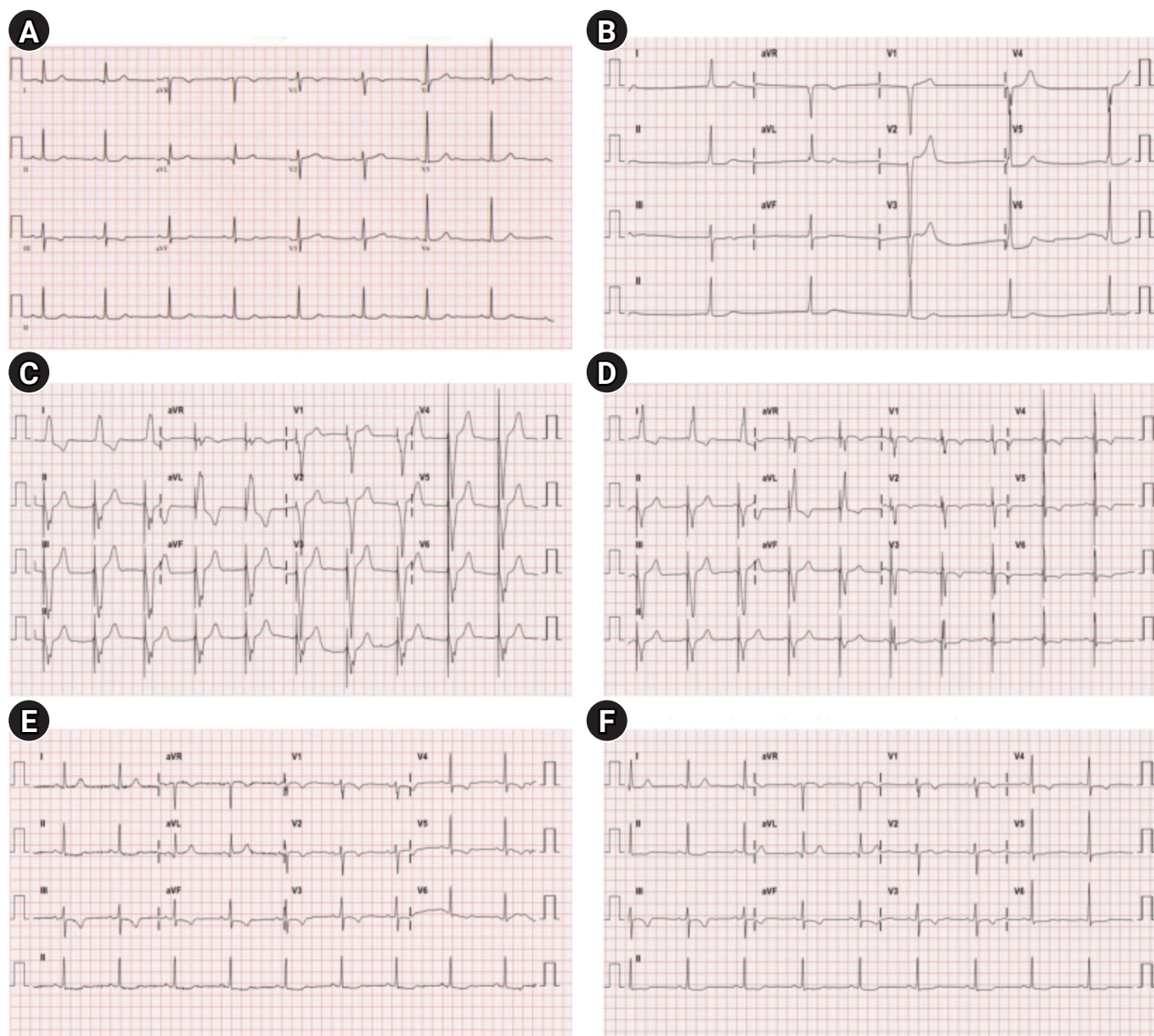


Fig. 1. Electrocardiogram. (A) Pre-operation (HR 50 beats/min). (B) Operative day (HR 30 beats/min). (C) POD 1 (HR 60 beats/min; temporary pacemaker inserted). (D) POD 2 (HR 60 beats/min; temporary pacemaker inserted). (E) POD 3 (HR 55 beats/min; temporary pacemaker inserted). (F) POD 4 (HR 53 beats/min; temporary pacemaker inserted). HR, heart rate; POD, postoperative day.

prone to occur when dexmedetomidine is administered in patients with multiple risk factors [3,4]. In the present case, the presumed risk factors for dexmedetomidine-related bradycardia were combined neuraxial block [6], patient's age [7], and multiple negative chronotropes [3].

Spinal anesthesia can also cause bradycardia, with a reported incidence of 10% to 15%, although, in most patients, significant changes in HR are not observed [8]. The

presumed mechanisms of bradycardia following spinal anesthesia include a block of sympathetic cardioaccelerators arising from T1 to T4 segments and a decrease in venous return and filling pressure [8,9]. In addition, Hong et al. [6] reported that concomitant use of dexmedetomidine as sedation during spinal anesthesia improves postoperative analgesia but increases the risk for bradycardia.

Advanced age is a risk factor for dexmedetomidine-relat-

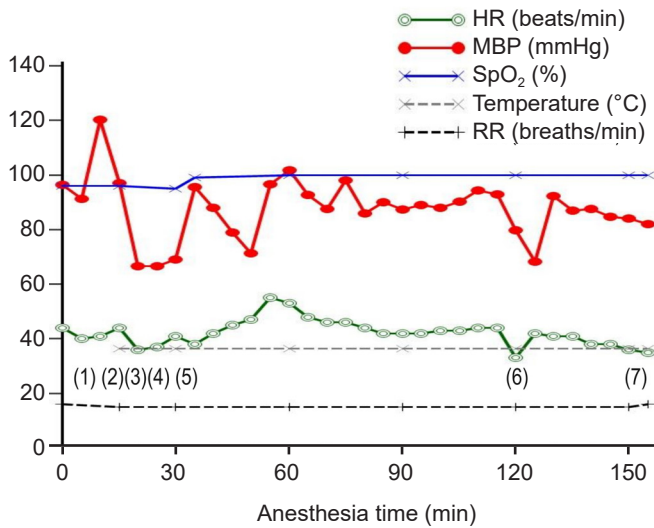


Fig. 2. Vital signs and drugs used during the operation. Drugs and events: (1) spinal anesthesia was performed, (2) femoral nerve catheterization was performed and dexmedetomidine administration was started, (3) atropine (500 μ g, intravenously), (4) junctional rhythm with hidden P waves was observed, (5) dopamine infusion was initiated and dexmedetomidine was discontinued, (6) severe bradycardia and junctional rhythm recurred and a dobutamine infusion was initiated, (7) the dobutamine infusion was terminated. HR, heart rate; MBP, mean blood pressure; SpO₂, oxygen saturation; RR, respiratory rate.

ed bradycardia [7], and many geriatric patients are exposed to polypharmacy. In particular, it has been reported that the prevalence of polypharmacy in hypertension, angina, and congestive heart failure, diseases related to the prescription of negative chronotropes, reached 51%, 42%, and 60%, respectively [5]. These results suggest that, before administering dexmedetomidine to elderly patients, the medication history covering both currently and recently prescribed drugs should be fully considered. In this case, the risk factors for junctional dysrhythmia among the patient's medications are bisoprolol and diltiazem, for which negative chronotropic effects have been reported [10].

The advantages of dexmedetomidine for reducing postoperative delirium, postoperative pain burden, and postoperative nausea and vomiting have been consistently demonstrated in patients who undergo total knee arthroplasty [11,12]; as such, the popularity of dexmedetomidine as a sedative agent is predicted to increase in these population. However, in this case, it was evident that the patient had multiple risk factors for developing cardiac conduction

disorder with dexmedetomidine; the patient was elderly, underwent spinal anesthesia, and took various negative chronotropes. Therefore, it is strongly suspected that there was an additive or synergistic interaction between dexmedetomidine and these risk factors, resulting in cardiac conduction disturbances leading to the junctional rhythm. In this case, the patient was also administered the usual dose of dexmedetomidine for procedural sedation. Unfortunately, there is no consensus on the safe and tolerated dose of dexmedetomidine in the high-risk population [13,14]. However, previous clinical trials have pointed out that aging and regional anesthesia reduce the amount of dexmedetomidine required for sedation [13,14]. In addition, the elimination half-life of dexmedetomidine, reported to be about 2.1–3.1 hours, is markedly prolonged with aging [14,15]. Thus, a reduction of dexmedetomidine administration should be considered in patients at high risk of dexmedetomidine-induced cardiac conduction disorder.

The management guidelines for acute symptomatic junctional dysrhythmia, associated with sinoatrial node dysfunction, are as follows [10,16]: (1) preferentially, 0.5–1.0 mg of atropine is administered as a bolus intravenously, except for patients who have undergone heart transplantation; (2) in case of hemodynamically unstable, acute temporary cardiac pacing should be performed; (3) without definitive findings of acute myocardial ischemia, administration of beta-agonists such as isoproterenol, dopamine, dobutamine, or epinephrine could be considered to increase HR and improve symptoms; or (4) as in this case, when junctional arrhythmia due to calcium channel blocker or beta-blocker overdose is suspected, calcium or glucagon could be additionally considered an antidote.

Compared with previously reported cases, the present case had the following features: the patient was not in critical condition and without substantial functional limitations; no other sedative or analgesic agents other than dexmedetomidine were used concomitantly, and all negative chronotropic agents concomitantly used were daily medications taken before surgery. In this context, the present case is a more general condition and common scenario encountered in the field of anesthesia; however, the incidence of dexmedetomidine-associated severe bradycardia has been considered rare. In this regard, Ohmori et al. [17] suggested that some cases of dexmedetomidine-induced cardiac conduction disorders may have been overlooked.

In summary, we report a case of severe junctional bradycardia in a patient receiving a dexmedetomidine infusion during spinal anesthesia. Close monitoring and effective treatment of this adverse event resulted in complete recovery without complications. Nevertheless, anesthesiologists should pay attention to the inhibitory effects of dexmedetomidine on the cardiac conduction system, especially in the geriatric population and in patients taking medications with negative chronotropic effects and in combination with neuraxial anesthesia.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: SJ, EK, SHL. Data curation: SJ, SHL, SIP. Funding acquisition: EK. Project administration: SJ, EK. Supervision: EK. Visualization: SIP, HSR. Writing - original draft: SJ, SIP, HSR, DL. Writing - review & editing: SJ, EK, DL.

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Bochdalek hernia presenting gastrointestinal symptoms in late childhood: a case report

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Most cases of congenital diaphragmatic hernia (CDH) can be diagnosed based on symptoms of severe respiratory failure during the neonatal period or fetal ultrasonography. However, some rare cases are diagnosed in late childhood or adolescence. In this case report, I describe an 11-year-old male patient diagnosed with late-onset CDH presenting with acute abdominal pain. The patient had recently experienced anorexia, nausea, and vomiting after eating. However, he reported no abdominal pain or past history of trauma. The abdomen was generally convex. All laboratory data were within normal limits. A chest X-ray revealed elevation of the left diaphragm. Chest computed tomography showed a defect in the left diaphragm. Based on the above radiologic findings, emergency surgery was performed after the diagnosis of diaphragmatic hernia. A surgical incision was performed in the left subcostal area. Finally, late-presenting Bochdalek hernia was diagnosed. The operation was completed and no specific findings on chest X-ray were found after surgery. The patient was discharged on the fourth day after surgery. In conclusion, CDH in late childhood or adolescence is rare and has various clinical manifestations. To avoid complications such as strangulation and bowel perforation, emergency surgery may be required. Thus, it is necessary to suspect CDH in children with recurrent gastrointestinal or respiratory symptoms, based on which an accurate diagnosis can be made and successful surgical treatment can be performed.

Keywords: Abdominal pain; Case reports; Congenital diaphragmatic hernias

Introduction

Congenital diaphragmatic hernia (CDH) is caused by malrotation of the pleuroperitoneal membrane during embryogenesis. More than 73% of CDH cases can be diagnosed through the use of fetal ultrasound [1-3]. Among various types of CDH, Bochdalek hernia was first described as a posterior congenital defect of the diaphragm in 1848 by Czechoslovakian anatomist Vincent Alexander Bochdalek

[4]. Most CDH can be diagnosed by confirming symptoms of severe respiratory failure during neonatal period or fetal ultrasound. However, some are diagnosed in late childhood or adolescence, although such cases are rare. The purpose of this study was to report an emergency surgery and subsequent course of a child who was diagnosed with late-onset CDH in a radiologic examination performed for acute abdominal pain.

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Case

Ethical statements: This case report was approved by the Institutional Ethical Committee of the Dong-A University Hospital (approval No. 22-183) and written informed consent was obtained from the parent of the child patient for this report.

An 11-year-old male patient presented with persistent upper abdominal pain that started on the day of admission. After he underwent a radiologic examination at another hospital, he was transferred to the emergency room of the hospital for surgery. Recently, he experienced anorexia, nausea, and vomiting after eating. However, he had no abdominal pain or past history of trauma. The abdomen was generally convex. All laboratory data were within normal limits. In chest X-ray performed at the hospital, elevation of the left diaphragm was found (Fig. 1). A chest computed tomography (CT) performed in another hospital for an accurate diagnosis showed a defect in the left diaphragm with some small and large bowel herniated into thoracic cavity, based on which emergency surgery was performed after diagnosis of diaphragmatic hernia (Fig. 2). A surgical incision was performed in the left subcostal area. Whole small bowel, transverse colon, and omentum were herniated through the defect in the left posterior site of the diaphragm. The color of the small bowel was slightly dark but peristalsis was confirmed. There were no signs of necrosis

or strangulation. The colon was healthy. The oval-shaped diaphragm defect of the 5×3-cm-size was confirmed in the posterolateral area. Hernia sac was not found. Consequently, late-presenting Bochdalek hernia was diagnosed. First, reduction was conducted in the order of small bowel

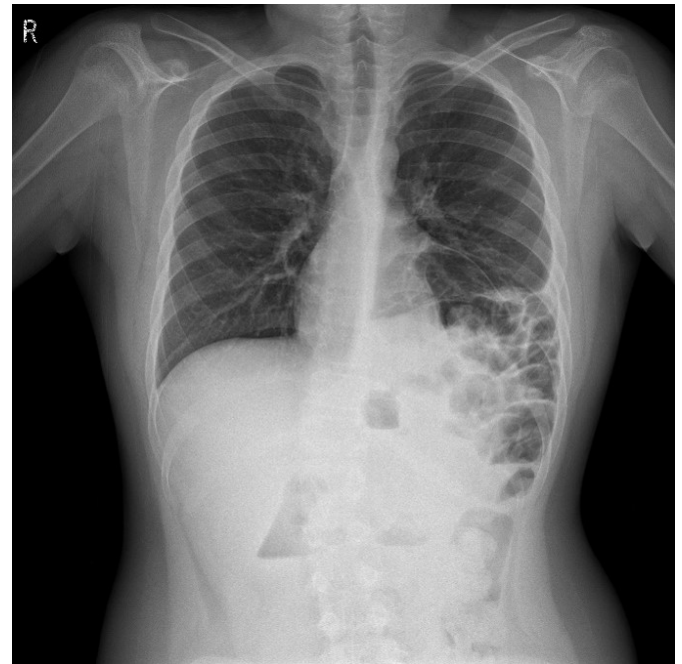


Fig. 1. Initial chest X-ray showing elevation of the left hemidiaphragm and volume reduction of the left lung.

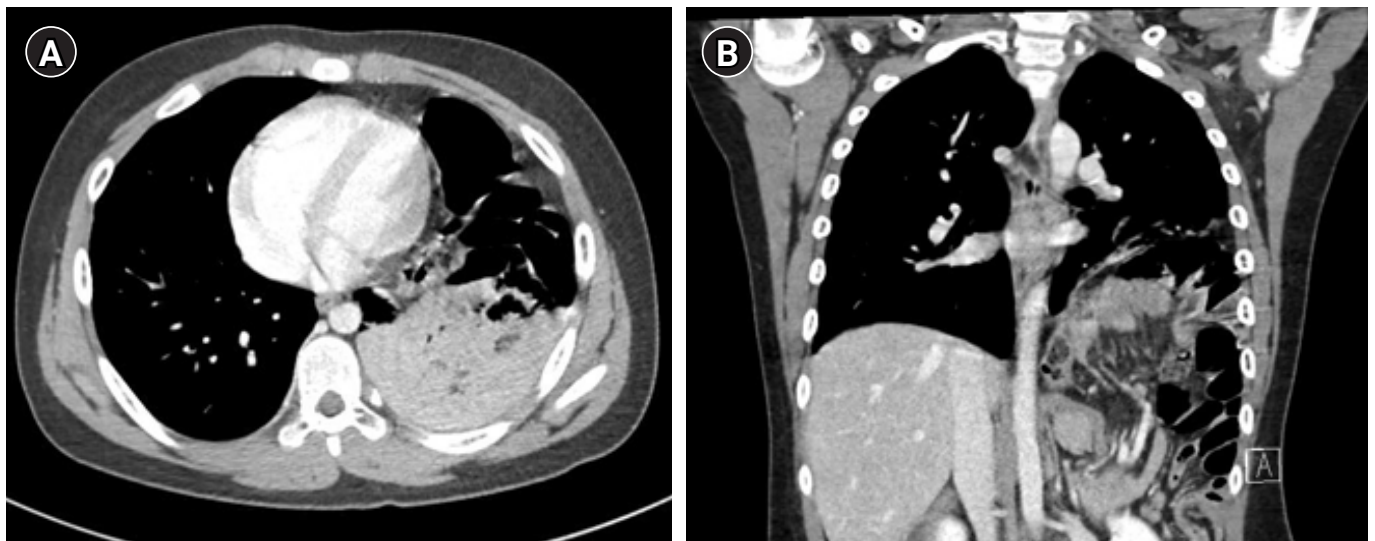


Fig. 2. A chest computed tomography (CT) image revealing a diaphragmatic defect in the left side. (A) Preoperative axial thoracic CT image. (B) Preoperative coronal thoracic CT image.

and colon. Primary repair of a diaphragmatic defect was performed with an interrupted, nonabsorbable suture using black silk 1-0. The operation was completed without placing the chest tube. No specific findings on chest X-ray were found after surgery (Fig. 3). The patient was discharged on the 4th day after surgery. He was clinically followed up for a year without signs of recurrence.

Discussion

CDH is a rare disease with an incidence of between 1 in 2,000 and 1 in 4,000 live births [5]. The most common type of CDH is a Bochdalek hernia and other types include Morgagni hernia, diaphragm eventration, etc. The majority of this disease is diagnosed within a few hours after birth and

5% to 25% of cases are found even after the neonatal period [6]. But, most cases of Morgagni hernia are diagnosed incidentally in childhood and it can present with acute chest symptoms or can be asymptomatic. Symptoms of a diaphragmatic hernia can include emesis, nausea, abdominal pain, chest pain, dyspnea, wheezing, cough, and absent breath sound [7]. It has been reported that respiratory symptoms are more common in younger patients, while gastrointestinal symptoms are more common in older patients [8]. Delayed presentation of CDH in late childhood or adolescence, in this case, may be confirmed late. As a result, patient's condition might deteriorate.

Haines and Collins [9] have also reported that chest X-rays of asymptomatic diaphragmatic hernia patients are interpreted as left pleural effusion. Hegarty et al. [10] have incorrectly diagnosed a diaphragmatic hernia as pneumothorax, resulting in two cases undergoing thoracentesis. Common misdiagnoses of diaphragmatic hernia include pneumothorax, pneumonia, pleural effusion, infectious etiology, and cystic malformation [11]. Although chest X-rays can be somewhat negative for an initial accurate diagnosis, it can be utilized most commonly for the diagnosis of diaphragmatic hernia [12]. Regarding patients with a diaphragmatic hernia, chest X-rays can also detect bowel gas patterns, air-fluid levels, or cardiac and mediastinal deviations, and lucency within the thoracic cavity, which may complicate or obscure the diagnosis [13]. A thoracic-abdominal contrast CT scan is specific for the diagnosis of diaphragmatic hernia. Currently, routinely using thin-section CT scanning can more accurately predict the prevalence and characteristics of late-presenting Bochdalek hernia. Mullins et al. [14] have reported that 0.17% of a large patient population is diagnosed with incidental Bochdalek hernia through an abdominal CT review. Although CDH is usually asymptomatic for a late-presenting type, immediate surgical treatment should be performed when its diagnosed to prevent complications such as strangulation and bowel perforation. By doing this, potentially fatal consequences in the future can be avoided. If late-presenting CDH can be accurately diagnosed, an excellent survival rate of about 97% to 100% can be ensured compared with neonatal CDH [13].

Late-onset CDH can be operated by approaching the chest or abdomen. Surgery consists of repositioning abdominal contents into the abdominal cavity and closing the

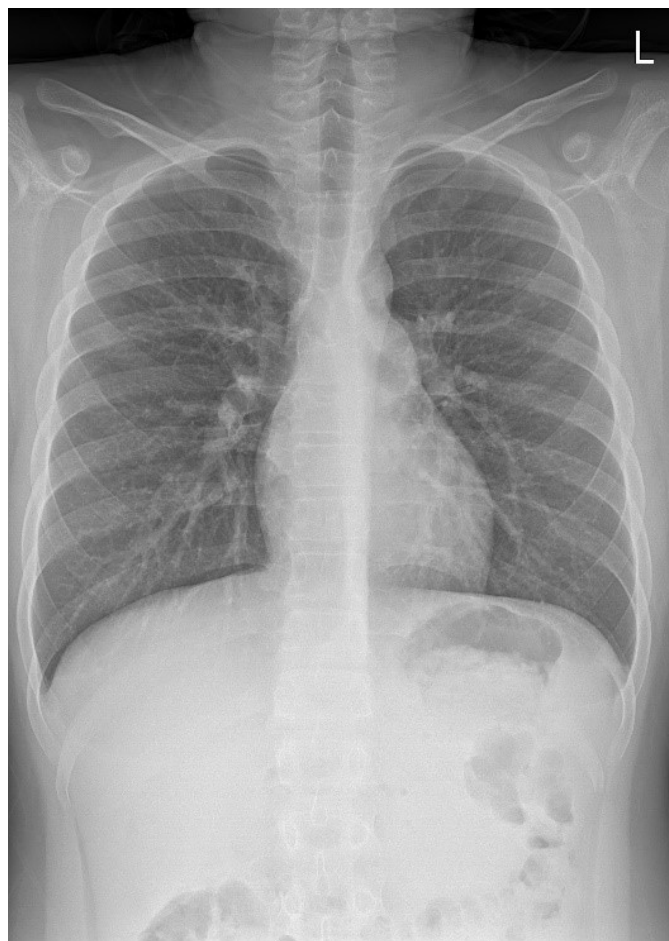


Fig. 3. Postoperative chest X-ray after congenital diaphragmatic hernia repair shows a clean contour of the diaphragm and normal parenchyma of the lung.

diaphragmatic defect. The traditional abdominal approach is often preferred. However, the evidence that the chest approach is not inferior to the abdominal approach in terms of efficiency has been growing [15]. Complications of CDH surgery in older children tend to occur more frequently in the gastrointestinal tract because of associated bowel malrotation and inadequate bowel fixation.

In conclusion, CDH in late childhood or adolescence is observed to be rare. Its clinical manifestations can appear in various symptoms. To avoid complications such as strangulation and bowel perforation in many patients, emergency surgery may be required. Thus, it is necessary to suspect CDH considering children with recurrent gastrointestinal or respiratory symptoms, based on which, accurate diagnosis and successful surgical treatment can be performed.

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Conflicts of interest

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Author contributions

All the work was done by SSJ.

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A case report of successfully treated metachronous gastrointestinal stromal tumor and colon cancer

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The diagnosis of gastrointestinal stromal tumor (GIST) has become relatively common in recent years, but little is known about its association with other malignancies. We present a rare case of successfully treated metachronous GIST and colon cancer with concurrent FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) chemotherapy and imatinib. A 63-year-old man presented with abdominal pain that had started 2 weeks ago, and endoscopic ultrasonography showed masses that were compatible with GIST on the duodenum. He underwent Whipple surgery. One year after the GIST diagnosis, two liver masses were found on abdominal computed tomography images taken for surveillance. A liver biopsy showed metastatic adenocarcinoma, not GIST. Colonoscopy was then performed to identify the primary site of the metastatic adenocarcinoma in the liver, and sigmoid colon cancer was found. He received 12 cycles of adjuvant FOLFOX concurrently with adjuvant imatinib. There were no serious adverse events of grade 3 or higher from either imatinib or chemotherapy. He has completed adjuvant imatinib and FOLFOX chemotherapy and there is no evidence of disease recurrence. When a synchronous or metachronous tumor is found in a GIST patient, the clinician should keep in mind the possibility of another primary tumor of different histopathology, as well as GIST recurrence.

Keywords: Adenocarcinoma; Case reports; Colonic neoplasms; Gastrointestinal stromal tumors

Introduction

Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal tract malignancy of mesenchymal origin. Most studies of GIST have reported that the worldwide incidence of GIST is approximately 10 to 15 cases per million people annually [1]. However, while it has been diagnosed relatively commonly in recent years, little is known about the association between GIST and other malignancies. Only a few cases have been reported of the synchronous or metachronous existence of GIST with other malignancies. And there are no treatment guidelines for both diseases

simultaneously. Herein, we report a rare case of metachronous GIST and colon cancer in which adjuvant FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) chemotherapy was concurrently administered with imatinib.

Case

Ethical statements: This report was exempted from review by the Institutional Review Board (IRB) of Busan Paik Hospital (IRB No. 2021-11-074). Written informed consent was obtained from the patients to participate in the study.

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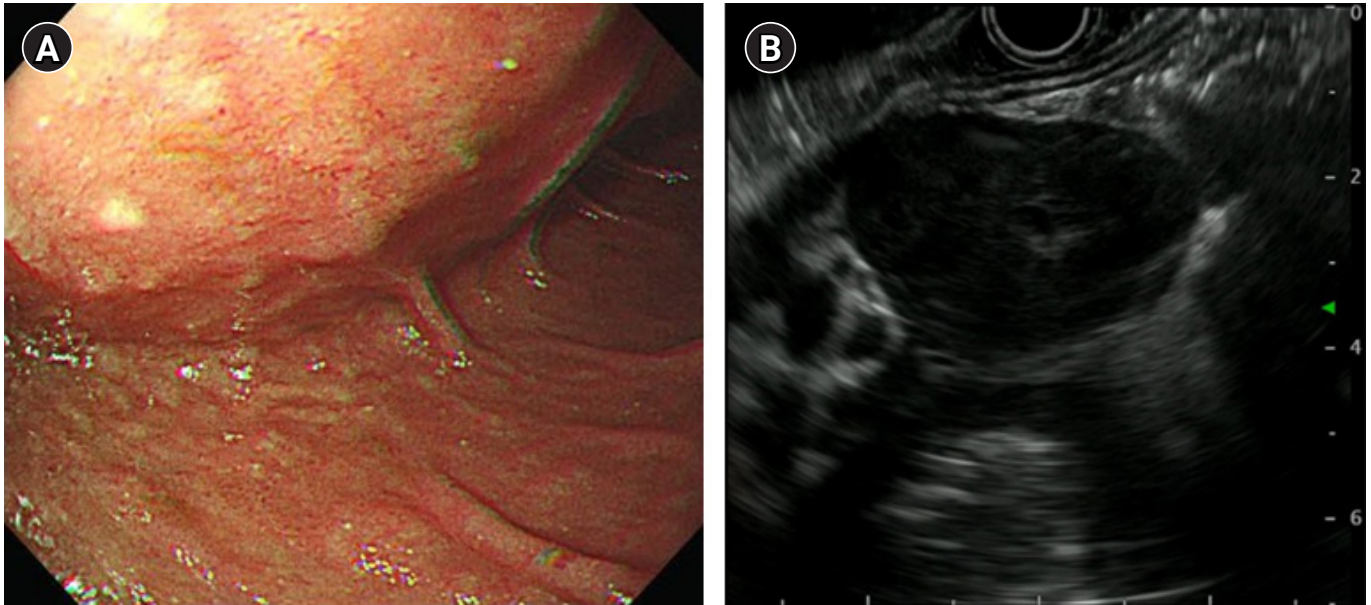


Fig. 1. Endoscopic and endoscopic ultrasonographic findings of gastrointestinal stromal tumor. (A) Bulging at the duodenal second portion and (B) an inhomogeneous hypoechoic oval mass with regular margins and a largest diameter of 42 mm.

A 63-year-old man presented with abdominal pain that started 2 weeks ago. The results of a physical examination were unremarkable. His vital signs were stable with blood pressure 110/70 mmHg, heart rate 77 beats/min, respiratory rate 16 breaths/min, and body temperature 36.3 °C. There were no laboratory abnormalities other than anemia with hemoglobin of 12.1 g/dL. There was a large extrinsic compression at the duodenum in endoscopy and a hypoechoic oval mass which is originated from the muscularis propria and is focally connected with serosa in endoscopic ultrasonography (Fig. 1). Endoscopic results were compatible with GIST. Computed tomography (CT) images showed marked circumferential wall thickening with dilatation of second and third portion of duodenum (Fig. 2). Neither metastasis nor other abnormal findings were observed on CT. He underwent Whipple surgery. The surgical specimen showed three masses and the largest was 9.0 cm. All were pathologically confirmed as GIST, and they showed 2 mitoses per 50 high-power fields. c-receptor tyrosine kinase (*KIT*) and cluster of differentiation 34 immunohistochemistry results were positive (Fig. 3). The patient started to take 400 mg of adjuvant imatinib mesylate daily for 3 years because he was a high-risk patient of GIST recurrence according to the revised National Institutes of Health risk criteria.



Fig. 2. Computed tomographic findings of gastrointestinal stromal tumor. There was circumferential wall thickening with aneurysmal dilatation of the second and third portions of the duodenum (arrow). There was no bowel obstruction or organ invasion by the mass.

One year after the GIST diagnosis, two liver masses, 2.4 cm and 0.6 cm in size, were detected in an abdominal CT scan taken for surveillance (Fig. 4). Liver biopsy was performed to differentiate recurrence of GIST. However, the result of liver biopsy showed metastatic adenocarcinoma, not GIST. Colonoscopy was performed to identify the pri-

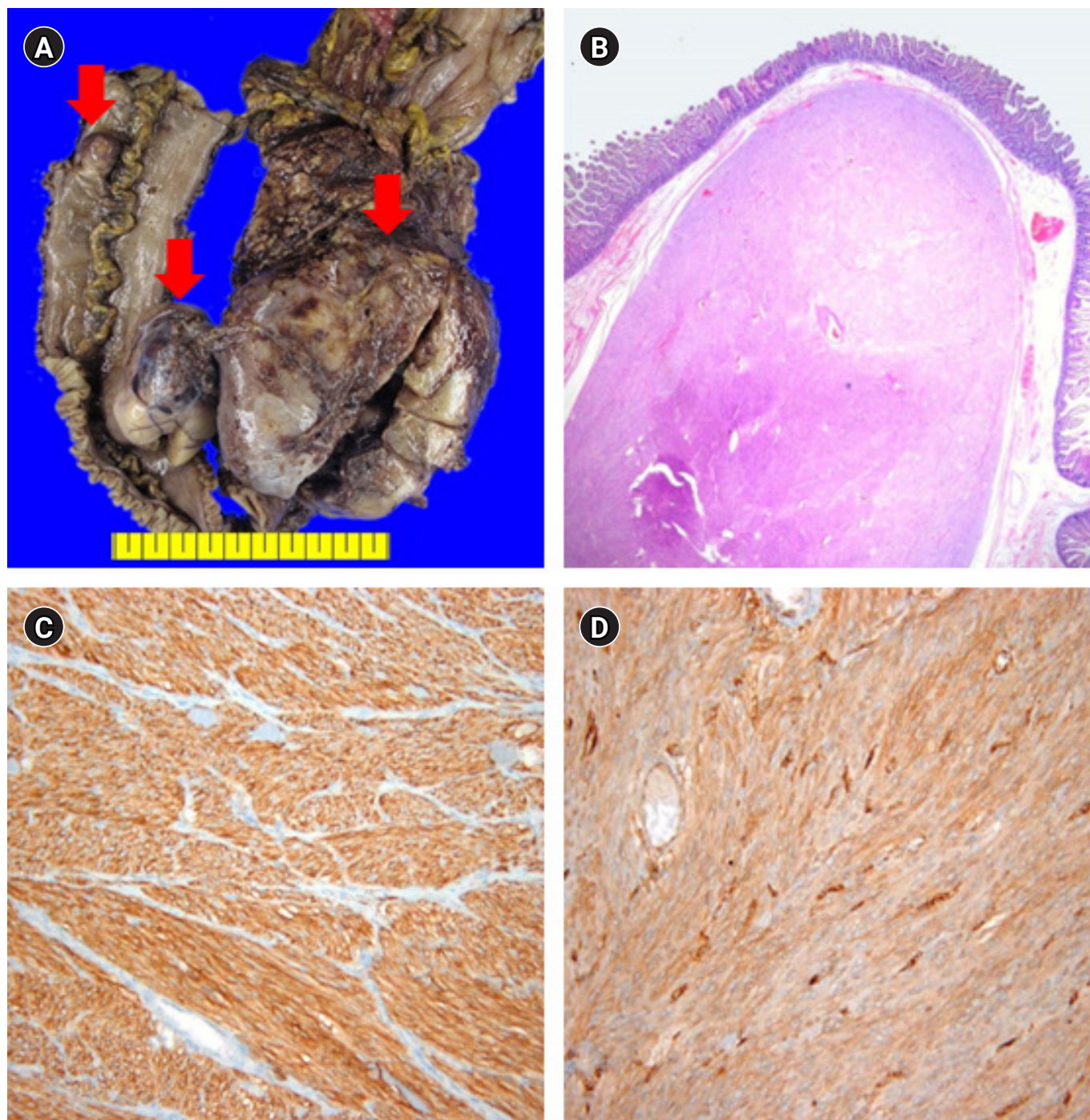


Fig. 3. Gross and microscopic findings of the surgically resected gastrointestinal stromal tumor specimen. (A) Three exophytic oval masses (arrows). (B) A well-defined submucosal tumor (hematoxylin and eosin staining, $\times 40$). The immunohistochemical staining results were positive for CD117 (C) and positive for CD34 (D) ($\times 100$). CD, cluster of differentiation.

mary site of the metastatic adenocarcinoma of liver, and sigmoid colon cancer was found (Fig. 5). The patient then underwent low anterior resection and liver wedge resec-

tion. Pathologic results showed moderately differentiated adenocarcinoma with four out of 22 positive lymph nodes. The colon cancer was stage IVA according to the seventh

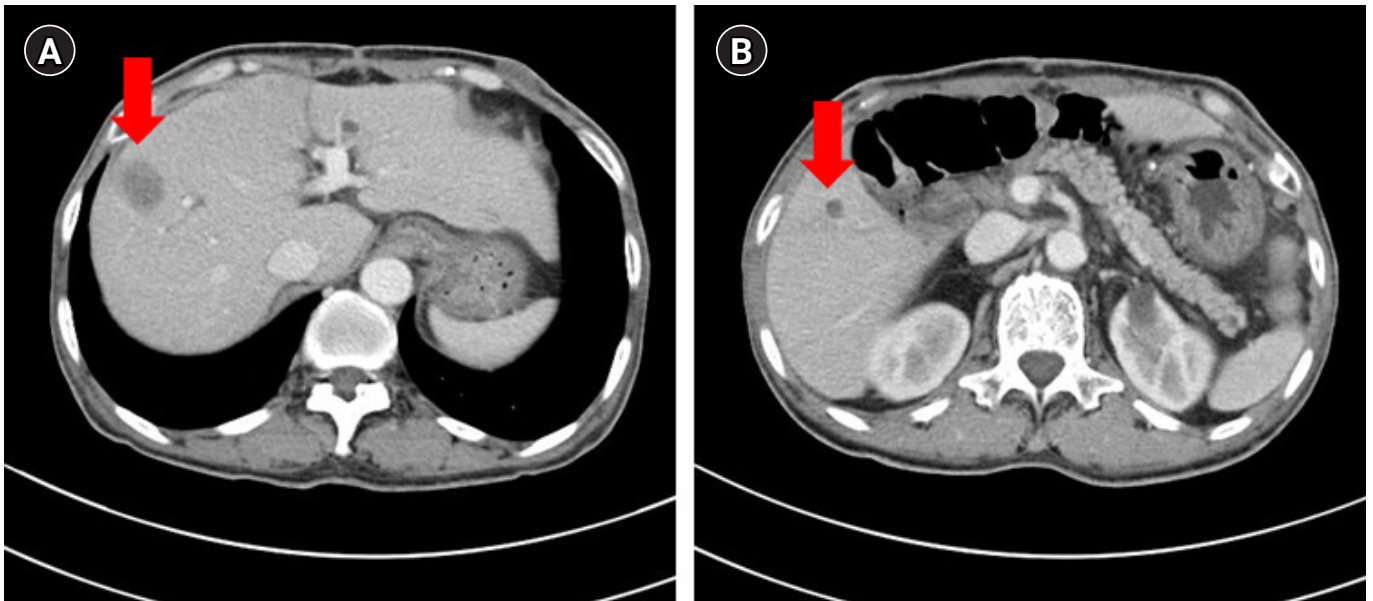


Fig. 4. Computed tomographic findings of two liver metastases (arrow). (A) A 2.4-cm metastatic mass at liver segment 8. (B) An 0.6-cm metastatic nodule at liver segment 5.

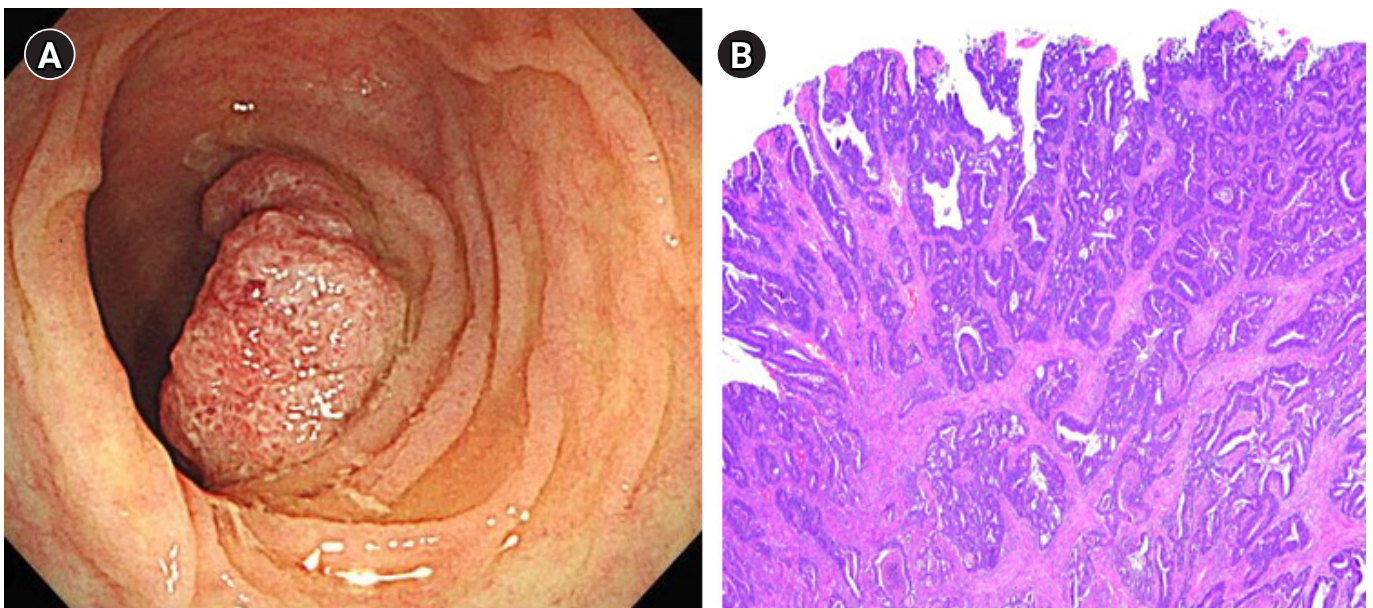


Fig. 5. Colonoscopic findings of colon cancer. (A) A large fungating mass at the sigmoid colon. (B) Microscopic findings of moderately differentiated colon adenocarcinoma (hematoxylin and eosin staining, $\times 40$).

edition of the American Joint Committee on Cancer Staging. He received 12 cycles of adjuvant FOLFOX chemotherapy (comprising an oxaliplatin 85 mg/m^2 ; folinic acid 400 mg/m^2 ; fluorouracil 400 mg/m^2 followed by a continuous infusion of fluorouracil $2,400 \text{ mg/m}^2$) concurrently with

adjuvant imatinib. He experienced grade 2 neutropenia and peripheral neuropathy. There were no unexpected side effects from either imatinib or chemotherapy. He has completed adjuvant imatinib and FOLFOX chemotherapy and there is no evidence of disease recurrence for 4 years.

Discussion

GIST is believed to arise from interstitial cells of Cajal present in the muscular layer of the gastrointestinal wall. It may occur anywhere in the digestive tract. The most common site of origin is the stomach (55.6%) followed by the small bowel (31.8%), colorectum (6.0%), and esophagus (0.7%) [1]. In addition to the gastrointestinal tract, it can also arise from the omentum, mesentery, and retroperitoneum. Although the incidence of GIST is increasing, little is known about the association between GIST and other malignancies [2]. Recently, many studies have reported data showing occurrence of other malignancies in patients with GIST [3-5]. The most commonly involved are stomach and colorectal malignancies [6-10]. These studies have reported an incidence of synchronous or metachronous gastrointestinal malignancy in patients with GIST up to about 30%. In addition to gastrointestinal malignancies, other tumors have been reported, such as renal cell carcinoma, uterine sarcoma, breast cancer, seminoma, and chronic myeloid leukemia [7,11]. Although there is no proven evidence of a common carcinogenic pathway between GIST and other malignancies, it is necessary to consider the possibility of the existence of another malignancy in patients with GIST. In our case, if liver metastasis on CT scan was mistakenly considered to be the GIST origin, and liver biopsy was not performed, we would have missed the diagnosis of colon cancer. Therefore, it is important to recognize that malignant lesions found during surveillance after GIST operation may not be GIST recurrence, but may be another malignant tumor with a different histopathology.

There are no prospective studies to investigate the optimal follow-up schedules and methods for resected GIST and the recommendations for surveillance vary in guidelines. The National Comprehensive Cancer Network guidelines recommend radiologic surveillance using abdominopelvic CT every 3 to 6 months for 3 to 5 years and then annually thereafter for completely resected primary GIST. The European Society for Medical Oncology guidelines also acknowledge that the optimal follow-up schedule is not known. Risk assessment based on the tumor size, tumor site, and mitotic count may be helpful in deciding the routine follow-up strategies [12]. In our case, the patient took a follow-up abdominopelvic CT scans every 3 months because he was at high risk of recurrence.

GIST was considered to be refractory to conventional chemotherapy or radiotherapy, and the prognosis was very poor until the 2000s. Over the last two decades, the molecular biology of GIST development has been revealed and its treatment has been markedly improved. Most GIST cases (approximately 80%–85%) are associated with mutations in the *KIT* gene. Platelet-derived growth factor receptor (*PDGFR*) mutation is an alternative oncogenic driver of GIST [13]. *KIT* or *PDGFR* mutations activate signaling pathways related to cell proliferation and apoptosis. Since mutations in these two genes are not present in all cases of GIST, it is believed that there may be mutations in other genes including rat sarcoma virus (*RAS*), succinate dehydrogenase (*SDH*), or rapidly accelerated fibrosarcoma (*RAF*). Imatinib, a tyrosine kinase inhibitor of *KIT*, has been approved for the treatment unresectable or metastatic GIST. It has also shown clinical benefit in the adjuvant setting. Imatinib is recommended for at least 3 years in patients with a high risk of recurrence after surgery [14,15].

In our case, the patient needed to receive adjuvant FOLFOX chemotherapy for colon cancer while he was taking adjuvant imatinib for GIST. We decided to administer both imatinib and FOLFOX chemotherapy because the drugs have different mechanisms of action against each cancer. But there is no proven data on the concurrent administration of imatinib and FOLFOX chemotherapy. We only found two case reports of imatinib and FOLFOX chemotherapy being concurrently administered in patients who were diagnosed with GIST and colon adenocarcinoma simultaneously [16]. In both cases, the patients were successfully administered both imatinib and FOLFOX chemotherapy without any unexpected side effects. Our patient also showed no other side effects except for grade 2 neutropenia and peripheral neuropathy. We suspect that the toxicity was tolerable because the duration of concurrent exposure to both drugs was short.

This is a rare case of metachronous colon cancer in a patient with GIST. Little is known about the association of these cancers. When a synchronous or metachronous tumor is found in the GIST patient, physicians should be alert to the possibility that tumors of different histological origin may coexist and careful diagnostic approach is required. Although further studies on efficacy and safety are needed, concurrent administration of FOLFOX chemotherapy and imatinib in patients with GIST and colon cancer can be

considered as a treatment option very carefully.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: YJH, JYL. Data curation: YJH, JYL. Formal analysis: YJH. Investigation: YJH. Methodology: YJH. Project administration: JYL. Resources: JYL. Software: JYL. Supervision: JYL. Validation: JYL, YJH. Visualization: JYL, YJH. Writing - original draft: YJH. Writing - review & editing: JYL. Approval of final manuscript: all authors.

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

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Traumatic neuroma (TN), also known as amputation neuroma, is a reactive hyperplasia of nerve fibers and connective tissue arising from Schwann cells after trauma or surgery. TN of the bile duct is usually asymptomatic, but rarely can lead to right upper quadrant pain, biliary obstruction, and acute cholangitis. It is very difficult to discriminate TN from malignancy before surgery, although doing so could avoid an unnecessary radical resection of the lesion. In the course of surgery, TN can be caused by unintentional injury of a nerve fiber near the common bile duct (CBD) and heat damage to an artery, complete ligation of an artery, and excessive manipulation of the CBD. Therefore, to prevent TN after cholecystectomy, surgery should be performed carefully with appropriate consideration of anatomic variations, and a cystic duct should not be resected too close to the CBD. The possibility of TN should be considered if a patient who has undergone CBD resection with hepaticojejunostomy or cholecystectomy long ago experiences symptoms of jaundice, cholangitis, or obliteration of the CBD. In this report, we present a case of TN mimicking cholangiocarcinoma that emerged from a cystic duct stump after cholecystectomy.

Keywords: Case reports; Cholangiocarcinoma; Neuroma

Introduction

Traumatic neuroma (TN) or amputation neuroma is a tumor-like hyperplasia that develops after trauma, surgery, or ischemia. It can occur in any location with nerve fiber distribution and can impact every nerve fiber, thereby causing symptoms. Considering that abundant nerve fibers are distributed near the common bile duct (CBD), TN that

arises from the bile duct is often related to cholecystectomy [1]. In addition, TN is very difficult to differentiate from malignancy preoperatively; distinguishing them is important to avoid unnecessary radical resection of the lesion. In this report, we present a case of TN mimicking cholangiocarcinoma that emerged from a cystic duct stump after cholecystectomy.

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Case

Ethical statements: This study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 2023-0013). The need for written informed consent from the participants was waived because of the retrospective nature of this study.

A 65-year-old male visited the emergency room with abdominal pain on the right upper quadrant. His past medical history included cholecystectomy for cholecystitis 39 years ago. His physical examination results were as follows: blood pressure, 110/70 mmHg; pulse rate, 78 beats/min; respiratory rate, 20 breaths/min; and body temperature, 36.6 °C. There was no tenderness on the right upper quadrant abdomen and Murphy sign was negative. His laboratory tests included the following: white blood cells, 7,530/ μ L; hemoglobin, 11.7 g/dL; platelet, 158,000/ μ L; total bilirubin, 0.5 mg/dL; aspartate aminotransferase, 346 IU/L; alanine aminotransferase, 255 IU/L; alkaline phosphatase, 298 IU/L; gamma-glutamyl transferase, 604 IU/L; amylase, 40 IU/L; lipase, 7 U/L; C-reactive protein, 14.41 mg/dL; carcinoembryonic antigen (CEA), 4.44 ng/mL; and

carbohydrate antigen 19-9, 25.3 U/mL. Viral markers for hepatitis A, B, and C were all negative, and blood culture showed no bacterial growth. Abdominal computed tomography revealed an 8 mm polypoid lesion at the right posterior hepatic duct (RPHD); intraductal papillary neoplasm of the bile duct was suspected (Fig. 1). On suspicion of cholangitis, we started empirical antibiotic therapy; subsequently, the symptoms and laboratory findings improved. In magnetic resonance cholangiopancreatography (MRCP), a triangular-shaped polypoid lesion at the RPHD was detected, suggesting early cholangiocarcinoma (Fig. 2). MRCP also revealed an anomalous variation of the RPHD directly draining into the common hepatic duct (Fig. 2). Positron emission tomography showed no evidence of a hypermetabolic lesion. Therefore, we performed endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound for the differential diagnosis of the RPHD lesion. ERCP revealed a focal filling defect with a smooth margin of the RPHD. In endoscopic ultrasound, a 7.8 mm hypoechoic lesion at the RPHD was noted, but infiltration into the hepatic duct wall was not clearly seen (Fig. 3). We decided a short-term follow-up because we could not rule out benign diseases such as fibrous change

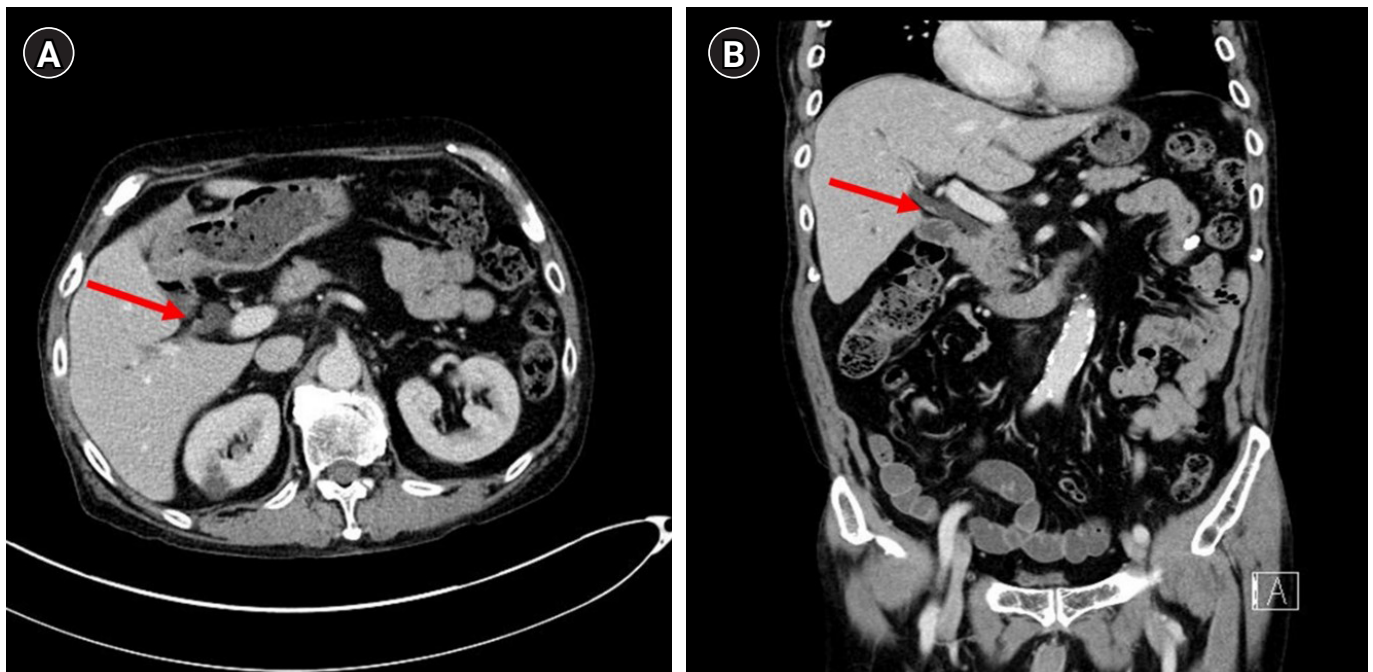


Fig. 1. An 8-mm polypoid lesion at the right posterior hepatic duct; (arrow) an intraductal papillary neoplasm of the bile duct was suspected. (A) Axial view. (B) Coronal view.

of the RPHD resulting from the previous cholecystectomy. One and a half month later, abdominal computed tomography identified an interval increase in size of the polypoid lesion at the RPHD, with strong contrast enhancement

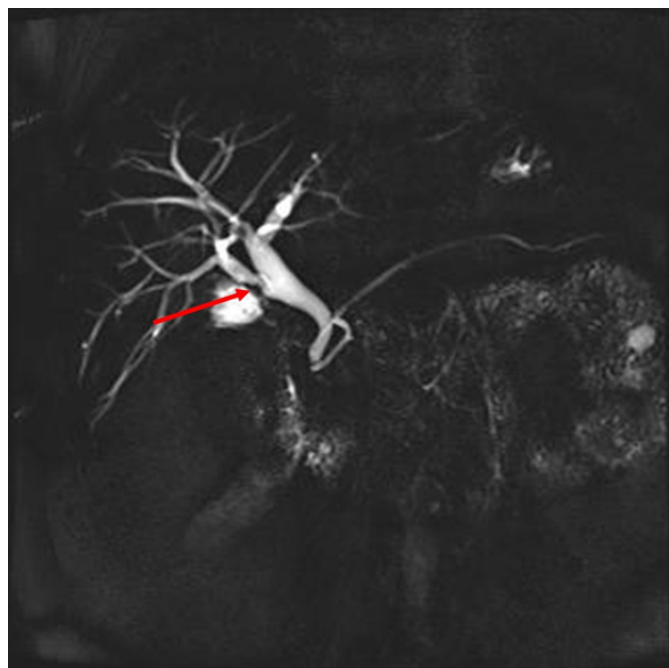


Fig. 2. A triangular-shaped polypoid lesion at the right posterior hepatic duct was detected (arrow), suggesting early cholangiocarcinoma.

(Fig. 4). Laboratory test included the following: aspartate aminotransferase, 17 IU/L; alanine aminotransferase, 29 IU/L; alkaline phosphatase, 62 IU/L; C-reactive protein, 0.54 mg/dL; CEA, 7.78 ng/mL; and carbohydrate antigen 19-9, 16.6 U/mL, and only CEA was increased. In ERCP, the filling defect of the RPHD became more prominent than that in the previous ERCP (Fig. 5). Hence, biopsy through ERCP was performed, but the pathologic result showed only a few benign biliary epithelial strips. Eventually, we decided to perform a surgery, considering that cholangiocarcinoma could not be excluded because of the progress of the lesion and the repeated right upper quadrant pain during the follow-up period. Intraoperatively, the palpable mass was found at the RPHD. The common hepatic duct and CBD remained patent. Therefore, we performed right posterior sectionectomy of the liver with a negative surgical margin of the RPHD (Fig. 6). The patient's postoperative course was uneventful, and he was discharged without any complication. Surgical pathology revealed TN, with no evidence of malignancy. Microscopically, an oval-shaped nodule was observed under the biliary epithelium. The nodule consisted of haphazardly arranged spindle cells with no nuclear atypia. Immunohistochemically, the spindle cells positively reacted to S100 protein (Fig. 6).

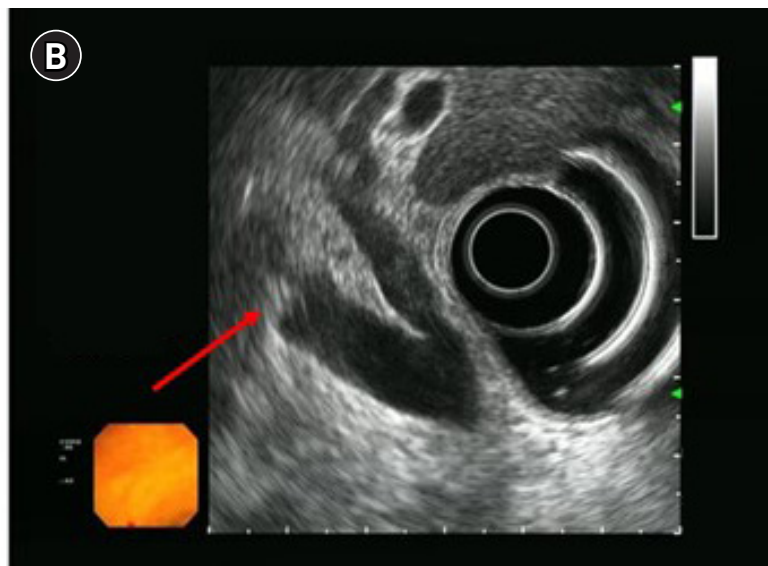
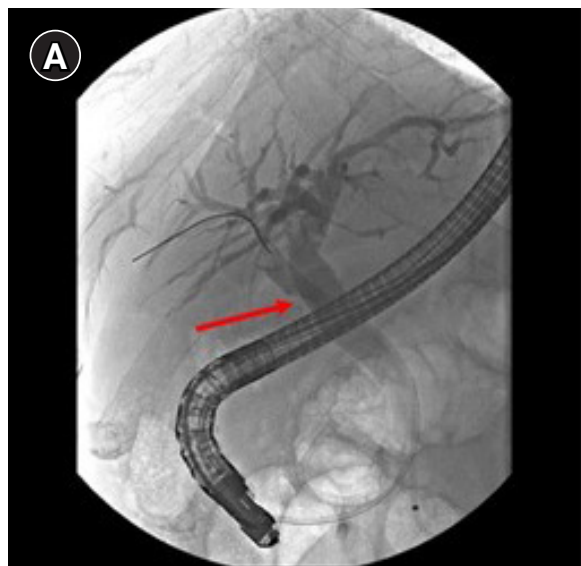


Fig. 3. A focal filling defect with a smooth margin at the right posterior hepatic duct (arrow). (A) Endoscopic retrograde cholangiopancreatography and (B) endoscopic ultrasonography.

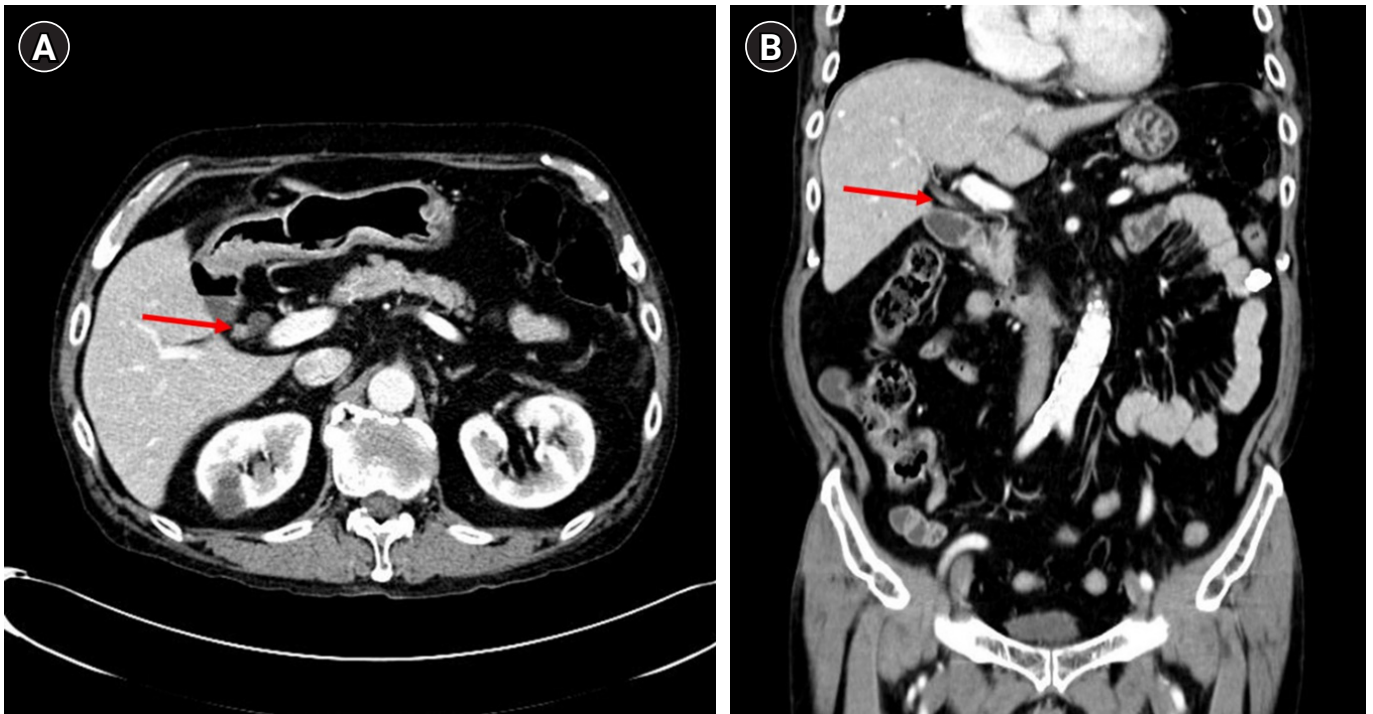


Fig. 4. An interval increase in the size of the polypoid lesion at the right posterior hepatic duct, with strong contrast enhancement (arrow). (A) Axial view. (B) Coronal view.

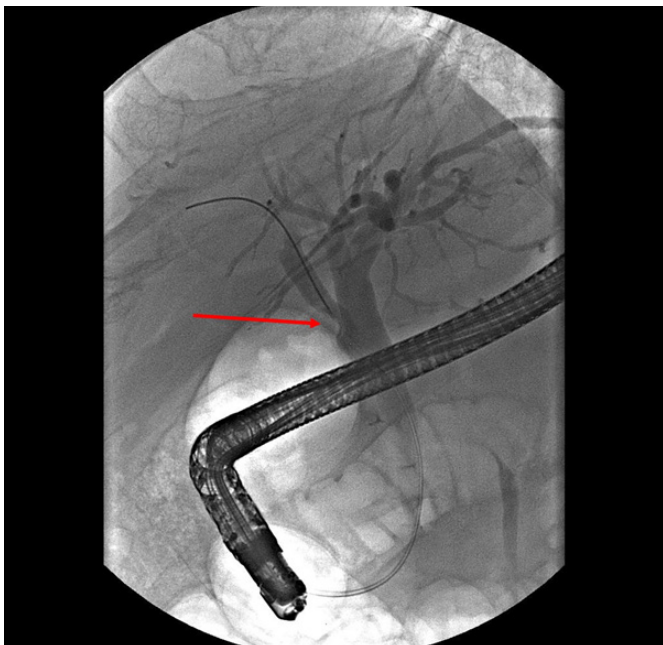


Fig. 5. The filling defect of the right posterior hepatic duct became more prominent than that in the previous endoscopic retrograde cholangiopancreatography (arrow).

Discussion

TN, also known as amputation neuroma, is a reactive hyperplasia of the nerve fiber and connective tissue arising from Schwann cells after a trauma or surgery. Especially, TN of the bile duct is usually asymptomatic; in rare cases, it can lead to right upper quadrant pain, biliary obstruction, and acute cholangitis. TN most commonly occurs in the cystic duct stump after a laparoscopic or open cholecystectomy, with a range of intervals from several months to 45 years [2]. Our patient underwent open cholecystectomy 39 years ago and had atypical variations of the RPHD draining into the common hepatic duct directly. Therefore, the cystic duct might directly emerge from RPHD, and its stump might develop TN, resulting in recurrent right upper quadrant pain.

Discriminating TN from malignancy preoperatively is crucial to avoid unnecessary radical resection of the lesion, but it is extremely difficult. In this case, intraductal growing-type neuroma was very difficult to differentiate from malignancy by imaging study, making the pathological diagnosis even more challenging. Despite specimen harvest,

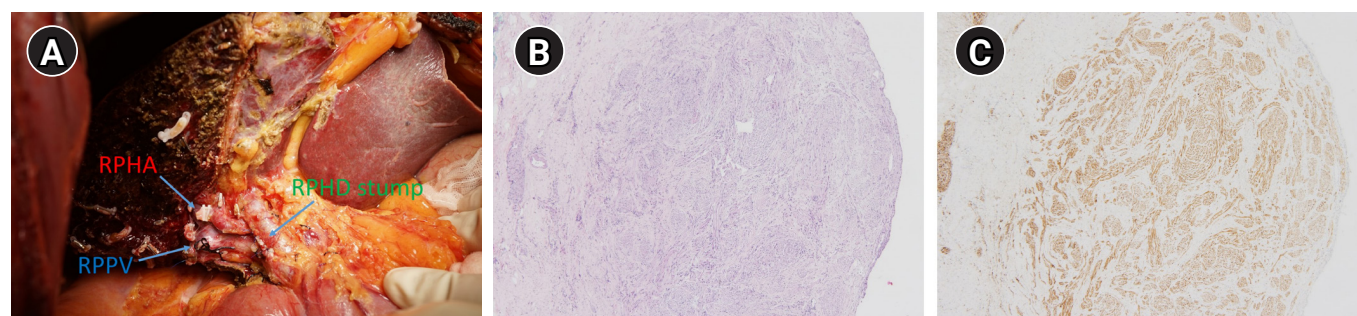


Fig. 6. (A) Right posterior sectionectomy of the liver with a negative surgical margin of the right posterior hepatic duct (RPHD). RPHA, right posterior hepatic artery; RPPV, right posterior portal vein. Oval-shaped nodule, consisting of haphazardly arranged spindle cells with no nuclear atypia. Immunohistochemically, the spindle cells positively reacted to S100 protein (B: hematoxylin and eosin stain, $\times 40$, C: $\times 40$).

the TN is still difficult to be confirmed as a nonmalignant lesion. Thus, great efforts are needed to avoid unnecessary radical resection of the lesion. For instance, an intraductal papillary lesion that develops in a patient who underwent CBD resection with choledochojejunostomy should be distinguished from cholangiocarcinoma.

Our patient only underwent right posterior sectionectomy without hepaticojejunostomy (HJ). Considering the severe adhesion caused by the previous surgery and the fibrotic change resulting from chronic inflammation, HJ was not performed to avoid postoperative complications. Additionally, an anatomic variation of the RPHD draining directly into the CBD was noted; thus, independent right posterior sectionectomy was possible. However, if no anatomic variation of the RPHD and development of TN occurred in the CBD, Roux-en-Y choledochojejunostomy would be preferable.

Nerve fibers are abundantly distributed around the CBD but are most intensively distributed around Calot triangle. TN can be developed from this area. Trauma, surgery, ischemia, or bleeding can cause proliferation of benign connective tissue from an injured nerve [3-5]. In the course of surgery, an unintentional injury of the nerve fibers near the CBD, as well as heat-induced arterial damage, complete arterial ligation, and excessive CBD manipulation, can cause TN. Hence, to prevent TN after cholecystectomy, surgeons should operate carefully while considering the anatomic variation and should not resect the cystic duct too close to the CBD.

In conclusion, TN is possible if a patient with a history of CBD resection with HJ or cholecystectomy manifests jaun-

dice, cholangitis, or CBD obliteration. So, TN and malignancy need to be distinguished in clinical practice to avoid unnecessary radical resection of the lesion.

Article information

Conflicts of interest

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

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Author contributions

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An example:

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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."

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(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).

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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.

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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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