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Aims and scope

Journal of Yeungnam Medical Science is a peer-reviewed and open access journal in the medical field published in English four times a year (January 31, April 30, July 31, and October 31). The journal's publishers are the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. The abbreviated title is *J Yeungnam Med Sci* (*JYMS*).

JYMS aims to deliver new medical information to health professionals of various disciplines as well as the general public, and to facilitate the advancement of medicine by publishing high-quality evidence-based articles.

JYMS covers all fields of medical science, including clinical research, basic medical science, and medical education. *JYMS* is especially interested in medical education for learners of all levels, from residents and fellows to medical students. Its regional scope is primarily Korea but we welcome submissions from researchers all over the world.

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

JYMS was first published in 1984. The original Korean title was "*Yeongnam yidae hagsulji*" (print ISSN 1225-7737). The Journal was renamed "*Yeungnam University Journal of Medicine*" (online ISSN 2384-0293) in 2015 and "*Journal of Yeungnam Medical Science*" (online ISSN 2799-8010) in 2022.

JYMS is indexed/tracked/covered by KoreaMed (2004–), KoreaScience (2012–), CrossRef metadata (2013–), Google Scholar (2013–), KoreaMed Synapse (2013–), Korea Citation Index (KCI, 2016–), PubMed Central (PMC, 2019–), PubMed (2019–), Directory of Open Access Journals (DOAJ, 2019–), Chemical Abstracts Service (CAS, 2020–), ScienceCentral (2022–), Scopus (2023–), and Emerging Sources Citation Index (ESCI, 2023–).

Open access

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"Nostalgia"

Photograph by Man Jin Park, Daegu, Korea

The "Imagery" section of *Journal of Yeungnam Medical Science* (*JYMS*) is devoted to the artistic and imaginative qualities of our readers. *JYMS* invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.

Editorial

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JYMS
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Appreciation to peer reviewers in 2023

So-Young Park

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Once again, I would like to thank all the authors, readers, and editorial board members for another successful year for the *Journal of Yeungnam Medical Science* (JYMS) in 2023. JYMS would not be where it is today without the dedication of the reviewers, who have put considerable time and effort into assessing the manuscript and supporting the authors with helpful suggestions. Reviewer devotion is always an essential part of the editorial process, and we are appreciative of all those who participated this year.

There was good news about JYMS in 2023. JYMS was finally accepted for indexing in Scopus (March 11, 2023) [1]. In addition, JYMS was accepted into the Emerging Sources Citation Index (ESCI) (September 20, 2023) [2]. The coverage in Scopus and ESCI begins with journal content published in JYMS, Volume 39 Issue 1, 2022. JYMS is currently indexed in the two databases.

JYMS published 95 articles in 2023, of which 82 (86.3 %) were by Korean authors, and 13 (13.7%) were by authors from 11 foreign countries (Fig. 1). Bibliometric statistics for the total citations are presented in Fig. 2 and Supplementary Table 1. Readership has expanded to 173 countries in 2023, according to access statistics (Fig. 3). The total number of citations has increased continuously. In 2023, JYMS was cited 381 times in the Crossref Metadata, 307 times in Scopus, and 313 times in the Web of Science Core Collection. The manually calculated impact factor in the Web of Science increased from 0.29 in 2020 to 1.29 in 2023 (137 citations/106 documents from 2021 to 2022; calculated on January 2, 2024). The CiteScore manually calculated by Scopus increased from 0.21 in 2020 to 0.93 in 2023 (235 citations/253 documents from 2020 to 2023; calculated on January 2, 2024). The overall acceptance rate for submitted manuscripts decreased from 55.1% in 2020 to 26.7% in 2023 (calculated on January 2, 2024).

JYMS is continuously growing towards becoming a prestigious journal in general medicine. To achieve this, the editorial board of JYMS will invite active researchers from all over the world as reviewers in 2024.

Below are the names and affiliations of the reviewers for 2023. The editorial board would like to thank the reviewers again for their contributions and would appreciate their ongoing interest and support in 2024.

India: Boyapati Ramanarayana, Sibar Institute of Dental Sciences

Italy: Felice Galluccio, University of Florence; Vincenzo Ricci, Luigi Sacco University Hospital

Korea: Pyunggoo Cho, Ajou University; Min-Ho Hong, Catholic University of Pusan; Ho Goon Kim, Kyo Seon Lee, and Kyung Jin Oh, Chonnam National University; Du Hwan Kim, Chung-Ang University; Chang-Won Moon, Chungnam National University; Hyunsuk Choi, Jun Woo Cho, Yun-Ho Jeon, Jae-seok Jang, Chang-Yeon Kim, Jinkyung Kim, Geon Ho Lee, Young Soo Lee, Suk-Bong Koh, Joonsoo Park, and Jeong Eun Song, Daegu Catholic University; Young-Eun Lee, Daegu Health College; Sang-Kyu Kim and Jeong Ill Suh, Dongguk University; Hyo-Jeong Kim, Eulji

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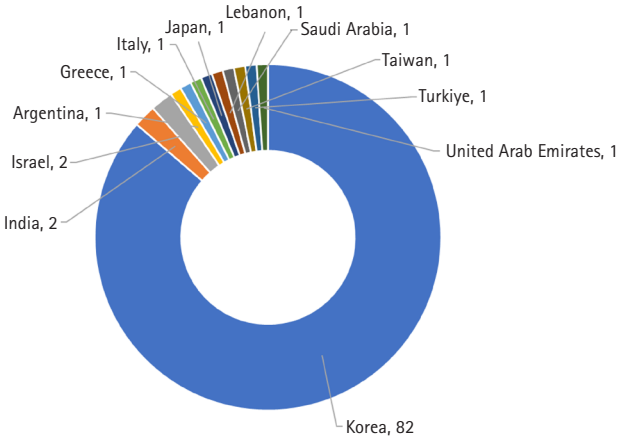

Fig. 1. Number of articles published in *Journal of Yeungnam Medical* Science in 2023 according to the authors' countries.

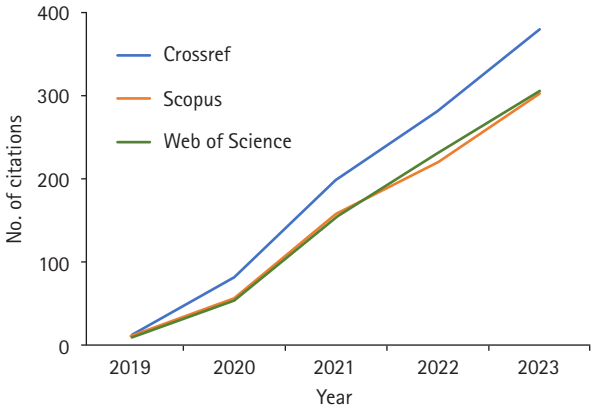

Fig. 2. Number of total citations of articles published in *Journal of Yeungnam Medical Science* articles in Crossref Metadata, Scopus, and Web of Science Core Collection from 2019 to 2023 (calculated on January 2, 2024).

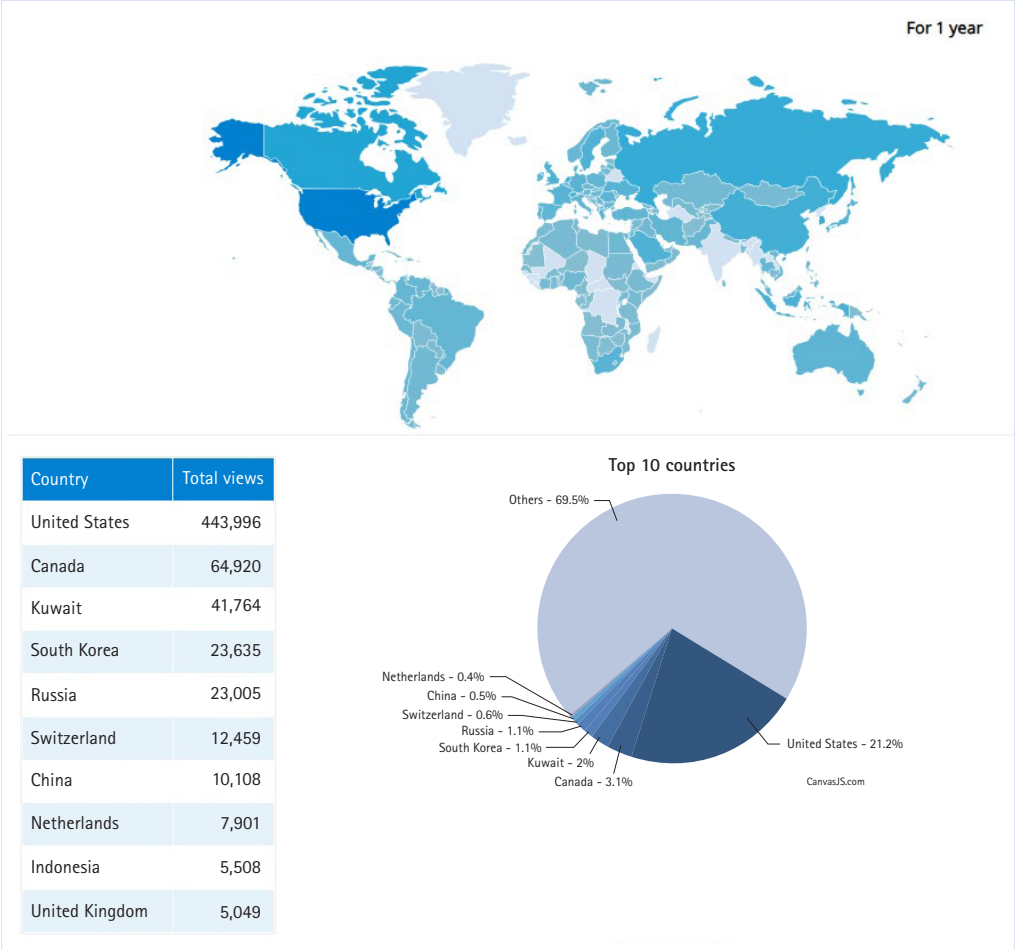

Fig. 3. Top 10 countries with access to *Journal of Yeungnam Medical Science* in 2023 (https://e-jyms.org/metrics/metrics_total_down_ref.php).

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University; Sun Jong Kim and You Gyoung Yi, Ewha Womans University; Seong-Uk Jeh and Young-Ji Lee, Gyeongsang National University; Jaeho Cho, Hallym University; Jay Chol Choi and Sang-Pil Yoon, Jeju National University; Jae Hong Lee, Jeonbuk National University; Mincheol Chae, Hochan Cho, Jang Hyuk Cho, Yong Min Choi, Ji Yong Ha, Mi Hwa Heo, Woo Sung Jang, Hye Ra Jung, Wonho Jung, Hee Cheol Kim, Mi-Young Lee, So Yun Park, Won Kyun Park, and Ye Jee Shim, Keimyung University; Chang Hee Kwon, Konkuk University; Jong Wook Kim and Nack Hwan Kim, Korea University; Chang Hoi Kim, Jiyoun Kim, and Young Lim Oh, Kosin University; Yong-Woon Im, Kyungdong University; Dong-Kuk Ahn, Yeung Woo Do, Jong-Moon Hwang, Namkyun Kim, Chul-hyun Kim, Yong-Gun Kim, Du-Hyeong Lee, Hui Joong Lee, Hyun Jung Lee, Jae-Mok Lee, Yu Rim Lee, Soo Yeun Park, Bum-Jin Shim, and Jinseok Yeo, Kyungpook National University; Eun Soo Kim, Sung Ae Son, and Jin A Yoon, Pusan National University; Dong-Il Chun, Jinmyoung Dan, Hyeonchul Kim, Seok Ju Seong, and Hyung Mo Sung, Soonchunhyang University; Jong Geol Do, Sungkyunkwan University; Donghwi Park, Ulsan University; June Hong Ahn, Chang Hoon Bae, Sangwoon Bae, Jong Hyun Baek, Seung Min Chung, Eun-Jin Cheon, Jong Soo Choi, Joon Hyuk Choi, Joon Hyun Cho, Kang Un Choi, Mi Jin Gu, Jian Hyuk Hur, Byung Ik Jang, Jong Geol Jang, Kyung Mi Jang, Min hye Jang, Ikchan Jeon, Jiyoon Jung, Sung Mee Jung, Tae Eun Jung, Min Kyu Kang, So Hee Kang, Hye-Geum Kim, Hyuckgoo Kim, Kyeong Ok Kim, Sang Won Kim, Ung Kim, Yeong Uk Kim, Yong Woon Kim, Yu Ra Kim, Eun Jung Kong, Young Hwii Ko, So Young Kwak, Dong Gyu Lee, Dong Hyup Lee, Gun Woo Lee, Jae Min Lee, Jang Hoon Lee, Jong Ho Lee, Jung-Hee Lee, Keun-Mi Lee, Seok Soo Lee, Young-Hwan Lee, Jun Sung Moon, Chulyong Park, Hosun Park, Jong Soo Park, So Hee Park, Yong-Eun Park, Dong Hoon Shin, Phil Hyun Song, Si Youn Song, Whee Sung Son, Chang Hoon Woo, Ji Sung Yoon, Dongwoo Yu, and Seokho Yun, Yeungnam University; Keun Jung Ryu, Yonsei Kim and Chung Hospital; Shinki An and Kyung Chul Oh, Yonsei University

Taiwan: Ke-Vin Chang, National Taiwan University Hospital

Supplementary materials

Supplementary Table 1 can be found at https://doi.org/10.12701/jyms.2023.01361.

Article information

Conflicts of interest

So-Young Park has been the editor-in-chief of *Journal of Yeungnam Medical Science* since 2021. She was not involved in the review process of this manuscript. There are no other conflicts of interest to declare.

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2. Park SY. Journal of Yeungnam Medical Science is indexed in Emerging Sources Citation Index (ESCI). J Yeungnam Med Sci 2023;40:317–8.

Review article

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Octacalcium phosphate, a promising bone substitute material: a narrative review

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Biomaterials have been used to supplement and restore function and structure by replacing or restoring parts of damaged tissues and organs. In ancient times, the medical use of biomaterials was limited owing to infection during surgery and poor surgical techniques. However, in modern times, the medical applications of biomaterials are diversifying owing to great developments in material science and medical technology. In this paper, we introduce biomaterials, focusing on calcium phosphate ceramics, including octacalcium phosphate, which has recently attracted attention as a bone graft material.

Keywords: Bioceramics; Biomaterials; Bone substitutes; Hydroxyapatite; Octacalcium phosphate

Introduction

1. What are biomaterials?

The term "biomaterials" is a complex concept with different interpretations that make it difficult to define in a few words. Different countries and agencies have various definitions [1-5]. From the simplest definition of "any materials used as implant" [1] to the more detail definition employed by the U.S. National Institute of Health that describes a biomaterial as "any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual" [2]. Those definitions can be narrowly summarized as materials that can complement and restore functions by replacing or repairing parts of damaged tissues and organs in the living body, and in a broad sense, materials for diagnosing and treating diseases of the human body (Table 1).

Biomaterials have been used for medical purposes since ancient times, as exemplified by, for example, sea shells as a substitute for missing teeth, skull prostheses using gold plates, and sutures using linen or catgut [5,6]; however, they were considered experimental because of poor surgical techniques and conditions [5].

At the turn of the 19th century, on the basis of the pioneering microbiology of Louis Pasteur (AD 1822–1895) [7] and aseptic surgical technique of Joseph Lister (AD 1827–1912) [8], the improvements in surgical environments promoted research and development in material science. The concept of biomaterial biocompatibility was also established as biological reactions based on the properties of the biomaterial were understood [9]. Modern material engineering has led to the development of biomaterials and has achieved unprecedented development along with the

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Table 1. Applications of biomaterials

Indication	Example
Replacement of diseased or damaged part	Artificial joints, bone substitute, and kidney dialysis machine
Assist in healing	Sutures, bone plates, and screws
Improve function	Cardiac pacemaker, intraocular lens
Correct functional abnormality	Cardiac pacemaker
Correct cosmetic problem	Augmentation mammoplasty
Aid to diagnosis	Probes and catheters
Aid to treatment	Catheters, drains

Adapted from Parida et al. [61] according to the Creative Commons License.

medical technology developed during World War II [10-12].

In this article, we introduce biomaterials focusing on calcium phosphate ceramics, including octacalcium phosphate (OCP), which has recently attracted attention.

2. Types and characteristics of biomaterials

The most common way to classify biomaterials is to divide them into metals, ceramics, polymers, and composites, according to the type of material (Table 2). Another classification method is based on their interaction with the biological environment, dividing them into bioinert, bioactive, biodegradable, and resorbable materials (Table 3). Depending on their origin, they can also be classified as natural or synthetic materials [5,13].

Metals are solid materials composed of elements such as Fe, Ni, Ti, Cr, Co, and Mo. Owing to the high toughness and ductility of metals, the manufacturing process is relatively simple and can easily be applied to various shapes [14,15]. Owing to their excellent mechanical properties, such as strength, abrasion, elasticity, and durability, metals are used as replacements for hard tissues such as teeth, bones, and joints. However, because of its low biocompatibility and susceptibility to corrosion, the material can lose its original properties, allowing the corrosion to penetrate the surrounding tissues and induce an inflammatory reaction [16]. In addition, metals can cause side effects due to metal ion elution; therefore, they are used in the form of alloys rather than pure metals [17].

Ceramics are nonmetallic inorganic solid materials composed of elements such as Ca, P, K, Na, and Si. Owing to their excellent biocompatibility, high compressive strength, and wear resistance, they are used in dental implants, crowns, bone substitutes, and bone cements. However, the inherent brittleness of ceramics and the complicated manufacturing process compared to other materials are obstacles to their medical application [18,19].

Polymers are substances or materials consisting of very large molecules called macromolecules that are composed of many repeating subunits. Polymers composed of a variety of materials are used in various medical fields because they can be manufactured with specific physical and chemical properties and relatively complex shapes [20]. However, the low mechanical strength, easy deformation, and deterioration of polymers are disadvantages for medical applications. Polymeric materials are used in a wider variety of fields than metal or ceramic materials, which are mainly used as substitutes for hard tissues. Polymers are frequently use in sutures, blood vessels, artificial joints, artificial tissues, and organs [21]. In addition to synthetic polymers, naturally derived polymers with excellent biocompatibility have been used. Natural polymers include collagen, gelatin, elastin, fibrin silk, hyaluronic acid, and heparin [22].

Composite materials involve the complex use of two or more materials. In the case of coating a scaffold surface, composite materials possess both the physical strength of the base material and the high biocompatibility of the coating material; however, the manufacturing process is complicated for composites [23,24].

3. Requirements of biomaterials

Because biomaterials replace damaged body parts, they must have adequate mechanical strength, chemical stability, and fatigue strength to maintain the biological function and shape of the tissues [25,26]. Another essential requirement for biomaterials that are inserted into the human body is biocompatibility [27]. Because most medical devices made of biomaterials are inserted into or make contact with the human body, the safety of cells and tissues around the inserted medical device is of paramount importance. The biomaterial should not be toxic or damage surrounding cells or tissues [28]. In addition, biomaterials must exhibit a high *in vivo* stability. Implanted materials are often easily hydrolyzed or deteriorated by the environment in the human body [29]. Therefore, it is necessary to improve the safety and efficacy of biomaterials in a living body through surface modification of the material.

For the production of medical devices, biomaterials must be easy to process and sterilize. In general, it is difficult to manufacture medical devices aseptically. Thus, post-manufacturing sterilization is required, and the mechanical, chemical, and biological properties of the final biomaterials must not be altered by this process [30].

Table 2. Classification and characteristics of biomaterials

Type	Advantage	Disadvantage	Example
Metal	Strong, ductile	Corrode	Titanium and its alloys, magnesium and its alloys, stainless steel alloys, Au, Ag, etc.
Ceramic	Biocompatible	Brittle property	Calcium phosphate, carbon, silica, alumina, zirconia, etc.
Polymer	Resilient	Low strength	Polycaprolactone, polyethylene, alginate, collagen, etc.
Composite	Tailor made, multiple properties	Difficult manufacturing	Metal-based composite, ceramic-based composite, polymer-based composite, etc.

Table 3. Classification of bioceramics according to bioactivity

Type	Interaction with adjacent tissue	Example
Bioinert	No interaction but fibrotic capsule formation	Carbon, zirconia, alumina, sintered hydroxyapatite, etc. Ti, stainless steels.
Bioactive	Surface interaction and direct bonding	Bioglass, AW-GC (apatite/wollastonite containing glass-ceramic), synthetic hydroxyapatite, etc.
Bioresorbable	Slow resorption and progressive replacement with tissues	β-tricalcium phosphate (β-TCP), octacalcium phosphate (OCP), calcium sulfate, etc.

Bioceramics

Biomaterials can be classified into organic and inorganic materials. Organic materials contain elements such as C, O, N, and H as their main components and include wood, paper, and natural fibers. Inorganic materials are nonorganic materials such as metals, stone, and soil, and are further subdivided into metallic and nonmetallic materials. Metallic materials are composed solely of metals such as Fe, Mg, Al, Ag, and Cu or a mixture (alloy) thereof. Materials in which the metallic elements are ionically bonded to anions, including oxygen, or covalently bonded to each other are called nonmetallic inorganic materials or ceramic materials [31]. A ceramic is a product obtained by forming a metal oxide or nonmetal compound and then sintering it at a high temperature.

In general, pottery, cement, and glass made through sintering after the formation of nonmetallic inorganic materials are called traditional ceramics. High-purity ceramic powders are called fine ceramics and are used to make bioceramics, electronic products, or communication products [32]. Bioceramics are materials used to treat, reinforce, replace, or restore the functions of human tissues or organs for short or long periods of time. Bioceramics can be divided into bioinert, bioactive, and biodegradable types, according to their biological reactions. Bioinert bioceramics do not cause inflammation or toxicity when implanted into a living body and are bonded through the formation of surrounding fibrous tissue rather than directly binding to the surrounding living tissue. Alumina (Al_2O_3), zirconia (ZrO_2), and carbon are included in this category [33]. Bioactive ceramics react with tissues and form chemical bonds directly, but only on the surface of the biomaterial. Bioglass and hydroxyapatite (HA) belong in this category. Biodegradable ceramics are chemically unstable biomaterials that gradually resorb and eventually disappear in the human body over time, and this resorbed space is filled with new human tissue. β-Tricalcium phosphate (β-TCP), OCP, metacalcium phosphate, and plaster of Paris (gypsum) are included in this category [33,34].

Calcium phosphate bioceramics

Calcium phosphate materials are composed of Ca, P, O, and H, and there are several types according to the atomic ratio of calcium to phosphorus [33] (Table 4). Because of their chemical similarity to human hard tissues, calcium phosphate-based bioceramics are attracting attention as they directly combine with hard tissue or regenerate bone without inflammatory reactions or new fibrous tissue formation when applied *in vivo* [35]. The term "bioceramics" refers to ceramic products manufactured using ceramic or precursor materials.

Calcium phosphate-based ceramics have different thermodynamic properties depending on the ratio of calcium to phosphorus and show solubility differences in the human body or in solutions similar to body fluids. When various calcium phosphate-based ceramics are inserted into a living body, they exhibit different biological reactions with surrounding tissues [36]. In particular, calcium and phosphate ions released into the tissue greatly influences bone regeneration [37]. Calcium phosphate-based ceramics are classified as bioactive and biodegradable, according to their Ca/P ratios. However, the dissolution properties of calcium phosphate-based minerals depend on the pH of the solution. Furthermore, calcium phosphate-based ceramics exhibit excellent hydrophilicity and promote cell attachment and proliferation [38]. By replacing monovalent cations such as Na^+, K^+, and Li^+, and divalent cations such as Sr^{2+}, Ba^{2+}, Pb^{2+}, Mn^{2+}, Sn^{2+}, Zn^{2+}, and Al^{3+}, or by creating defects,

 https://doi.org/10.12701/jyms.2023.00010

Table 4. Types of calcium orthophosphate ceramics according to Ca/P ratio

Ca/P ratio	Chemical formula	Compound	Abbreviation
0.5	$Ca(H_2PO_4)_2·H_2O$	Monocalcium phosphate monohydrate	MCPM
1.0	$CaHPO_4·2H_2O$	Dicalcium phosphate dihydrate	DCPD
1.33	$Ca_8H_2(PO_4)_6·5H_2O$	Octacalcium phosphate	OCP
1.5	α-$Ca_3(PO_4)_2$	α-Tricalcium phosphate	α-TCP
1.5	β-$Ca_3(PO_4)_2$	β-Tricalcium phosphate	β-TCP
1.67	$Ca_{10}(PO_4)_6(OH)_2$	Hydroxyapatite	HA
1.67	$Ca_{10}(PO_4)_6F_2$	Fluorapatite	FA

the physical properties of minerals can be changed. They can also be subjected to high-temperature treatment to impart other properties. During high-temperature treatment, some calcium phosphate-based ceramics may change into minerals with low Ca/P ratios owing to the volatilization of phosphate [39].

1. Dicalcium phosphate dihydrate

The mineral name for dicalcium phosphate dihydrate (DCPD) is brushite, and it is a component of calculi in the body. It is stable in an acidic environment and has a fast growth rate; therefore, it can be easily obtained in aqueous solutions. In addition, clinical results have shown that DCPD is more soluble than HA; therefore, DCPD is absorbed quickly *in vivo* and promotes bone formation [40]. Calcium is widely used in the food industry in addition to bone cement.

2. Hydroxyapatite

Synthetic HA is more crystalline and richer in calcium ions than natural bone is. Although CO_3^{2-} ions are partially substituted in the crystal structure of HA in natural bone, the basic chemical formula or crystal structure is very similar to that of synthetic HA [33,34]. Therefore, when an HA medical device is implanted into the body, an amorphous Ca-P mineral is formed on the surface of the HA, and after several months, an apatite layer similar to bone is formed. After a longer period (more than 6 months), direct bonding between the bone collagen fibers and HA occurs. Owing to these bioactive properties, HA is most commonly used as an artificial bone substitute. HA is more stable when the c-axis length in the unit cell is short and the pH is high. In contrast, solubility increases as pH decreases. When the OH of HA is substituted with F, the c-axis length in the unit cell shortens significantly, resulting in chemical stability. However, the use of fluoroapatite in large quantities is restricted because it must be within the permissible range of fluorine compounds in the body [41].

Comparing the mechanical properties of natural bone and sintered artificial HA, the tensile strength of natural cortical bone is approximately 150 MPa and that of sintered artificial HA is approximately 100 MPa. Artificial HA has low strength and is prone to fracture, while natural bone has higher toughness than artificial bone because the collagen and nanometer-sized HA crystals form a complex. Therefore, synthetic HA is suitable when large loads are not required, and metal implants are commonly coated with HA for load-bearing applications. HA powder is easily synthesized by dry, wet, or hydrothermal treatments. Xenogeneic HA bone obtained by high-temperature treatment of natural bone has crystallinity and strength similar to that of synthetic HA, but its Ca/P ratio and surface morphology are similar to those of natural bone [42].

3. Tricalcium phosphate

α-Tricalcium phosphate (α-TCP) possesses good biocompatibility, but it is chemically unstable and its biodegradation rate is fast. Therefore, in the past, cell attachment, proliferation, and differentiation on the surface of α-TCP biomaterials were difficult, limiting their applications as bone graft materials. However, in recent years, many studies have been conducted on the use of α-TCP as calcium phosphate-based cement. Thus, bone cement can be obtained by mixing α-TCP with other calcium phosphate-based materials. α-TCP can be obtained by heating β-TCP to a temperature of 1,300°C or higher and rapidly cooling it. α-TCP has the same chemical formula as β-TCP and both have excellent biocompatibilities; however, α-TCP is metastable at room temperature and is resorbed more rapidly in the body. When α-TCP is used as cement, calcium-deficient HA is finally produced after the cement reaction and is rapidly hydrolyzed in the human body [33,43].

β-TCP, similar to α-TCP, does not exist naturally in the body; therefore, it is artificially synthesized and used. β-TCP is mainly produced by treating HA at high temperatures. Because β-TCP is rapidly biodegraded in the human body, it is used as a bone graft material by mixing with nonbiodegradable HA. This bone graft material is called biphasic calcium phosphate, which is mixed in varying proportions to control the biodegradation rate. In general, products with a mixing ratio of HA and β-TCP of 6:4 or 7:3 are common, and more types of these products are being commercialized than those manufactured with HA or β-TCP alone [34,44].

Unlike α-TCP, β-TCP is used as resorbable filler for bone cement

and is used for the purpose of controlling the rate of biodegradation. Bone cement hardener and β-TCP powder are mixed to form a slightly viscous paste, similar to toothpaste, which is then used to fill bone defects. Over time, the material hardens through cement reactions (hydration reactions, acid-base reactions, etc.). These products can be used clinically to fill bone defects more effectively than products in powder form [19].

4. Octacalcium phosphate

OCP is a calcium phosphate-based material with a calcium to phosphorus ratio of 1.33 and is a precursor of biological HA in the human body. OCP is a thermodynamically unstable substance that is ultimately converted into HA, a stable substance, in the human environment [45,46]. The OCP crystal has a water layer between two layers of apatite, similar to the chemical formula ($Ca_8H_2(PO_4)_6 5H_2O$) (Fig. 1). In a physiological environment, the water layer is removed from the OCP and the two apatite layers combine to form HA crystals (Fig. 1) [47,48]. Because of its crystallographic and chemical similarities, OCP has been proposed as a precursor to bioapatite crystals in bones and teeth [49]. The excellent osteoconductivity of OCP has been demonstrated in many animal studies [50,51]. Nevertheless, there have been limitations to many clinical applications due to the OCP bone graft production process and lack of mass production of OCP material [52].

Owing to the problem of mass production of OCP materials, the Suzuki research group has been conducting investigations on combining OCP with other materials, such as collagen, gelatin, and alginate, rather than using pure OCP [53]. In a series of *in vitro*, animal, and clinical studies, this group demonstrated that bone graft materials containing OCP had much better bone regeneration than those made of HA or TCP [54,55]. For the first time, this research team recently developed a method for the mass production of OCP materials and published excellent animal and clinical research results for new bone regeneration with high-purity OCP bone graft materials.

Anada et al. [56] examined the osteoblast differentiation capacity of OCP after seeding mouse bone marrow stromal ST-2 cells on dishes pre-coated with OCP and HA. When the ST-2 cells were cultured in OCP-coated wells, alkaline phosphatase (ALP) enzymatic activity gradually increased with increasing OCP concentrations. However, in the HA-coated group, ALP activity remained constant regardless of the HA content. In addition, OCP enhanced the expression of osteogenic markers, including osterix, collagen I, and ALP, on day 21 of culture. Therefore, OCP has the potential to improve osteoblast differentiation than HA.

In another study, Shiwaku et al. [57] showed that large tartrate-resistant acid phosphatase–positive cells, representing multinucleated osteoclasts, were more frequently observed in cultures with biodegradable OCP or β-TCP discs than in those with non-degradable HA discs. The ability of OCP to form osteoclasts was almost the same as that of β-TCP, whereas the expression patterns of the coupling factors varied depending on the type of calcium phosphate. β-TCP and an HA/β-TCP mixture induced ephrin B2 and collagen triple helix repeat containing 1 expression, whereas OCP and HA/OCP mixtures promoted complement 3a expression.

The superiority of OCP bone graft material was demonstrated in a comparative study between HA and β-TCP. Kamakura et al. [58] used a composite material by adding collagen to OCP, HA, and β-TCP and implanted it into a rat calvarial defect, followed by radiographic and histological examinations. They found that implanted OCP/collagen composites improved bone regeneration more than HA and β-TCP/collagen bone graft materials. New bone formation was also observed in the transplanted β-TCP/col-

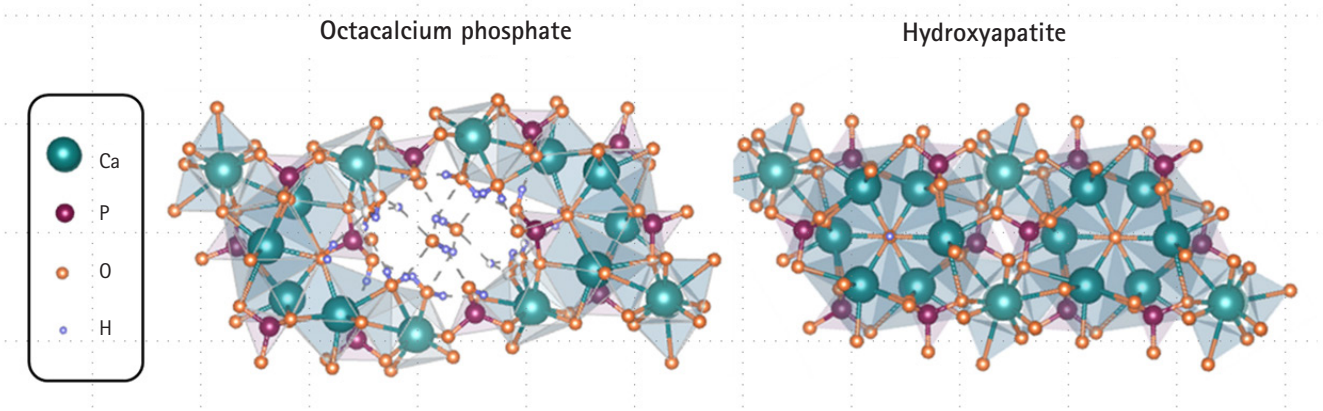

Fig. 1. The unit cell of the octacalcium phosphate and hydroxyapatite phase is visualized with the VESTA (Visualisation for Electronic Structural Analysis) program.

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lagen group, and β-TCP resorption was not evident. In the case of HA/collagen, new bone formation was less pronounced than that of OCP/collagen and β-TCP/collagen. The authors concluded that the OCP/collagen composite material showed superior osteogenesis compared to the other materials.

In an animal study by Kim et al. [51], implanted pure OCP bone substitutes showed significant levels of osteogenic activity after 4 weeks. A high density of osteoblasts and new bone formation were observed around the implanted OCP granules (Fig. 2A). These histological findings strongly suggest that in addition to providing the basis for the crystallographic structure during bone regeneration, the OCP material itself promotes the homing and proliferation of bone-forming cells. After 12 weeks, most of the OCP bone graft material was resorbed, providing space for new bone formation (Fig. 2B).

Several clinical trials have been conducted using OCP bone graft materials. OCP/collagen was placed in the nasal cavity and extraction socket of the left maxillary lateral incisor [59]. No infections or neoplastic lesions were observed at the treatment sites during the 7-year follow-up period. Moreover, no negative effects on neighboring teeth, such as mobility or loss, were confirmed. Hence, it can be stated that OCP/collagen was properly resorbed and replaced with new bone tissue. In addition, the newly formed bone due to the OCP/collagen showed affinity for and stably fixed the inserted dental implant.

In another clinical study by Kim et al. [60], eight implants were placed in three patients who underwent maxillary sinus or alveolar bone grafting using OCP bone graft material. Except for mild swelling at the surgical site, none of the patients developed any postoperative complications. Four months after implantation, the implant stability quotient values were above 60 for all implants, indicating good implant stability. For site No. 16 of case 3, in which the maxillary sinus and ridge grafts were performed using OCP bone graft material, histological analysis revealed that new bone was deposited around the remaining grafted bone and the new bone was well integrated. No foreign body reactions or signs of inflammation were observed. Thus, the unique and excellent ability of OCP to generate new bone has been clinically and radiologically confirmed. Unlike HA and β-TCP, OCP appears to provide a starting site for new bone formation and eventually promotes bone regeneration [54].

Conclusion

The results of studies on the excellent osteogenesis performance of OCP bone substitutes are of great significance in that they have emerged as a breakthrough that can overcome the disadvantages of existing naturally derived bones (allogeneic bone, xenogeneic

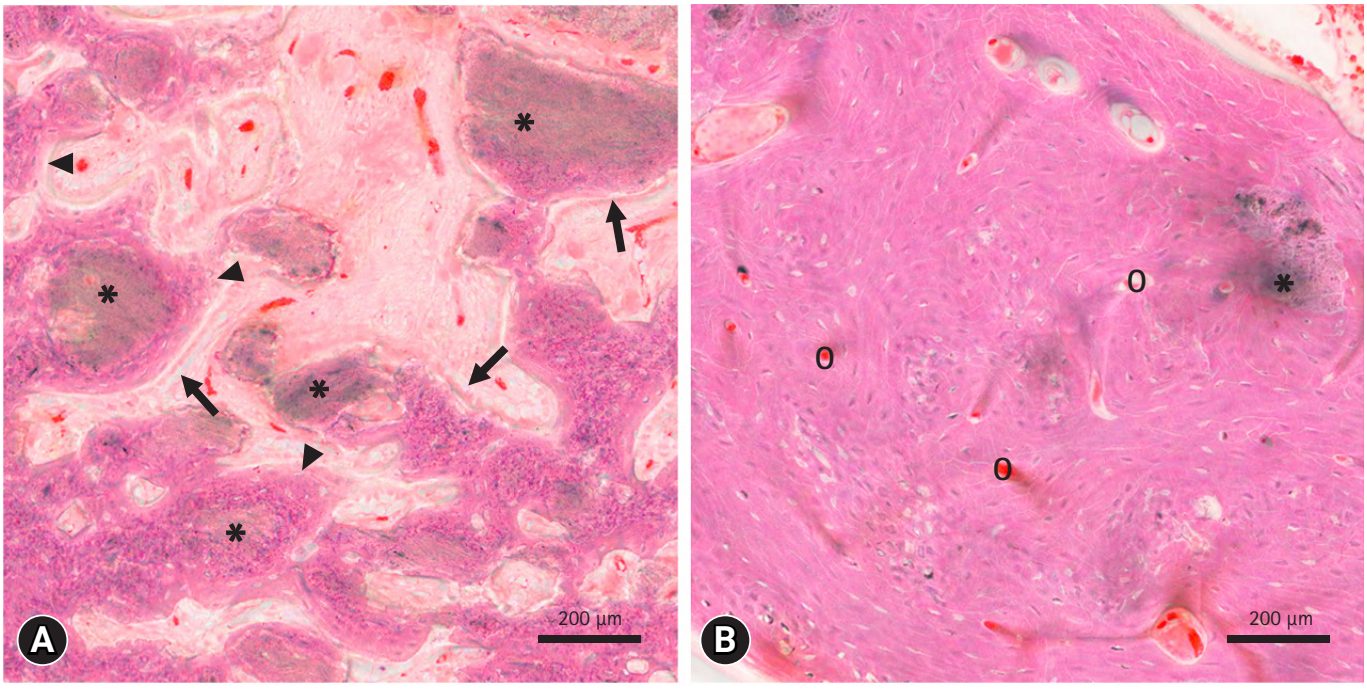

Fig. 2. Micrographs of octacalcium phosphate (OCP)-implanted tibial defect in the rabbit after 4 weeks and 12 weeks. (A) At 4 weeks, OCP granules (*) are visible. Active new bone formation is observed with osteoblasts (arrows) and osteocytes in lacunae (arrowheads). (B) At 12 weeks, compact bone is achieved via new bone formation with osteons (O). OCP granules are largely absorbed (hematoxylin and eosin stain).

bone) and synthetic bones. Despite the excellent capacity of OCP to generate new bone, its commercialization and applications have been limited in the past by the inability to produce high-purity OCP materials. Research on the mass production of OCP has been continuously conducted in countries around the world for the past 40 years, but only recently has the world's first high-purity OCP synthesis method and low-temperature manufacturing process for OCP bone been developed in Korea. Recently, domestic companies using these technologies have succeeded in commercializing bone substitutes based on OCP, and it is expected that the limitations of current bone graft materials can be overcome in clinical applications.

Article information

Conflicts of interest

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

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Review article

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Role of gene therapy in treatment of cancer for craniofacial regeneration—current molecular strategies, future perspectives, and challenges: a narrative review

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Gene therapy involves the introduction of foreign genetic material into host tissue to alter the expression of genetic products. Gene therapy represents an opportunity to alter the course of various diseases. Hence, genetic products utilizing safe and reliable vectors with improved biotechnology will play a critical role in the treatment of various diseases in the future. This review summarizes various important vectors for gene therapy along with modern techniques for potential craniofacial regeneration using gene therapy. This review also explains current molecular approaches for the management and treatment of cancer using gene therapy. The existing literature was searched to find studies related to gene therapy and its role in craniofacial regeneration and cancer treatment. Various databases such as PubMed, Science Direct, Scopus, Web of Science, and Google Scholar were searched for English language articles using the keywords "gene therapy," "gene therapy in present scenario," "gene therapy in cancer," "gene therapy and vector," "gene therapy in diseases," and "gene therapy and molecular strategies."

Keywords: Craniofacial regeneration; Genetic therapy; Neoplasm; Vector

Introduction

The human genome consists of approximately 25,000 genes that encode an expanded category of proteins commonly known as the building blocks of the cell that initiate each biological process [1,2]. Some genes remain unchanged but show changes due to disruptions, mutations, and deletions. These basic and uncontrollable genetic modifications transform protein functions to directly influence the cell structure and physiological appearance of severe diseases, disorders, and deficiencies [3,4]. Gene therapy is a unique method for treating various diseases by transferring a recombinant gene. Gene therapy is a favorable therapeutic option for various diseases such as viral infections, hereditary disorders, and cancer. Various gene delivery techniques have been reported for gene therapy [5,6].

Currently, gene therapy is being investigated only for diseases for which there is no alternative therapy. Genetic molecules must enter the nucleus of host cells to activate gene expression. Gene therapy transmits genetic instructions to somatic cells for the production of distinct therapeutic proteins that regulate genetic diseases.

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It is important to develop an interaction between the gene delivery system and target cells to create a competent gene delivery system [7,8]. Alipogene tiparvovec (Glybera; UniQure, Amsterdam, the Netherlands), the earliest gene therapy product, was certified by the European Medicines Agency. This was considered a notable initial advancement in gene-based medicine [9,10].

Methods in gene therapy

These methods include gene modification, gene transfer, gene transfer to specific cell types, and gene insertion. Gene modification is a replacement treatment and modified gene therapy is a method that corrects flawed genes. In substitute therapy, a natural gene is replaced with a nonnatural gene via recombination. Gene transfer methods utilize chemical, biological, and physical means for gene transfer. Gene transfer to specific cell types can be divided into gamete gene therapy and somatic gene therapy. Gene insertion (eugenic approach) or gene injection is another gene therapy method. Other modes involving genetic engineering include gene targeting and the eradication of specific genes through nuclease engineering, such as developing I-CreI homing endonucleases, zinc-finger nucleases (ZFNs), or transcription activator-like effector nucleases (TALENs). These methods are currently used in clinical trials [11].

Gene therapy history and future

On September 14, 1990, a girl was treated by Dr. William French Anderson and colleagues at the National Institutes of Health Clinical Center in Bethesda, MD, USA. White blood cells were extracted from the patient. After gene implantation, the cells were transferred back into the patient's body. Noticeable progression of the immune system was observed. Currently, gene therapy trials for various diseases are ongoing. Patients with melanoma and other skin cancers have been treated using gene therapy techniques [12].

Technologies for gene delivery

From the time of development of recombinant DNA methods, safe, and efficacious administration of gene products has been a major challenge. Gene delivery is performed using a vector. A vector adequately delivers a gene to a target tissue, allows the delivery of a gene of sufficient size, and accomplishes correct transgenic expression to regulate the defective gene. The distribution of gene products is achieved using viral vectors, nonviral vectors, and bactofection [13].

Ideal properties of vectors

The properties of ideal vectors include the following: (1) the vector should be stable and easy to produce; (2) it should possess low toxicity, high efficiency, and high specificity; (3) it should be nonimmunologic and inexpensive; and (4) ideally, it should be able to deliver DNA into the cell nucleus [13-15].

Viral vectors

Currently, viral vectors are the most favored vectors. Viruses deliver their genes to human cells in a pathogenic manner. Scientists favor this efficiency, replacing parts of the viral genome with the gene therapy candidate. This recombinant virus may be utilized to transfer genes inside cells. Various categories of viruses can be used as gene therapy vectors. These include adenoviruses, retroviruses, and adeno-associated viruses [16].

1. Adenovirus

Adenoviral vectors are non-enveloped, double-stranded (ds)-DNA viral vectors. Adenoviral vectors are most extensively used for gene delivery. Adenoviral DNA does not integrate into the genome or replicate during cell division. This limits the use of adenoviruses to basic investigations, although adenoviral vectors have been used in both *in vivo* and *in vitro* studies. The primary uses of this vector are in vaccination and gene treatment [17,18].

Considering that humans are frequently exposed to wild-type adenoviruses, the majority of individuals have established neutralizing antibodies that intercept the virus before it arrives at its target cell. Adenovirus-mediated gene therapy has been used to treat chronic pain in a rodent model. These studies have encouraged the development of criteria for chronic pain therapy of the central nervous system. Adenovirus-mediated gene therapy has also been used to treat liver cancer. Gendicine (Shenzhen SiBiono GeneTech, Shenzhen, China), a p53-based adenoviral vector, was the first gene therapy certified for the treatment of head and neck cancer. Compared to retroviruses, adenoviruses infect a larger array of cells [19,20].

2. Retrovirus

Retroviruses were the first viruses to be used in gene therapy experiments as vectors. They are considered the backbone of the existing concept of gene therapy. Recombinant retroviruses can integrate into the host genome in a balanced manner. They encode a reverse transcriptase that produces DNA copies of the RNA genome. They also encode an integrase that permits integration into the host genome. Retroviruses have been utilized in various U.S.

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Food and Drug Administration (FDA)-recognized clinical studies such as the SCID-X1 study [21,22].

3. Adeno-associated virus

Adeno-associated viruses are extremely promising vectors. They can infect a wide variety of cells. They are small-scale viruses that belong to the parvovirus classification and have single-stranded DNA. They may integrate their genome at a definitive location on chromosome 19. Some scholars have presumed that many individuals harbor adeno-associated viruses that do not elicit an immune response or cause disease. Scientists have conducted animal experiments using adeno-associated viruses to amend genetic deformities. The principal shortcoming of adeno-associated viruses is that they are tiny and exclusively encode only two genes in their wild-type form. Hence, their applicability is restricted. As the virus integrates its genes directly into the DNA of the host cells, it causes unpredictable damage. Researchers face difficulties in producing large quantities of recombinant viruses. Recently, this problem was resolved by Amsterdam Molecular Therapeutics [23].

4. Lentivirus

These viruses are a retrovirus subtype. They are periodically used as vectors for gene therapy. A unique feature of lentiviruses is their ability to integrate into the genome of nondividing cells [24]. When the virus invades cells, the viral RNA genome is reverse-transcribed. It is then integrated at a random position in the genome by an integrase enzyme. The vector, now known as a provirus, persists in the genome and is passed on to the cell's progeny [25].

5. Vaccinia virus

Vaccinia virus is a complex and enveloped virus belonging to the *Poxviridae* family. It contains a dsDNA genome encoding approximately 250 genes [26]. Vaccinia virus produces four infectious forms during its replication cycle. These are the extracellular, intracellular, cell-associated enveloped, and intracellular mature virions [27,28].

6. Herpes simplex viruses

They are members of the *Herpesviridae* family and cause viral infections in most humans [29].

7. Electroporation

This is the transitory permeabilization of cell membranes of the target tissue by application of an electric field, which results in the penetration of DNA molecules into the nucleoplasm and cytoplasm of the cell [30,31]. These DNA molecules are initially present in the medium surrounding the membranes. Electroporation is mainly utilized *in vivo* for different tissues such as muscle, skin, and lung [32-34].

8. Hydrodynamic delivery

Hydrodynamic delivery is a highly efficient and simple technique for rapid intracellular distribution of water-soluble particles and compounds within internal organs [35,36]. The hydrodynamic method has been successfully used for the delivery of genes into rodent liver for the expression of erythropoietin, cytokines, and hepatic growth factors [37-39].

9. Chemical methods

Chemical delivery systems include oligonucleotides, lipoplexes and polyplexes, dendrimers, and inorganic nanoparticles such as gold, silica, and iron oxide [40].

Present molecular approaches in cancer gene therapy

Gene transportation technology permits an ample spectrum of therapeutic potential that can be integrated with traditional therapies or used to implement new treatment approaches. New delivery systems for cancer treatment and eradication are currently being studied. As a result, the use of various nucleic acid-based systems such as TALENs, interfering RNA (iRNA), ZFNs, recombinant DNA, suicide genes, and clustered regularly interspaced short palindromic repeats have provoked much interest within the scientific community [41-43].

1. Antisense oligonucleotide technology in cancer

Antisense oligonucleotides are characterized as highly modified synthetic DNA or RNA oligonucleotides that are designed to selectively target gene-encoded RNA molecules through Watson-Crick base pairing. The binding of antisense oligonucleotides to their corresponding targets can generate unique mechanisms of action [44,45]. These mechanisms can be categorized as those that promote RNA degradation and those that confine RNA and hinder its activity without activating RNA degradation. Regardless of mechanism, antisense oligonucleotide-mediated intervention is a promising therapeutic approach for cancer treatment [46,47].

2. Interfering RNAs

RNA interference was first described in *Caenorhabditis elegans* in 1988. This technology has made appreciable advances in cancer treatment. iRNA is a dsRNA-mediated gene silencing method. This mechanism recognizes and targets pathogenic dsRNA parti-

cles for destruction. Three types of small RNAs have been identified in animals, specifically small interfering RNAs (siRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs) [48-50].

Some miRNAs are overexpressed in cancer and induce tumor development, whereas others are downregulated and block inhibitory control over a few oncogenes [51,52]. siRNA is eminently selective toward its target microRNA. Compared with miRNAs, this selectivity is greater, as siRNAs can distinguish between sequences with even a single distinctive nucleotide [53]. piRNAs are mainly involved in epigenetic regulation [54]. Short hairpin RNAs (shRNAs) are also used for RNA interference. These shRNA molecules are synthesized from expression vectors inside the nucleus of the cell, transferred to the cytoplasm, and processed by automatic machinery to produce shRNAs [55-57].

Gene therapy for craniofacial regeneration

The regeneration or reconstruction of oral tissue, in addition to craniofacial tissue, is a difficult process that requires a blend of engineering technology and clinical and basic science. The recognition of the relevant stage, spatial and temporal signals, and cell sources is essential for enhancing the development of single tissues, tissue interfaces, and hybrid organs consisting of numerous tissues. The regeneration of craniofacial tissues using gene therapy utilizes genetic vectors as supporting building blocks for tissue repair and growth. The harmonious association between craniofacial tissue engineering and viral gene therapy substantially strengthens the potential for regenerating and repairing tissues *in vivo*.

1. Head and neck squamous cell carcinoma

The treatment of head and neck squamous cell carcinoma (HNSCC) is the most advanced application of gene therapy in the craniofacial region. Three main strategies are used to target each solid tumor using genetic treatments.

First, immunomodulatory treatment enhances the perceptibility of tumor cells to the immune system *in vivo* or customizes effector cells to enhance their tumor-targeting capacity by establishing the expression of a particular gene [58]. Second, oncolytic viruses have evolved to select a target cancer cell, enter, and destroy it. Third, suicide genes can be imported into cancer cells to broaden cell sensitivity to antiviral drugs like acyclovir [59-61]. Additional strategies for targeting HNSCC include the introduction of endostatin, genes encoding p53, and antiviral interleukin (IL)-2 or IL-12 [62-65].

2. Mineralized tissues

Gene therapy based on animal models and the architecture of a particular craniofacial structure, such as cartilage or bone, has provided an advantageous and innovative way to regenerate composite mineralized tissues, such as the temporomandibular joint and tooth [66,67]. Delivery of bone morphogenetic proteins and platelet-derived growth factors (e.g., PDGF-B) at the location of the periodontal deformity is known to increase the healing and repair of gingiva and bone. At the therapeutic level, gene delivery permits the sustained synthesis of proteins in defined locations [68-70].

3. Salivary gland

Insufficient function of the salivary gland can occur due to the side effects of radiation therapeutics or as an aftereffect of autoimmune diseases, such as Sjögren syndrome. Researchers are engaged in designing salivary gland alterations that are perhaps confined to the location of the parotid gland. Acinar cells in the salivary gland require membrane proteins to develop an osmotic gradient for the unidirectional movement of fluids [71,72].

Salivation occurs because of the reaction to agonists that increase intracellular Ca^{2+} concentrations and is promoted by an osmotic gradient that directs the movement of fluid by means of water passage through apical membrane proteins called aquaporins (AQPs). It has been observed that confined ductal epithelial cells do not express AQPs, and hence are unable to mediate fluid movement [73,74].

4. Wound healing of mucosa

For esthetic reconstruction in persons mutilated by surgery, trauma, or severe burns, a proportionate structure of mucosa and skin is necessary. For coverage of wounds and burns, Apligraf (Integra LifeSciences, Princeton, NJ, USA) and Dermagraft (Organogenesis Inc., Canton, MA, USA) are used [75,76].

Gene remedies for cancer treatment

Cancer develops because of the loss of regulation of normal cell apoptosis and proliferation. Advancements in cancer treatment require unique remedies with unusual mechanisms of action, different means of cell death, and harmony with traditional therapies. Gene therapy has all these characteristics. Various gene therapy approaches have been established for cancer treatment. These approaches include suicide gene therapy, oncolytic virotherapy, antiangiogenic gene therapy, immunotherapy, gene-directed enzyme prodrug therapy, and siRNA therapy. Immunogenetherapy is a promising treatment method for p53-deficient tumors (e.g., Yescarta [axicabtagene ciloleucel; Kite Pharma, Inc., Santa Monica,

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CA, USA], Imlygic [talimogene laherparepvec; Amgen, Inc., Thousand Oaks, CA, USA], Kymriah [tisagenlecleucel; Novartis International AG, Basel, Switzerland], and Gendicine) [77].

1. Oncolytic virotherapy

This is the most promising method of tumor immunotherapy. Oncolytic virotherapy utilizes replication-competent viruses that grow rapidly, particularly in tumor cells. Genetically modified or commonly occurring oncolytic viruses are used. Viruses such as measles, vaccinia, and vesicular stomatitis viruses are genetically modified to decrease viral pathogenicity and enhance tumor specificity. Wild-type viruses, such as the Newcastle disease virus or parvoviruses, are carefully replicated in tumor cells without gene modification. Oncolytic viruses respond by precisely lysing tumor cells and inserting wild-type tumor suppressor genes into cells that do not express these genes [78,79].

2. Gendicine (recombinant human p53 adenovirus)

Gendicine is a nonreplicating adenoviral vector that was first accepted as a gene therapy for HNSCC in 2003. The E1 gene in the adenoviral genome was replaced with the tumor suppressor p53 complementary DNA (cDNA). In tumor cells, the expression of wild-type p53 has an antitumor effect by triggering the apoptotic pathway and relieving blockage of DNA repair and apoptotic p53 translocation. p53 gene mutations are prevalent in various cancers. Hence, Gendicine promotes the function of p53, restores its translocation, and damages tumor cells [80,81].

3. Oncorine (rAd5-H101)

Oncorine (Shanghai Sunway Biotech, Shanghai, China) is an oncolytic recombinant adenovirus-5 (with a deletion in the *E1B55K* gene) recognized for the treatment of refractory nasopharyngeal cancer. Elimination of the *E1B55K* gene results in the inhibition of viral expansion in normal cells, permitting proliferation only in p53-impaired host cells. After the lysis of cancer cells, the adenovirus is released and infects other cells, leading to Oncorine-mediated cell death [82,83].

4. Imlygic

Imlygic is an inherently altered oncolytic type 1 herpes simplex virus (HSV-1) used for the treatment of metastatic melanoma. The HSV-1 genome was modified by substitution of the α47 and γ34.5 genes with agranulocyte-macrophage colony-stimulating factor cDNA. The deletion of γ34.5 results in the suppression of pathogenicity and tumor cell-selective replication. During viral infection, the γ34.5 gene normally hinders the translation of host-cell proteins in favor of viral production. Hence, suppression of γ34.5 blocks proliferation of the virus in normal cells [78,79].

5. Rexin-G

Rexin-G (Epeius Biotechnologies Corp., San Mateo, CA, USA) is a major targeted injectable vector accepted for the treatment of various cancers. It has a signature (SIG)-binding peptide that binds to abnormal SIG proteins in tumor cells, which results in an increase in vector accumulation in tumor cells, and it expresses human cyclin G1 inhibitor. After entry into tumor cells, it expresses the cytocidal fibronectin 1 protein, which results in inhibition of the cell cycle, leading to apoptosis [84,85].

6. Chimeric antigen receptor T-cell therapy

This therapy uses T cells that have been altered *in vitro* to express chimeric antigen receptors (CARs) that specifically recognize tumor-associated antigens. CAR is known as "chimeric" because it consists of the antigen-binding domain of the B-cell receptor and the T-cell receptor activation domain. Stimulated CAR T cells provide target-distinct memory cells that promote tumor regression [86].

7. Kymriah (tisagenlecleucel)

Kymriah is used to treat relapsed B-cell acute lymphoblastic leukemia and was the first FDA-permitted CAR T cell-positioned gene therapy. Kymriah consists of T cells, which are mutated with lentivirus to encode a CAR consisting of murine single-chain variable fragment, which is specific for CD3 zeta, the CD8 transmembrane hinge, intracellular domain 4-1BB (CD137), and CD19. Kymriah, after binding to CD19, commences its antitumor activity via the CD2 domain [87,88].

8. Yescarta (axicabtagene ciloleucel)

Yescarta is used to treat aggressive non-Hodgkin lymphoma. It is based on CAR T-cell therapy. Yescarta encodes a CAR that consists of extracellular murine anti-CD19, which binds to the cytoplasmic region carrying the CD3 zeta and CD28 co-stimulatory domains [89,90].

9. Zalmoxis

Zalmoxis (MolMed S.p.A., Milan, Italy) is used to treat various hematopoietic malignancies. Zalmoxis consists of genetically altered allogeneic T cells, which have been transduced to express a truncated human low-affinity nerve growth factor receptor and HSV-1 virus thymidine kinase.

The administration of genetically altered donor T cells rebuilds immunity to resist infection. However, the donor cells may attack

host cells in graft-versus-host disease. Zalmoxis provides immune reconstitution, graft-versus-leukemia improvement, and post-transplant graft-versus-host disease control [91,92].

Risks affiliated with viral vectors

The most common concerns associated with viral vectors are the risk of inflammation, insertional mutagenesis, and off-target effects [93,94]. Inflammation was observed in the death of Jesse Gelsinger in 1999 resulting from an excessive dosage of adenovirus. Insertional mutagenesis is a major challenge that must be overcome when using gene therapeutics. Sometimes, the vectors integrate into undesirable regions of the genome. To avoid this problem, using a vector that does not integrate is advisable [95].

Challenges and the way forward

Gene therapy has been widely used since its discovery as a treatment option for cancers, neuronal and infectious diseases, and metabolic disorders. Gene therapy is effective in treating Leber congenital amaurosis, beta-thalassemia, and immunodeficiency diseases such as adenosine deaminase severe combined immunodeficiency. For the large-scale production of viral particles, different approaches, such as insect cell-based baculovirus expression and cell lines expressing capsid proteins, are useful [96].

Conclusion

Various gene therapy trials are underway for single-gene and complex diseases, and vector collection and engineering approaches have been greatly enhanced, as apparent by the number of recent stage III studies. Although the gene therapy field has been accustomed to major obstacles and limited success, it is particularly important to encourage active areas of medical research. Interest in this therapy has been established based on its potential to treat and cure some of the most virulent and overwhelming diseases affecting individuals. The goal of gene therapy is to express therapeutic genes in host cells to produce favorable biological effects. However, the effectiveness of current strategies is inadequate for realizing the full potential of gene therapy.

Gene therapy has the capability to improve genetics by correcting an altered gene or performing site-specific modifications intended for therapeutic treatment. This treatment has been achieved through advances in genetics and biotechnology that allow the manipulation of vectors to deliver extra chromosomal agents to target cells. New experimental vector designs, improved efficiencies, specific delivery systems, and a better understanding of the induction of inflammatory responses can improve safety and extend the technology for clinical utilization.

Thousands of clinical studies have been conducted since the introduction of gene therapeutics in humans. It is supportive that number of gene therapy trials for various disorders are now completed. The selection of vectors and their design strategies have substantially improved. In the future, gene therapy will surely help in the medical field, with promising results in the management of diseases with limited treatment options.

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Review article

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Breakthrough pain and rapid-onset opioids in patients with cancer pain: a narrative review

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Breakthrough pain is transitory pain that occurs despite the use of opioids for background pain control. Breakthrough pain occurs in 40% to 80% of patients with cancer pain. Despite effective analgesic therapy, patients and their caregivers often feel that their pain is not sufficiently controlled. Therefore, an improved understanding of breakthrough pain and its management is essential for all physicians caring for patients with cancer. This article reviews the definition, clinical manifestations, accurate diagnostic strategies, and optimal treatment options for breakthrough pain in patients with cancer. This review focuses on the efficacy and safety of rapid-onset opioids, which are the primary rescue drugs for breakthrough pain.

Keywords: Breakthrough pain; Cancer pain; Rapid-onset opioids

Introduction

Pain is a common symptom in patients with cancer. Cancer pain can occur during anticancer treatment, after curative treatment, or in advanced, metastatic, or terminal disease [1]. Cancer pain occurs in 24% to 60% of patients receiving active treatment, and the incidence of pain is 58% to 69% in advanced stages. This rate has not decreased in decades [2].

Cancer pain is a complex phenomenon resulting from several factors, including genetic variants, microenvironmental alterations, nociceptor activation, tumor growth, and tumor metastasis [3]. It can be classified according to the pathophysiology (nociceptive and neuropathic), cause (related or unrelated to the disease and its treatment), temporal characteristics, and nature of the pain experience [3].

Pain control in patients with cancer is essential but remains challenging for clinicians [4]. Cancer pain management has improved over the decades; however, one-third of patients with cancer do not receive pain medication because of barriers to reporting pain, lack of assessment, and undermanagement [5]. Breakthrough pain is commonly described as transitory pain that occurs despite adequate background pain control with opioids [6]. It commonly occurs in patients with cancer who suffer from pain, leading to complications and reduced quality of life. Despite effective analgesic therapy, patients and their caregivers often feel that the pain is not adequately controlled. In addition, breakthrough pain increases healthcare utilization and costs [7]. Therefore, an improved understanding of breakthrough pain and its management is essential for all physicians caring for patients with cancer. This review aims to provide a comprehensive overview of the definition, clinical pre-

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sentation, appropriate diagnosis, and treatment strategies for breakthrough pain in patients with cancer, focusing on the efficacy and safety of rapid-onset opioids.

Definition of breakthrough pain

Breakthrough pain was first defined in 1990 as "a transient increase in pain to greater than moderate intensity, which occurred on a baseline pain of moderate intensity or less" [8]. This definition excludes patients with severe baseline pain, indicating uncontrolled pain. Some researchers argue that breakthrough pain should be defined as pain that occurs despite regular opioid treatment for baseline pain, because breakthrough pain indicates a transient increase in pain breaking through the background pain protected by opioids. Based on this opinion, breakthrough pain is defined as "a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids" [9]. There is no consensus on the definition of breakthrough pain. The most widely accepted definition of breakthrough pain is that of the Association for Palliative Medicine of Great Britain and Ireland (APM), namely "a transient exacerbation of pain that occurs spontaneously or in relation to a specific predictable or unpredictable trigger despite relatively stable and adequately controlled background pain" [6,10]. According to this APM definition, background pain should be assessed and appropriately controlled before breakthrough pain is diagnosed.

The National Comprehensive Cancer Network (NCCN) guideline defines breakthrough pain as "pain that fails to be controlled or breaks through a regimen of regularly scheduled analgesics" [11]. Pain at the end of a regular opioid dose interval is known as end-of-dose failure pain. End-of-dose failure pain is frequently related to an underdose of the opioids used to control background pain and occurs more often during the titration phase [6]. The NCCN guideline includes end-of-dose failure pain as a subtype of breakthrough pain, but the APM definition excludes end-of-dose failure pain from breakthrough pain [6,11].

In 2002, an Expert Working Group of the European Association for Palliative Care suggested that the term "breakthrough pain" should be replaced by "episodic pain" [12]. Patients with cancer may experience a transient exacerbation of pain in the absence of background pain. Therefore, the experts suggested that episodic pain should be defined as any transient exacerbation of pain in patients with cancer [13].

Clinical presentation of breakthrough pain

Breakthrough pain is a spectrum of heterogeneous conditions that vary among and within individuals according to different clinical features, disease stages, and treatments [14]. Tumor growth, cancer treatment, metastasis, and comorbidities can cause breakthrough pain, which can be nociceptive, neuropathic, or mixed. It negatively affects daily living in 80% of the patients with cancer pain [15]. Two to three episodes of breakthrough pain per day have been reported. It is most prevalent in the late morning, with 60% of pain episodes occurring during the daytime [16]. The proposed mechanisms for the circadian rhythm of breakthrough pain flare-ups are as follows: (1) late morning is the time of maximum physical activity, (2) pain sensitivity has a circadian rhythm, and (3) the pharmacokinetics or pharmacodynamics of opioids have a circadian rhythm [16]. The pain usually peaks within 5 minutes and is moderate-to-severe [14,17]. Peak pain intensity rarely occurs after 15 minutes [18,19]. Untreated breakthrough pain lasts for a median of 60 minutes and a maximum of 180 minutes [14].

The overall prevalence of breakthrough pain was reported to be 59.2% [20]. It was lower in outpatients (39.9%) and higher in hospice patients (80.5%). This difference was mainly due to disease progression. Additionally, hospice clinicians have more knowledge and experience in identifying breakthrough pain, which increases the likelihood of reporting it. The prevalence of breakthrough pain has decreased in recent publications compared to that in previous publications [21]. This decrease may be due to improvements in diagnostic criteria, especially the exclusion of end-of-dose failure, control of background pain, and use of analgesics.

Breakthrough pain is categorized as incident or spontaneous. Incident pain is predictable. It can be triggered by voluntary movements, such as walking; involuntary movements, such as coughing; or therapeutic interventions, such as wound dressing. Spontaneous pain is unpredictable because it has no identifiable cause. Davies et al. reported that 44% of breakthrough pain cases were incident, 41.5% were spontaneous, and 14.5% were mixed [14]. Episodes of breakthrough pain did not differ between the two types. However, incident pain has a shorter duration and faster onset, whereas spontaneous pain has a gradual onset and longer duration [21]. The characteristics of the two types of pain are summarized in Table 1.

Table 1. Characteristics of breakthrough pain

Variable	Incident pain	Spontaneous pain
Predictable cause	Identified	Unidentified
Duration of untreated episodes (median)	45 min	60 min
Time to peak intensity (mean)	5 min	10 min
Intensity of pain	Not different	
Stop doing something	More	Less
Interferes with walking ability	More	Less
Interferes with mood and sleep	Less	More

Assessment of breakthrough pain

Adequate patient assessment is essential to determine the cause, severity, and characteristics of pain [6]. However, distinguishing breakthrough pain from poorly controlled background pain remains challenging [22]. Breakthrough pain is diagnosed based on multiple sources. A patient's history is an essential component of the diagnosis of breakthrough pain. In patients with normal cognitive function, self-reporting is the best source of information regarding breakthrough pain. A pain diary is valuable for the assessment and monitoring of breakthrough pain [17]. It provides the date and time of each episode, duration and intensity of pain, rescue dose administration, pain relief, and side effects. However, patient adherence to keeping a diary is generally poor. The Numerical Rating Scale (NRS) is a useful tool for measuring pain intensity. The NRS is associated with higher adherence and better responsiveness than the visual analog and verbal rating scales [23]. Patients with cancer preferred to use the NRS to measure pain exacerbations, and the NRS performed better in distinguishing between background pain and peak pain intensity [24]. Patients usually request breakthrough pain medications when their NRS pain scores are >7 [25]. The Brief Pain Inventory and McGill Pain Questionnaire are multidimensional tools that can provide information on the location of pain, daily function, and treatment effects. These tools are complex and do not differentiate breakthrough pain from background pain, although they provide helpful information [26].

A diagnostic algorithm is valuable for screening breakthrough pain (Fig. 1) [6]. It has a high positive predictive value (0.84) when using mild as a cutoff level to define controlled background pain [27]. However, the positive predictive value was lower when using moderate as the cutoff level [27].

The Alberta Breakthrough Pain Assessment Tool (ABPAT) and Breakthrough Pain Assessment Tool (BAT) are specific tools for assessing breakthrough pain. The ABPAT consists of 15 self-answer questions on breakthrough pain, asking about the association with background pain, previous pain experience time, pain frequency, peak pain intensity, pain location, pain quality, cause of pain, and pain predictability [28]. The BAT comprises 14 questions evaluating pain and current pain treatments for previously diagnosed breakthrough pain [29]. ABPAT is usually used for research, and BAT is used to improve pain management in clinical settings [26].

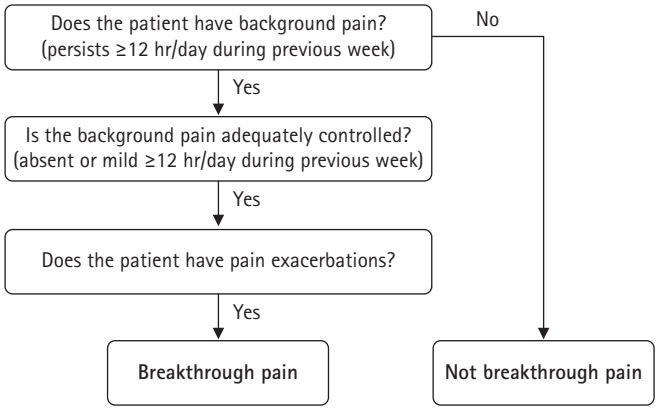

Fig. 1. Diagnostic algorithm for breakthrough pain.

Management of breakthrough pain and rapid-onset opioids

Because of the heterogeneous nature of breakthrough pain, its management should be individualized [6]. Management should be considered based on the cause, pathophysiology, and clinical features of the pain. A direct effect of cancer is the most common cause of cancer-related pain. Treatment of underlying causes, such as bone metastasis, includes conventional radiotherapy, bisphosphonates, and nuclear factor kappa-B ligand-receptor activator inhibition [30]. Avoiding the cause of pain reduces incident pain when using orthotic devices.

Modification of the background analgesic regimen, including titration of opioid analgesics, switching of opioid analgesics, and addition of adjuvant analgesics such as antiepileptics for neuropathic pain or antispasmodics for visceral pain, also reduces breakthrough pain [6]. The patient's condition, including disease stage, physical performance, and personal preferences, should be considered to manage breakthrough pain effectively [6]. Younger patients, those with high physical performance, and those without advanced disease were not satisfied with breakthrough pain management in a previous study and experienced more interference in daily living activities due to breakthrough pain [31].

Non-pharmacological methods include massage, heat or cold application, relaxation or distraction techniques, mindfulness intervention, and physical therapy [25]. However, there is limited evidence supporting the use of these methods [6].

Interventions such as neural blockade, chemical neurolysis, neuraxial drug infusion, direct tumor ablation, cementoplasty, and surgery may help manage breakthrough pain [6].

Opioids are the mainstay of analgesics used for cancer pain treatment. The use of opioids as rescue medications is the cornerstone of controlling breakthrough pain episodes [6]. Orally administered morphine and short-acting opioids are the traditional backbones for the pharmacological management of breakthrough pain. Orally administered morphine or oxycodone has a slow onset of action

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(onset of analgesia, 30–45 minutes) and a prolonged duration of effect (3–6 hours) [32]. These characteristics of oral opioids can delay the management of breakthrough pain and increase the incidence of adverse effects.

Consequently, alternative methods may be better for treating this type of pain [33]. Intravenous or subcutaneous administration of opioids has been attempted to manage breakthrough pain and satisfy hospitalized patients [34]. Intravenous or subcutaneous administration of opioids can provide rapid analgesia for breakthrough pain. Infusion using patient-controlled analgesia devices has also been attempted; however, these methods are limited to primary care settings.

The demand for more rapid and accessible breakthrough pain relief has led to the development of rapid-onset opioid therapies. Transmucosal routes deliver drugs more rapidly than oral routes in a noninvasive manner. The oral and nasal mucosa are easily accessible and more permeable than the skin. They are rich in blood supply, enabling the fast absorption of drugs, and the absorbed drugs have the advantage of bypassing first-pass metabolism. Fentanyl, a highly lipophilic μ receptor agonist with high potency, quickly crosses the blood–brain barrier to provide fast analgesia [35]. It has a rapid blood–brain equilibration time constant of 5 to 6 minutes [36]. Transmucosal administration of fentanyl provides an immediate analgesic effect that closely mimics the duration of breakthrough pain episodes and increases bioavailability by bypassing first-pass metabolism. The following are commonly utilized forms of transmucosal administered fentanyl: oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), sublingual fentanyl (SLF), fentanyl intranasal spray (INFS), and fentanyl pectin nasal spray (FPNS). The characteristics of the rapid-onset opioids are shown in Table 2.

OTFC is a sweetened fentanyl citrate lozenge on a stick to help the patient spread the medication over the buccal mucosa. The buccal mucosa only absorbs 25% of the administered dose. The remaining 75% of the OTFC dose is swallowed and slowly absorbed through the gastrointestinal tract. Approximately two-thirds of the absorbed dose is eliminated through first-pass metabolism. The bioavailability of OTFC is approximately 50% of the total dose. OTFC must be taken for 15 minutes. Absorption is reduced if the patient has decreased saliva levels, applies the OTFC to the tongue or gums rather than the buccal mucosa, chews the OTFC, ingests liquids that alter the oral pH before OTFC administration, or applies the product for less than or longer than 15 minutes [18]. The time to maximum plasma concentration (T_{max}) is 20 to 40 minutes after administration, depending on the dose [37]. In cases of incomplete pain relief, a second dose may be administered 15 minutes after complete dissolution of the first lozenge. The sugar in the lozenges increases the risk of dental decay.

FBT is an effervescent tablet intended to modify the pH of the buccal cavity and enhance drug absorption. This alteration enhances the dissolution of ionized fentanyl and absorption of non-ionized fentanyl across the buccal mucosa [38]. FBT is inserted between the upper cheek and gum within the buccal cavity above the rear molars. FBT dissolves in the buccal mucosa for 14 to 25 minutes; 48% of the administered dose is absorbed by the buccal mucosa, whereas 52% is absorbed by the gastrointestinal tract [39]. The absolute bioavailability is 65%. Pain intensity is reduced as early as 10 minutes after administration [40].

SLF is a tablet that contains fentanyl citrate mixed with carrier particles and a mucoadhesive agent. It uses a rapid disintegration system and dissolves under the tongue within 2 minutes. The drug is rapidly absorbed through the oral and sublingual mucosa, obtaining a detectable plasma concentration within 10 minutes [40]. The estimated bioavailability of SLF is 70% because of its rapid absorption through the sublingual mucosa [40].

Fentanyl administration through the oral mucosa requires time to dissolve and adequate amounts of saliva. However, salivary gland dysfunction and xerostomia are common in patients with cancer, and fentanyl absorption across the oral mucosa may pose a challenge [41]. The nasal mucosa has a large surface area and an extensive blood supply, facilitating the absorption of lipophilic drugs. The nasal route bypasses first-pass metabolism and delivers opioids directly to the site of action in the central nervous system through the olfactory and trigeminal nerves, vessels, cerebrospinal fluid, and lymphatic fluid.

INFS has a pH of 6.4 to minimize nasal mucosa irritation and is

Table 2. Characteristics of rapid onset opioids

	Dose (μg)	Dwell time	Onset of action (min)	Availability (%)	Time to maximum plasma concentration	Elimination half-life (hr)
OTFC	200–1,600	15 min	15	50	20–40 min for doses 200–1,600 μg	7.6
FBT	100–800	14–25 min	15	65	34–45 min for doses 100–800 μg	13.3
SLF	100–800	70–100 sec	15	70	30–60 min for doses 100–800 μg	11.5–25
INFS	50–200	NA	5–10	89	12–15 min for doses 50–200 μg	3–4
FPNS	100–800	NA	5–10	70	19.8–21 min for doses 100–800 μg	15–54.9

OTFC, oral transmucosal fentanyl citrate; FBT, fentanyl buccal tablet; SLF, sublingual fentanyl; INFS, fentanyl intranasal spray; FPNS, fentanyl pectin nasal spray; NA, not applicable.

administered at 100 μL per nostril separately to prevent pharynx runoff. Moreover, 50, 100, or 200 μg of fentanyl is delivered in 100 μL per spray. Its bioavailability is 89% because less of the administered dose is swallowed than with transbuccal or sublingual formulations [42]. INFS has a fast onset of action (5–10 minutes), a T_{max} of 12 to 15 minutes, and a duration of action of approximately 2 hours. The long-term use of INFS can cause nasal congestion, epistaxis, and changes in nasociliary function [43].

FPNS is a nasal spray containing pectin as a food additive. It reduces local irritation and improves the nasal mucosal penetration of fentanyl. The pectin-containing fentanyl citrate solution applied to the nasal mucosa transforms into a gel that prolongs the residence time at the application site and prevents intranasal runoff. The bioavailability of FPNS is 70% [44]. It attenuates the peak plasma concentration of fentanyl and has a prolonged elimination half-life compared to that of INFS. FPNS has a rapid T_{max} (15–21 minutes) and long elimination half-life (15–25 hours). The recommended starting dose of FPNS is 100 μg. A 2-hour interval must be observed before treating any subsequent episode of breakthrough pain because of the long elimination half-life of FPNS.

All types of transmucosal fentanyl decrease breakthrough pain within 30 minutes. OTFC, FBT, INFS, and FPNS significantly reduce pain within 15 minutes. SLF shows significant pain reduction at 30 minutes, but not at 15 minutes. INFS shows superior efficacy compared to all other medications at 15 and 30 minutes. INFS also shows greater efficacy at 5 minutes than FBT and OTFC but not FPNS [45]. INFS and FPNS provide the fastest meaningful pain relief even though they are administered at relatively low doses, possibly because of their faster analgesic effects [46]. Nasal transmucosal fentanyl is preferred in patients with severe mucositis [46].

Most patients were satisfied with transmucosal fentanyl administered for breakthrough pain. Patients were more likely to use FPNS and SLF than OTFC [46]. A study indicated that breakthrough pain management with rapid onset transmucosal fentanyl improved quality of life, including physical and emotional status [47].

For patients who are opioid tolerant, transmucosal fentanyl is recommended for the treatment of incident pain not relieved by conventional immediate-release opioids, but it is not recommended for use when background pain control is inadequate [11]. Starting with the lowest possible dose of transmucosal fentanyl and up-titrating is recommended. However, repeated dosing during titration may prolong the duration of uncontrolled pain. This discourages patients who may refuse treatment and increases the uncertainty, inconvenience, and cost of care. A recent study showed that the opioid doses required for breakthrough pain were significantly associated with those required for background pain [48]. The treatment of breakthrough pain was attempted by starting the first dose of transmucosal fentanyl based on the total daily dose of opioids. This method appears to be effective and well-tolerated based on available evidence [48,49].

It is recommended that no more than four doses of all forms of transmucosal fentanyl be administered per day. However, there is no pharmacological reason for this limit, and clinicians frequently administer more than four doses daily to appropriate patients [10]. However, a higher frequency of breakthrough pain episodes was associated with suboptimal pain management [50]. Therefore, optimization of background analgesia may reduce the frequency of breakthrough pain.

Fentanyl is highly addictive, carries a risk of abuse, and increases mortality in patients who are not opioid tolerant [51]. Therefore, transmucosal fentanyl is recommended for patients who are opioid tolerant and take > 60 mg of oral morphine or equivalent daily. Recent studies have demonstrated the safety and efficacy of transmucosal fentanyl for managing breakthrough pain in patients receiving low-dose opioids [52]. Opioid-use disorder in patients with cancer is low (8%), and evidence that transmucosal fentanyl is more addictive is scarce [53]. Despite concerns regarding opioid abuse and dependence, clinicians should not hesitate to use opioids to manage cancer pain in patients with only a few months to live.

Conclusion

The management of breakthrough pain in cancer remains challenging. It requires individualized treatment based on the cause, pathophysiology, and clinical features of the pain. Strategies for managing breakthrough pain include the use of oral opioids, adjuvant analgesics, neuraxial opioids, orthotic devices, interventions, and surgery. The primary treatment is a rescue medication using rapid-onset opioids with adequate background pain control. Clinicians should use their knowledge of rapid-onset opioids to identify the formulation that best treats a patient with breakthrough pain.

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Conflicts of interest
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The characteristics of elderly suicidal attempters in the emergency department in Korea: a retrospective study

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Background: Although Korea ranks first in the suicide rate of elderly individuals, there is limited research on those who attempt suicide, with preventive measures largely based on population-based studies. We compared the demographic and clinical characteristics of elderly individuals who attempted suicide with those of younger adults who visited the emergency department after suicide attempts and identified the factors associated with lethality in the former group.
Methods: Individuals who visited the emergency department after a suicide attempt from April 1, 2017, to January 31, 2020, were included. Participants were classified into two groups according to age (elderly, ≥65 years; adult, 18–64 years). Among the 779 adult patients, 123 were elderly. We conducted a chi-square test to compare the demographic and clinical features between these groups and a logistic regression analysis to identify the risk factors for lethality in the elderly group.
Results: Most elderly participants were men, with no prior psychiatric history or suicide attempts, and had a higher prevalence of underlying medical conditions and attributed their attempts to physical illnesses. Being sober and planning suicide occurred more frequently in this group. In the elderly group, factors that increased the mortality rate were biological male sex ($p<0.05$), being accompanied by family members ($p<0.05$), and poisoning as a suicide method ($p<0.01$).
Conclusion: Suicide attempts in elderly individuals have different characteristics from those in younger adults and are associated with physical illness. Suicides in the former group are unpredictable, deliberate, and fatal. Therefore, tailored prevention and intervention strategies addressing the characteristics of those who are elderly and attempt suicide are required.

Keywords: Aged; Disease; Psychiatric emergency services; Suicide

Introduction

Despite remarkable advances in modern medicine and technology that have led to a decrease in mortality rate and an increase in life expectancy every year, the number of deaths by suicide has not diminished. Korea ranked first in suicide rate among the Organization for Economic Co-operation and Development (OECD) member countries in 2003 and has been in first or second place thereafter. The average suicide rate in OECD member countries in 2019 was 11.0 per 100,000 population, and Korea ranked first with 24.6 suicides per 100,000 population, which was more than twice the OECD average suicide rate [1]. Suicide is a tragic issue with significant social and economic costs. In 2019, the Centers for Disease Control and Prevention of the United States estimated the so-

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cial cost of suicide and suicide attempts in 2020 at approximately $165 billion [2]. Regarding Korea, the Health Insurance Policy Research Institute under the National Health Insurance Service published a socioeconomic cost analysis report of the ten major causes of death in 2015. According to this report, the socioeconomic costs related to suicide were estimated at 6.448 trillion won [3].

Korea has a high suicide rate in all age groups; however, the suicide rate among the elderly population is particularly high. Korea set a record for the highest suicide rate of elderly individuals among OECD member countries from 2013 to 2020. As of 2019, the suicide rate per 100,000 people by age group in Korea was 33.7, 46.2, and 67.4 for people in their 60s, 70s, and ≥ 80 years old, which is 2.2, 2.8, and 3.1 times higher than the OECD averages (15.2, 16.4, and 21.5), respectively [1]. According to the statistics on the causes of death announced by the Statistics Korea in 2020, 3,392 people aged 65 years or older died from suicide attempts in Korea [4]. Although the global population is aging, the Korean population is aging at a faster rate than that of other countries. Most countries, including Korea, follow the United Nations (UN) definition of elderly as those over 65 years of age. The UN defines an aging society as a population aged 65 years or older that accounts for 7% or more of the total population, an aged society as 14% or more, and a super-aged society as 20% or more. Korea became an aging society in 2000, and this trend has accelerated remarkably. It is predicted that 20.6% of Koreans will be 65 years or older by 2025, making Korea a super-aged society at an unprecedented speed [5]. This demographic shift has significant implications for various social and economic sectors, and preparations are crucial for future development and well-being.

Research has shown that suicide attempts are more serious and more likely to result in mortality in those who are elderly than in those who are younger [6]. In addition, it has been reported that physical illness or disability in elderly individuals is strongly associated with suicide attempts and that limited social connections are associated with suicidal ideation, non-suicidal self-harm, and suicide [7]. There are several risk factors for suicide in the elderly population, including serious psychiatric disorders, depression, and a history of suicide attempts [8]. In a Korean study, suicidal ideation was significantly higher among elderly men living alone than not living alone. This study also revealed that higher levels of depression, lower self-esteem, and poor economic status were associated with suicide [9]. As part of a regionally tailored suicide prevention project, local governments are implementing preventive measures targeting elderly individuals and those living alone and are continuing attempts to lower the suicide rate in the elderly population [10]. However, systematic studies and indicators of the characteristics and risk factors of suicide attempts among elderly individuals are insufficient. Most existing studies are epidemiological and investigated sociodemographic characteristics and revealed associations with suicidal thoughts through questionnaires. Therefore, studies involving sufficient numbers of people who attempted suicide are rare. This study investigated the demographic and clinical characteristics of elderly individuals visiting the emergency department who had attempted suicide. Consequently, we confirmed existing research results, identified risk factors related to suicide in the elderly population, and used them to classify risk groups for prevention.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2023-01-016), and the requirement for informed consent was waived due to the retrospective nature of the study.

1. Patients

A total of 2,011 patients visited the Department of Emergency at Yeungnam University Hospital between April 1, 2017, and January 31, 2020, after attempting suicide. Among them, cases in which a suicide attempt was confirmed through the information provided by the patient or when the patient denied having attempted suicide, but a guardian or rescuer provided objective information confirming such an attempt were included in the study. The exclusion criteria were as follows: children under 18 years of age and cases in which only suicidal thoughts were reported but no suicide attempt was made. A total of 779 individuals who attempted suicide, including 656 non-elderly (18–64 years) and 123 elderly (≥ 65 years) individuals, were studied.

2. Study procedure and assessment

This study used the interview records of case managers of the "Emergency Department-Based Suicide Attempts Post-Management Project," a national suicide prevention project, and the medical records of the Departments of Psychiatry and Emergency Medicine at Yeungnam University Hospital was designated as a regional emergency medical center in 2019 and receives approximately 25,000 patients annually. The institution has participated in this project since 2017. Through case management, this project promotes the emotional stability of those who attempt suicide and visit the emergency department, and it prevents the recurrence of suicide attempts by linking them with necessary treatment and counseling services.

If a patient who visits the emergency department of a research

institution is recorded as having made a suicide attempt in the National Emergency Department Information System, the emergency medicine and psychiatric departments, and the case managers are automatically contacted. Emergency medicine doctors provide physical treatment, and the psychiatric department records psychosocial and clinical factors, including the presence of mental illness, psychiatric symptoms, suicidal ideation, and suicide plans, through interviews and then provides psychotherapy. Case managers receive education and records management training through the Korea Respect for Life Hope Foundation (formerly the Central Suicide Prevention Center) and evaluate the items in the suicide attempt follow-up management manual. The demographic data of patients who attempted suicide, history of suicide attempts, coexisting diseases, medical conditions, and clinical data necessary for this study were included in the case manager's questionnaire prepared in advance.

3. Statistical analysis

Data obtained from the medical and clinical records were processed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Statistical significance was found when the *p*-value was less than 0.05. Adult patients aged 19 years or older were divided into elderly (≥ 65 years) and non-elderly adult (hereafter adult; < 65 years) groups, and the characteristics and specific relationships of the collected demographic and clinical data of suicide attempts were compared. When the dependent variable was categorical, the chi-square test or Fisher exact test was used. A *post-hoc* analysis was conducted using Bonferroni correction. When the dependent variable followed a normal distribution, the Student *t*-test was used. In addition, logistic regression analysis was performed within the elderly suicide attempt group to analyze the independent factors influencing the reasoning of these patients.

Results

1. Comparison of demographic characteristics between elderly and adult groups

The elderly group had significantly higher and lower proportions of male and female ($p < 0.001$), respectively, than the adult group. The elderly group had a lower percentage of highly educated individuals with at least a college degree and a higher percentage of individuals who were illiterate ($p < 0.001$) and held a job ($p = 0.019$) than the adult group. The proportion of unmarried participants was lower and that of married participants was higher in the elderly group than in the adult group ($p < 0.001$). In addition, no significant differences were found between the two groups in terms of cohabitation ($p = 0.997$), religion ($p = 0.124$), health insurance ($p = 0.359$), or monthly household income ($p = 0.880$). When conducting a *post-hoc* analysis using the Bonferroni correction, the results were found to be comparable (Table 1, Supplementary Table 1).

2. Comparison of clinical characteristics between elderly and adult groups

The elderly group had lower suicide attempt rates among those with a history of suicide attempts ($p = 0.007$) and a significantly lower number of previous suicide attempts than the adult group ($p < 0.001$). The proportion of individuals who had never received psychiatric treatment was higher and the percentage of individuals currently receiving psychiatric medication was lower in the elderly group than in the adult group ($p = 0.018$). The number of past psychiatric admissions was lower in the elderly group than in the adult group ($p < 0.001$). There was a significant difference in suicide awareness; however, this was attributable to the proportion of individuals whose status could not be assessed ($p = 0.006$). The elderly group had more recent acute and chronic diseases than the adult group ($p < 0.001$). There were no significant differences in physical ($p = 0.295$) and psychiatric ($p = 0.372$) treatments after past suicide attempts or family histories of psychiatry ($p = 0.789$) and suicide attempts ($p = 0.542$) (Table 1, Supplementary Table 2).

3. Comparison of suicide-related characteristics between elderly and adult groups

Among the suicide attempt methods, the elderly group had a higher prevalence of poisoning than the adult group ($p < 0.001$). In the elderly group, the proportion of those choosing houses and hospitals as places to attempt suicide was higher than in the adult group ($p < 0.001$). The ratios of hospital visits with family and friends were higher and lower, respectively, in the elderly group ($p = 0.021$). The elderly group had fewer suicide attempts in a drunken state ($p = 0.002$), and more planned suicide attempts ($p < 0.001$) than the adult group. In the elderly group, the rate of not asking for help before attempting suicide was higher and that of asking for help was lower ($p < 0.001$). Among the events that triggered suicide attempts, the proportion of diseases was higher, whereas that of intersocial, psychiatric, and socioeconomic problems was lower ($p < 0.001$). The sincerity of suicide attempts ($p < 0.001$) and transfer or discharge rates ($p < 0.001$) were higher in the elderly group than in the adult group. In the elderly group, there were fewer individuals with clear consciousness, and more were in a comatose state than in the adult group ($p = 0.003$). Elderly individuals had a lower incidence of no or slight injury but a higher rate of needing admission or mortality ($p < 0.001$). There was a difference in referrals to psychiatric treatment; however, this

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Table 1. Demographic and clinical characteristics of the elderly and adult groups

Variable	Adult group (n = 656)	Elderly group (n = 123)	χ^2 or Fisher exact test	*p*-value
Sex			13.148	< 0.001
Male	263 (40.1)	71 (57.7)		
Female	393 (59.9)	52 (42.3)		
Education			82.339	< 0.001
Illiteracy	0 (0)	10 (45.5)		
Below high school	80 (46.8)	7 (31.8)		
College or above	91 (53.2)	5 (22.7)		
Employed			5.480	0.019
Yes	167 (48.0)	50 (62.5)		
No	181 (52.0)	30 (37.5)		
Marital status			62.323	< 0.001
Single	233 (43.4)	0 (0)		
Married	257 (47.9)	78 (89.7)		
Divorced/separated/widowed	47 (8.8)	9 (10.3)		
Past suicide attempt history			7.398	0.007
Yes	190 (33.9)	23 (20.7)		
No	371 (66.1)	88 (79.3)		
Past psychiatric treatment			11.946	0.018
Likely to have had psychiatric problems (never seen a doctor)	201 (37.5)	57 (50.0)		
Likely to have not had psychiatric problems (never seen a doctor)	47 (8.8)	14 (12.3)		
Discontinued treatment	58 (10.8)	13 (11.4)		
Currently in treatment (with medication)	227 (42.4)	29 (25.4)		
Currently in treatment (no medication)	3 (0.6)	1 (0.9)		
Awareness of suicide			10.334	0.006
Admit	84 (16.0)	10 (10.5)		
Deny	430 (82.1)	78 (82.1)		
Uncheckable	10 (1.9)	7 (7.4)		
Past medical history			177.934	< 0.001
No underlying disease	404 (72.0)	15 (12.6)		
Recent acute disease	9 (1.6)	7 (5.9)		
Chronic disease (not interfering with daily life)	125 (22.3)	58 (48.7)		
Chronic disease (interfering with daily life)	23 (4.1)	39 (32.8)		
Past psychiatric admission count[a]	2.01	0.15	13.120	< 0.001

Values are presented as number (%) or mean value only.
[a]t-test.

difference was due to mental deterioration or death ($p < 0.001$). No significant differences were found between the two groups regarding suicide notes ($p = 0.371$) or suicide with other people ($p > 0.99$) (Table 2, Supplementary Table 3).

4. Factors affecting lethality of elderly individuals who attempted suicide

In the univariate logistic regression analysis performed on the variables used in the correlation analysis, biological male sex (odds ratio [OR], 5.804; 95% confidence interval [CI], 1.248–26.984), a family member accompanying the person to the emergency department (OR, 0.064; 95% CI, 0.005–0.760), and suicide attempt by poisoning (OR, 0.191; 95% CI, 0.058–0.633) were identified as significant risk factors for mortality (Table 3).

Discussion

This study found differences in demographic, clinical, and suicide attempt-related characteristics between elderly and adult individuals who attempted suicide. The findings support the results of previous epidemiological studies showing differences in suicidal ideation and suicide attempts between individuals who are elderly and those who are younger [11,12].

The proportion of male participants was significantly higher in the elderly group than in the adult group. Women make more suicide attempts; however, the suicide mortality rate is higher among men [13]. Considering previous reports that the rates of suicidal ideation and attempts increase with age in men who are elderly [14], assessments of suicide risk and immediate interventions for

Table 2. Suicide-related characteristics of elderly and adult groups

Variable	Adult group (n = 656)	Elderly group (n = 123)	χ^2 or Fisher exact test	*p*-value
Suicide method			11.467	< 0.001
Poisoning	463 (70.6)	105 (85.4)		
Non-poisoning	193 (29.4)	18 (14.6)		
Suicide place			30.618	< 0.001
House	515 (85.8)	112 (95.7)		
School	52 (8.7)	0 (0)		
Commercial facility	6 (1.0)	0 (0)		
Accommodation	6 (1.0)	0 (0)		
Car	14 (2.3)	1 (0.9)		
Hospital	1 (0.2)	4 (3.4)		
Outdoor	5 (0.8)	0 (0)		
Drunk during suicide attempt			9.820	0.002
Drunken	281 (48.0)	35 (31.8)		
Sober	304 (52.0)	75 (68.2)		
Current suicide thoughts			8.520	0.014
Yes	286 (64.6)	40 (51.3)		
No	140 (31.6)	30 (38.5)		
Uncheckable	17 (3.8)	8 (10.3)		
Suicidal plan			11.501	< 0.001
Planned	75 (13.4)	28 (26.4)		
Impulsive	484 (86.6)	78 (73.6)		
Seeking help			18.979	< 0.001
Do not need help	353 (58.8)	92 (79.3)		
Giving a clue	101 (16.8)	12 (10.3)		
Help (before attempt)	42 (7.0)	1 (0.9)		
Help (after attempt)	104 (17.3)	11 (9.5)		
Reason for suicide attempt			98.829	< 0.001
Intersocial	142 (25.1)	12 (10.8)		
Family	116 (20.5)	19 (17.1)		
Psychiatric	124 (21.9)	10 (9.0)		
Socioeconomic	108 (19.1)	10 (9.0)		
Disease	72 (12.7)	58 (52.3)		
Death or severe illness around people	4 (0.7)	2 (1.8)		
Sincerity			29.604	< 0.001
Sincerely chose a way to die	326 (53.9)	95 (79.2)		
Wanted to die, but chose a way that might not die	152 (25.1)	18 (15.0)		
Helping	125 (20.7)	6 (5.0)		
Others	2 (0.3)	1 (0.8)		
Refer for psychiatric treatment			21.021	< 0.001
Referred	321 (49.2)	53 (43.1)		
Not necessary	210 (32.2)	44 (35.8)		
Patient refused	104 (15.9)	13 (10.6)		
Mental deterioration	13 (2.0)	7 (5.7)		
Expired	5 (0.8)	6 (4.9)		
Status after visiting emergency department			27.609	< 0.001
Inpatient	192 (29.4)	28 (22.8)		
Transfer	86 (13.1)	27 (22.0)		
Discharge	355 (54.3)	53 (43.1)		
Others	21 (3.2)	15 (12.2)		
Level of consciousness			14.284	0.003
Alert	419 (64.2)	58 (47.5)		
Drowsy	115 (17.6)	28 (23.0)		
Stupor/semicoma	90 (13.8)	24 (19.7)		
Coma	29 (4.4)	12 (9.8)		
Medical lethality			43.997	< 0.001
No or slight injury	273 (42.2)	28 (23.1)		
Injury needing moderate attention	224 (34.6)	34 (28.1)		
Injury needing admission	132 (20.4)	44 (36.4)		
Expired	18 (2.8)	15 (12.4)		

Values are presented as number (%).

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Table 3. Factors affecting lethality of suicide attempts in participants who are elderly

Variable	Odds ratio (95% CI)	*p*-value
Sex, male	5.804 (1.248–26.984)	<0.05
Covisitor, family	0.064 (0.005–0.760)	<0.05
Suicide method, poisoning	0.191 (0.058–0.633)	<0.01

CI, confidence interval

this population are particularly necessary. There were fewer college graduates and more illiteracy in the elderly group than in the adult group. According to the 2020 elderly survey report [11], approximately 10.6% of elderly individuals aged 65 years or older had no education; 31.7%, 23.3%, and 28.4% had graduated from elementary, middle, and high schools, respectively; and only 5.9% had a community college or higher education. This could be considered a characteristic of the elderly group that is unrelated to suicide attempts. However, existing studies have shown that suicidal ideation, hopelessness, and depression are higher in elderly people with low education, and that low education [15] in the elderly population is related to low self-efficacy [16] and subjective quality of life [17]. Therefore, lack of education and low educational attainment, which are more prominent in the elderly group, may have contributed to the increase in suicide attempts. The rate of suicide attempts of elderly individuals living alone was high (57.72%), but there was no difference compared with that of the adult group [11]. There was no significant difference between the two groups in terms of type of medical insurance or monthly household income; however, the proportion of participants receiving medical aid was similarly high in both groups. As of 2021, 592,807 of the 1,516,525 beneficiaries of medical aid, or approximately 39%, were seniors aged 65 years or older [18]. In this study, among the elderly participants who visited the emergency department because of a suicide attempt, 74.8% were medical aid beneficiaries, which is higher than that of the general elderly population. This is consistent with previous findings that socioeconomic status in the elderly population is associated with depression and suicidal ideation [19,20].

When examining psychiatric history, the elderly group had a higher proportion of individuals with no history of and a lower proportion of individuals currently receiving psychopharmacological treatment and past psychiatric hospitalizations. This appears to contrast with established studies that identify psychiatric history as an important risk factor for reattempting suicide and a major factor in increasing suicide risk and completion rates [21]. However, this could be due to negative perceptions and neglect of mental health care in the past, as well as low accessibility to such services. It should also be considered that these societal impacts may be even more pronounced among older individuals. In the elderly group, a higher proportion of individuals had no history of suicide attempts, and the number of past suicide attempts was lower than in the adult group. In the elderly population, the presence of a suicide attempt is associated with an even higher suicide risk [22,23]. When connecting these findings to previous studies indicating lower levels of depression, anxiety, and suicide-related scales in individuals who attempted suicide and are elderly than in those who are non-elderly, suicide among elderly individuals may exhibit characteristics that make it more easily overlooked and difficult to predict [24]. Therefore, heightened attention should be paid to elderly individuals who appear to have a lower suicide risk, considering their psychiatric history, scales, and even suicide history.

In our study, elderly individuals were more likely than adults to have underlying chronic diseases. Although physical diseases commonly increase with age, it is important to pay attention to the high prevalence of depression and suicidal ideation in hospitalized patients who are elderly [25]. In older adults, both physical and mental illnesses can independently increase the risk of suicide, and multiple diseases can further increase such risk [25-27]. This is consistent with the higher rate of physical illness as a reason for suicide in the elderly group than in the adult group. Physical discomfort or underlying diseases in older adults are mediated by feelings of depression and hopelessness, which increase the severity of suicide attempts [26,27]. Additionally, considering that elderly individuals with depression often complain of physical discomfort rather than emotional discomfort [28], their suicide risk needs to be assessed in not only psychiatry but also in other departments. According to a psychological autopsy study, nearly 50% of those aged 60 years or older who died by suicide visited a medical institution in the month of death, 26% in the week before death, and 7% on the day before death, but more than half of the counseling was for physical discomfort [29].

The proportion of those who chose poisoning as the suicide method was higher in the elderly group than in the adult group. According to global statistics, hanging is the most common method of suicide, and it is the same in Korea [10,30]. However, the probability of survival in the emergency department owing to the high fatality rate is significantly lower than that of poisoning. Compared with adults who are younger, the severity and prognosis of patients who are elderly are worse for poisoning; therefore, more attention and care are needed [12].

The finding that suicide attempts in the elderly group are more deliberate is consistent with previous reports [29]. This is because, in the case of suicides in the elderly population, attempts are often made because of existing suicidal thoughts that have lasted for a long time rather than those that have been triggered by a specific

event [31,32].

The rate of asking for help immediately before the suicide was significantly lower in the elderly group. Paradoxically, suicidal ideation in the elderly population tends to be chronic because it is often long-standing. In one study, 49% of suicide attempts in individuals over the age of 60 years revealed suicidal intentions within the year prior to death, and 18% of cases overtly expressed suicidal ideation [30]. Therefore, there is a period during which intervention is possible for elderly individuals, and it is necessary to devise timely and appropriate intervention methods.

Suicide attempts by the elderly group were more genuine and medically lethal. This supports previous findings that suicide by older individuals has a high fatality rate [23,33] and is consistent with previous reports that older adults have higher suicidal intentions than younger adults [34].

In the elderly group, the factors that increased fatality were (1) biological male sex, (2) being accompanied by family members, and (3) poisoning as a suicide method. Although female participants had a higher rate of suicidal thoughts and attempts than their male counterparts, male mortality rates were higher in previous studies [35]; the same results were confirmed in the elderly group in our study. In 37 OECD countries, persons aged 70 years and older are more likely to die by suicide than any other age group, and the tendency toward fatal suicidal behavior prevails in men aged 75 years, with rates six times higher than those in women [36]. Many younger adults visited the emergency department by themselves or with friends. However, among the elderly participants, there were many cases in which they could not reach the emergency department on their own because of their physical fragility after a serious suicide attempt. Many patients were transferred and, under these circumstances, being accompanied by a family member may be related to the mortality rate. According to 2017 data from the Korea Emergency Medical Information System, poisoning was the most common suicide attempt method, and the rate of choosing poisoning for suicide attempts increased with age [37]. Another study that evaluated suicide attempts by poisoning showed that psychiatric drugs (43.4%) were the most common substances used across all age groups, whereas pesticides (50.3%) were the most common substances used for self-poisoning among elderly individuals [38]. Self-poisoning is also associated with poorer clinical outcomes in elderly patients than in younger adult patients. Fatal substances are often selected by older individuals. Additionally, more serious medical situations may be caused by toxic substances due to preexisting diseases and aging, which are believed to increase the mortality rate of the elderly population. In one study, demographic and clinical factors, such as older age, biological male sex, interpersonal stress, and impression of schizophrenia, were associated with mortality among those who attempted suicide and were younger than 65 years. However, in the same study, no factors affecting the mortality of suicide attempts in elderly individuals were found, but there may have been limitations, as only 37 suicide attempts by older individuals were included [6].

The limitations of this study were as follows. First, considering the results of a previous study in which less than 30% of those attempting suicide visited the hospital, the current study was conducted on those who visited the emergency department of a university hospital; therefore, there may be limitations in generalizing the results. Second, this study included critically ill participants who attempted suicide and visited the emergency department, which limited the use of validated scales owing to time and environmental constraints. However, this study was not indirectly performed via a questionnaire survey but rather by directly assessing high-risk patients who attempted suicide, including a sufficient number of elderly participants who were compared with younger adults. In addition, this study attempted to identify the predictors of suicide mortality in the elderly group and found significant results. These findings highlight the importance of conducting large well-designed studies to replicate and validate our results.

In conclusion, our study revealed distinct characteristics of elderly individuals who attempted suicide compared with those of younger adults who attempted suicide. Physical illness plays a significant role in suicide attempts and related life events among older adults. Suicide attempts among the elderly were more premeditated and serious, employing lethal methods such as pesticide poisoning. Moreover, these patients were less likely to receive appropriate psychiatric treatment, were hesitant to seek help, and faced higher lethality due to underlying medical conditions. These findings underscore the need for a tailored preventive strategy aimed at addressing the specific needs of the elderly population.

Supplementary materials

Supplementary Tables 1–3 can be found via https://doi.org/10.12701/jyms.2023.01004.

Article information

Conflicts of interest

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

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Incidence and severity of medication-related osteonecrosis of the jaw in patients with osteoporosis using data from a Korean nationwide sample cohort in 2002 to 2019: a retrospective study

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Background: Medication-related osteonecrosis of the jaw (MRONJ) is a significant concern, particularly among patients taking bisphosphonates (BPs), denosumab, and selective estrogen receptor modulators (SERMs) for osteoporosis. Despite the known risks, large-scale cohort studies examining the incidence and severity of MRONJ are lacking. We aimed to ascertain the incidence and risk of MRONJ among these patients, whom we stratified by age groups, medication types, and duration of use.

Methods: We utilized data from the National Health Insurance Service's sample cohort database, focusing on patients aged 40 years and above diagnosed with osteoporosis. The patients were divided into three groups: those prescribed BPs only, those prescribed SERMs only, and those prescribed both.

Results: The overall incidence rate of MRONJ was 0.17%. A significantly higher incidence rate was observed among those taking osteoporosis medications, particularly among females with a relative risk of 4.99 (95% confidence interval, 3.21–7.74). The SERM group also had an incidence rate comparable to that of the BP group. Severity was assessed based on the invasiveness of the treatment methods, with 71.3% undergoing invasive treatment in the medication group.

Conclusion: This study provides valuable insights into the incidence and severity of MRONJ among a large cohort of patients with osteoporosis. It underscores the need for comprehensive guidance on MRONJ risks across different medication groups and sets the stage for future research focusing on specific populations and treatment outcomes.

Keywords: Bisphosphonate; Osteonecrosis of jaw; Osteoporosis; Selective estrogen receptor modulators

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a debilitating oral condition characterized by the exposure of necrotic jawbone, typically occurring in patient on certain medications, such as bisphosphonates (BPs) [1]. It is precipitated by dental surgery but occasionally manifests spontaneously. While this disorder has multiple etiologies, its association with BP medication is of particular

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concern, especially given the widespread use of BPs for managing osteoporosis and cancer-related conditions like metastasis to the bone [2]. In the management of osteoporosis, BPs, selective estrogen receptor modulators (SERMs), and denosumab are commonly utilized as first-line pharmacological agents. These medications are frequently cited in multiple clinical guidelines pertaining to the treatment of osteoporosis [3].

One of the most significant adverse effects associated with BPs is osteonecrosis of the jaw (ONJ). Notably, ONJ related to surgical dental procedures, such as tooth extraction, periodontal treatment, and implantation, is a well-documented complication [4]. Additionally, individual comorbidities and lifestyle factors, such as steroid use, cancer, diabetes, and smoking, elevate the risk of ONJ occurrence [5].

As the aging population continues to grow, the prevalence of osteoporosis is also on the rise, leading to an increase in the number of individuals prescribed BPs. The incidence of ONJ among those taking BPs has been reported to range from 0.05% to 0.21% [6]; however, large-scale cohort studies to accurately determine this incidence rate have been lacking. In an aging population where the demand for dental treatments such as implantation is increasing, the potential for complications like ONJ poses a risk of diminished quality of life [7].

In particular, some epidemiological evidence exists regarding the increased risk of ONJ among BP users based on the duration of medication use, sex, and age. However, studies specifically examining the severity of ONJ related to medication use have been lacking. Therefore, we aimed to ascertain the incidence and risk of ONJ among patients with osteoporosis prescribed with BPs and SERMs. We provided data on the incidence rate and risk of these patients stratified by age groups, medication types, and duration of use. Additionally, we presented data on the severity outcomes of MRONJ based on dental treatments.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YU 2021-12-007), and the requirement for informed consent was waived.

1. Study population and cohort data

The National Health Insurance Service's (NHIS) sample cohort database is a standardized dataset for academic research. The database provides health insurance data from 2002 to 2019 for one million individuals and is organized into tables for eligibility and premiums, birth and death records, medical treatment, health examinations, healthcare facilities, and long-term care. We aimed to analyze data from at least a 10-year period, considering adverse effects that could occur over several years; thus, we set the enrollment year at 2006.

The 2006 data comes from one million individuals who maintained eligibility as health insurance enrollees or medical aid beneficiaries for that year, representing 2% of the entire South Korean population. For the purpose of this study, we excluded 886,082 individuals who were under the age of 40 years and had no diagnosis of osteoporosis from these one million individuals. We also excluded those who were diagnosed with osteoporosis prior to 2006. A total of 113,918 patients aged 40 years and above were identified as having been diagnosed with osteoporosis, among whom 61,183 had been prescribed osteoporosis medications. The data on the prescription of osteoporosis medication was based on the date of the initial prescription.

The definition of an osteoporosis-diagnosed patient in this study was based on the presence of an osteoporosis diagnosis code as either the primary or secondary condition. The criteria for osteoporosis diagnosis were based on the International Classification of Diseases, 10th Revision codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere). The osteoporosis medications were identified based on prior literature and are listed in Table 1. Those prescribed to the study participants consisted of BPs and SERMs, both of which were orally administered.

In this study, we divided the cohort into three groups for analysis: those prescribed only BPs, those prescribed only SERMs, and those prescribed both. Among the 61,183 patients who had been prescribed osteoporosis medications, 195 were diagnosed with ONJ and constituted the final population for analysis.

2. Definition of medication-related osteonecrosis of the jaw

MRONJ is defined as the presence of exposed bone in the maxillofacial area or oral and extraoral fistulas that do not heal within 8 weeks in patients who have been administered bone-modifying agents such as antiresorptive drugs or angiogenesis inhibitors and who have no history of radiation therapy to the head and neck area [8].

To identify MRONJ, the diagnostic codes used were M87.1 (osteonecrosis due to drugs) and K10.2 (inflammatory conditions of jaws). We referred to the dental insurance claim codes used in general hospitals and defined patients with MRONJ based on the following treatment codes, which are listed in Table 2.

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Table 1. List of medications of osteoporosis

Type	Medication	Code
Bisphosphonates	Alendronic acid 10 mg	228301ATB
	Alendronic acid 5 mg	228302ATB
	Alendronic acid 70 mg	228303ALQ
		228303ATB
		228305ATB
	Alendronic acid 5 mg+calcitriol 0.5 μg	468000ATE
	Alendronic acid 70 mg+cholecalciferol (vitamin D3 2.8 kIU)	481100ATB
	Alendronic acid 70 mg+cholecalciferol (vitamin D3 5.6 kIU)	500200ATB
	Disodium etidronate 0.2 g	147401ATB
	Zoledronic acid 5 mg (50 μg/mL)	420732BIJ
	Zoledronic acid 4 mg (40 μg/mL)	420730BIJ
	Zoledronic acid 4 mg (0.8 μg/mL)	420731BIJ
	Risedronate sodium 5 mg	442301ATB
	Risedronate sodium 35 mg	442302ATB
	Risedronate sodium 2.5 hydrate (enteric coated) 35 mg	442302ATE
	Risedronate sodium 75 mg	442303ATB
	Risedronate sodium 0.15 g	442330ATB
	Risedronate sodium 35 mg+ cholecalciferol 5.6 kIU	511200ATB
	Risedronate sodium 0.15 g+ cholecalciferol 30 kIU	518400ATB
	Ibandronic acid 3 mg (1 mg/mL)	480330BIJ
	Ibandronic acid 0.15 g	480304ATB
	Ibandronic acid 0.15 g+cholecalciferol 24 kIU	523900ATB
	Pamidronate 15 mg (15 mg/mL)	207930BIJ
	Pamidronate 0.1 g	207901ACS
SERMs	Raloxifene 55.71 mg	358001ATB
	Raloxifene 55.71 mg+cholecalciferol (as vitamin D3 800 IU)	659200ACH
		659200ATB
	Bazedoxifene 20 mg	617101ATB
	Bazedoxifene 20 mg+cholecalciferol (as vitamin D3 800 IU)	674500ATB
	Toremifene citrate (as toremifene 40 mg)	242101ATB
	Toremifene citrate (as toremifene 20 mg)	234502ATB
	Toremifene citrate (as toremifene 10 mg)	234501ATB
	Clomipramine hydrochloride 25 mg	136302ACH
	Clomipramine hydrochloride 25 mg	136301ACH
	Clomiphene citrate 50 mg	136201ATB

kIU, kilo-international unit; IU, international unit; SERMs, selective estrogen receptor modulators.

3. Data analysis

The data were analyzed using SAS 9.4 and IBM SPSS ver. 27.0 (IBM Corp., Armonk, NY, USA) statistical software, with the statistical significance level set at a p-value of < 0.05. A cross-analysis was conducted to examine the general characteristics of patients with ONJ and the presence or absence of osteoporosis medication. Relative risk (RR) of ONJ occurrence based on the prescription of osteoporosis medication was also analyzed.

Table 2. Treatment codes of osteonecrosis of the jaw

Code	Treatment	Category
U4457	Intraoral antiphlogosis-osteitis of jaw, osteomyelitis of jaw, etc.	Noninvasive treatment
U4467	Extraoral antiphlogosis-osteitis of jaw, osteomyelitis of jaw, etc.	
U4533	Surgery of osteomyelitis of mandible or maxilla-limited alveolar bone	Invasive treatment
U4534	Surgery of osteomyelitis of mandible or maxilla-one side mandible 1/3 below	
U4535	Surgery of osteomyelitis of mandible or maxilla-one side mandible 1/3 over	

Results

Among the 61,183 osteoporosis patients aged 40 years and above who were confirmed to have been prescribed osteoporosis medication, 5,537 were male and 55,646 were female, indicating a female majority. When examined by age group, there were 3,903 individuals aged 40 to 49 years, 14,945 in their 50s, 22,465 in their 60s, and 19,870 aged 70 years and above. There were 52,743 were taking BPs, 3,101 patients taking SERMs, and 5,339 were taking both types of medications (Table 3).

The occurrence of ONJ was examined based on sex, age group, and whether osteoporosis medication was administered (Table 4). The incidence of ONJ was significantly higher in the osteoporosis medication group (RR, 3.81; 95% confidence interval [CI], 2.66–5.48), particularly among females with an RR of 4.99 (95% CI, 3.21–7.74). In the 40s age group, the RR was relatively low at 1.44 and was statistically insignificant (95% CI, 0.26–7.84).

The time from the initial medication administration to the occurrence of ONJ was analyzed during the study period. In both the BP and SERM groups, the majority of cases occurred after 5 years, with 74 cases (51.0%) for the BP group and six cases (42.8%) for the SERM group (Table 5).

In the treatment of ONJ, we examined both invasive and noninvasive surgical treatment methods (Table 6). Among the group that received osteoporosis medication, invasive treatment was more common, accounting for 127 cases (71.3%). In contrast, in the group that did not receive medication, invasive treatment was relatively less common, with 20 cases (55.6%), although this difference was not statistically significant. When examined by medication type, invasive treatment was performed in 69.9% of the BP group, 85.7% of the SERM group, and 75.0% of the group receiving both medications.

Discussion

MRONJ is considered a rare condition due to its low incidence

Table 3. Medications of osteoporosis with regards to sex and age

Variable	Total	Osteoporosis medication			*p*-value
		Bisphosphonates	SERMs	Both	
Sex					
Male	5,537 (9.0)	5,432 (98.1)	58 (1.0)	47 (0.8)	<0.001
Female	55,646 (91.0)	47,311 (85.0)	3,043 (5.5)	5,292 (9.5)	
Age (yr)					
40–49	3,903 (6.4)	2,839 (72.7)	733 (18.8)	331 (8.5)	<0.001
50–59	14,945 (24.4)	12,353 (82.7)	1,125 (7.5)	1,467 (9.8)	
60–69	22,465 (36.7)	19,468 (86.7)	759 (3.4)	2,238 (10.0)	
≥70	19,870 (32.5)	18,083 (91.0)	484 (2.4)	1,303 (6.6)	
Total	61,183 (100)	52,743 (86.2)	3,101 (5.1)	5,339 (8.7)	

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

Table 4. Numbers of cases of osteonecrosis of the jaws (ONJs)

Variable	Cases of osteoporosis	Cases of ONJ			RR (95% CI)
		Total	Osteoporosis medication		
			Yes	No	
Sex					
Male	14,934 (13.1)	25 (0.17)	12 (48.0)	13 (52.0)	1.57 (0.72–3.44)
Female	98,984 (86.9)	170 (0.17)	147 (86.5)	23 (13.5)	4.99 (3.21–7.74)
Age (yr)					
40–49	15,105 (13.3)	6 (0.04)	2 (33.3)	4 (66.7)	1.44 (0.26–7.84)
50–59	33,063 (29.0)	26 (0.08)	20 (76.9)	6 (23.1)	4.05 (1.62–10.08)
60–69	34,150 (30.0)	92 (0.27)	77 (83.7)	15 (16.3)	2.68 (1.54–4.66)
≥70	31,600 (27.7)	71 (0.22)	60 (84.5)	11 (15.5)	3.23 (1.70–6.14)
Total	113,918 (100)	195 (0.17)	159 (81.5)	36 (18.5)	3.81 (2.66–5.48)

Values are presented as number (%).
RR, relative risk; CI, confidence interval.

Table 5. Time to occurrence of osteonecrosis of the jaw with regard to osteonecrosis medication

Time to incident (yr)	Osteoporosis medication			*p*-value
	Bisphosphonates	SERMs	Total	
<1	10 (6.9)	3 (21.4)	13 (8.2)	
≥1, <2	10 (6.9)	1 (7.2)	11 (6.9)	
≥2, <3	13 (9.0)	3 (21.4)	16 (10.1)	
≥3, <4	16 (11.0)	1 (7.2)	17 (10.7)	
≥4, <5	22 (15.2)	0 (0)	22 (13.8)	
≥5	74 (51.0)	6 (42.9)	80 (50.3)	
Total	145 (91.2)	14 (8.8)	159 (100)	0.171

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

Table 6. The number of invasive or noninvasive treatments of osteonecrosis of the jaw according to medication

Medication	Total	Noninvasive surgery	Invasive surgery	*p*-value
Yes	178 (83.8)	51 (28.7)	127 (71.3)	0.062
Bisphosphonates	143 (80.3)	43 (30.1)	100 (69.9)	0.650
SERMs	7 (4.0)	1 (14.3)	6 (85.7)	
Both	28 (15.7)	7 (25.0)	21 (75.0)	
No	36 (16.2)	16 (44.4)	20 (55.6)	
Total	214 (100)	67 (31.3)	147 (68.7)	

Values are presented as number (%).
SERMs, selective estrogen receptor modulators.

rate, and its treatment and prognosis are often poor, necessitating prevention and caution. The condition involves complex prescriptions and treatments across multiple specialties, including internal medicine, orthopedics, dentistry, oral and maxillofacial surgery, and plastic surgery. While it is challenging to manage solely within one specialty, there is room for prevention if healthcare providers from any specialty take the risk of MRONJ into account and communicate appropriately with colleagues from other departments. Through this study, we confirmed the incidence rate of MRONJ among patients with osteoporosis who were taking BPs and assessed its severity based on the invasiveness of the treatment methods. While epidemiological studies on the relationship between

BP use and MRONJ are somewhat known, this is the first study, to the best of our knowledge, that evaluates the severity of MRONJ based on medication use in a large-scale cohort.

The prevalence of osteoporosis is increasing and is currently known to be 18.3% worldwide [9]. Elderly women are specifically at risk. Over 90% of patients with osteoporosis are women, particularly those older than 50 years. The demand for dental treatment also increases with age. Consequently, it was hypothesized that the incidence of MRONJ would also increase with age among those taking osteoporosis medications. This study confirmed epidemiological evidence to support this. Given that over 90% of patients with osteoporosis are women and that BP prescriptions are also more common among female patients, it was observed that the incidence of MRONJ is higher in women. Specifically, when examined by sex, it was confirmed that women are more vulnerable to MRONJ while on medication than men, which contrasts with previous studies that suggested a higher incidence of MRONJ among men taking BP compared to women [10,11].

A significantly higher incidence of MRONJ was observed in the group taking osteoporosis medications compared to those who were not. The incidence rate of MRONJ was found to be 0.17%. The incidence rate of MRONJ among patients with osteoporosis varies from study to study; for instance, a study in Japan reported an incidence rate of 0.06% [12]. This finding is consistent with previously known incidence rates, lending credibility to the reliability of this sample cohort.

We aimed to examine the differences between the BP group and the SERM group as a control. Interestingly, the incidence rate of MRONJ in the SERM group was found to be at the same level as that in the BP group. While MRONJ is generally not well-known to occur in patients taking SERMs, it has been reported to occur even in those receiving SERMs alone [13,14]. However, the association between MRONJ and SERMs should be carefully interpreted. The number of MRONJ cases should be considered as it is a relatively small number compared to that of the BP group. In addition, we observed MRONJ cases only in patients with osteoporosis. This may have resulted in increased cases in the SERMs group, not in breast cancer or other SERM users. Although the results could be interpreted as an effect of past BP use in the SERM group, it suggests the need for comprehensive guidance on the risks of MRONJ for patients with osteoporosis undergoing drug treatment, including those in the SERM group.

There are several limitations in this study. First, the representativeness of the data extracted from the sample cohort was limited as it was secondary data. Although the data from the NHIS claims to cover the entire population, the 2% of the allegedly entire population uniformly extracted may still have lacked representativeness. Second, securing statistical significance was challenging due to the rarity of MRONJ. Lastly, while it would have been ideal to evaluate the severity of MRONJ through staging in actual clinical settings, this was not feasible due to poor staging and limitations in accessing medical records. Therefore, we utilized a research method based on treatment method names.

The evaluation concerning the severity and stage of MRONJ in clinical setting was as follows [15]. Stage 1 patients had exposed bone and were asymptomatic with no localized soft tissue infection. Stage 2 patients had exposed bone, pain, and regional soft tissue inflammation or infection. Stage 3 patients had exposed bone with associated pain, localized soft tissue inflammation (or secondary infection), pathological fracture, and extraoral or oral-antral fistulas. Radiographically, the bone showed osteolysis extending to the inferior mandibular border or maxillary sinus floor. However, those staging systems rarely applied to the patient, and the stage information was not available in NHIS.

Despite these limitations, we were able to utilize nationwide data accumulated over a long period in this study. Particularly, we evaluated the severity of MRONJ by using treatment methods as variables. Future research should focus on specific populations such as patients with osteoporosis and cancer and further explore the relationship between medication use and the location and severity of MRONJ.

Article information

Conflicts of interest

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

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Author contributions

Conceptualization: all authors; Data curation, Formal analysis: SYK, TYH; Funding acquisition, Methodology, Validation: TYH, KB, CP; Resources, Software: SYK; Supervision: TYH; Writing-original draft: SYK; Writing-review & editing: KB, CP

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Case report

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Sciatic neurotmesis and periostitis ossificans progressiva due to a traumatic/unexpected glass injury: a case report

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Peripheral nerves may be affected or injured for several reasons. Peripheral nerve damage can result from trauma, surgery, anatomical abnormalities, entrapment, systemic diseases, or iatrogenic injuries. Trauma and iatrogenic injuries are the most common causes. The ulnar, median, and radial nerves are the most injured nerves in the upper extremities, while the sciatic and peroneal nerves are the most injured nerves in the lower extremities. The clinical symptoms of peripheral nerve damage include pain, weakness, numbness/tingling, and paresthesia. Therefore, early diagnosis and appropriate treatment of peripheral nerve injuries are crucial. If a peripheral nerve injury is left untreated, it can lead to severe complications and significant morbidity. The sciatic nerve is one of the most affected nerves. This nerve is generally injured by trauma and iatrogenic causes. Children are more susceptible to trauma than adults. Therefore, sciatic nerve injuries are observed in pediatric patients. When the sciatic nerve is damaged, pain, weakness, sensory loss, and gait disturbances can occur. Therefore, the diagnosis and treatment of sciatic nerve injuries are important to avoid unexpected consequences. Ultrasound can play an important role in the diagnosis of peripheral nerve injury and the follow-up of patients. The aim of this case report is twofold. First, we aimed to emphasize the critical role of ultrasonographic evaluation in the diagnosis of peripheral nerve injuries and pathologies. Second, we aimed to present this case, which has distinguishing features, such as the existence of periostitis ossificans progressiva with sciatic neurotmesis due to a traumatic glass injury.

Keywords: Periostitis; Peripheral nerve injury; Rehabilitation; Ultrasonography; Wounds and injuries

Introduction

Although sciatic mononeuropathy is rare in children, its involvement is the most common type as far as traumatic peripheral nerve injuries are concerned [1]. The etiology usually involves direct cutting of the nerve, compression, vascular diseases, malignancy, and infections [1,2]. In this report, we present a 2-year-old child who suffered an unexpected sciatic nerve injury due to direct cutting by glass. During follow-up, he was also found to have periosteal involvement in addition to the deep soft tissue injuries. We discuss the role of ultrasound examination in monitoring this patient and the rehabilitation challenges that he faces.

Case

Ethical statements: Informed consent for this case report was obtained from the patient's legal guardian.

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One year ago, a 2-year-old patient was examined 3 weeks after surgery (left sciatic nerve coaptation and hamstring muscle repair) to repair a severed sciatic nerve resulting from a traumatic glass injury (falling on a glass vase while playing/running). He was prescribed home-based exercises and an ankle-foot orthosis. Electrodiagnostic evaluations 4 months after the surgery had revealed severe axonal injury to the left sciatic nerve. Range of motion, ankle stretching, and lower limb strengthening exercises were gradually added to the rehabilitation protocol.

One year after surgery, physical examination during a control visit showed improved strength in the gastrocnemius and plantar flexor muscles, as well as the sensation of the plantar surface. Repeat electrodiagnostic evaluations revealed denervation potentials and neurogenic motor unit action potentials in the tibialis anterior and gastrocnemius muscles. Ultrasound examination (Fig. 1, Supplementary Video 1) was performed on the sciatic nerve, which was significantly swollen and irregular compared with the right side (cross-sectional areas of 155 mm^2 and 19 mm^2, respectively). While scanning the peroneal and tibial branches (which were normal), a cortical/periosteal spur-like lesion was incidentally detected on the lateral side (Supplementary Video 2), which did not cause any compression of the sciatic nerve. Radiographs confirmed the diagnosis of periostitis ossificans progressiva (Fig. 1). An outpatient physical therapy program, including neuromuscular electrical stimulation of the left sciatic nerve-innervated muscles, was initiated, along with strengthening exercises. The patient is still undergoing conservative follow-up, and further surgical intervention is not currently being considered.

Discussion

Sciatic nerve injury is the most common type of traumatic neuropathy in children [3]. Depending on the extent of trauma, the scenario can turn into a complex injury involving nearby soft tissues. Considering its numerous advantages (high resolution, lack of radiation, dynamic imaging, etc.), ultrasound examination appears to be the paramount initial approach for uncovering any nerve or adjacent pathology. Owing to its patient friendliness and the possibility of dynamic assessment, ultrasound improves the examination, especially in children, where imaging would otherwise necessitate additional techniques/medications [4]. One of the main purposes of this report was to draw attention to the role of ultrasound examinations in pertinent cases, particularly during long-term follow-up, when repeat evaluations might be required. As a side note, ultrasound also led us to recognize another complication while scanning the healing sciatic nerve [5]. Indisputably, the need for extra imaging should always be part of the agenda in case sound waves fail to provide the "complete picture." Radiography was performed to image the periosteum, cortex, and bone to identify additional pathologies. Certain ossifications can be detected by ultrasound even before radiography or computed tomography [6].

The second aim for presenting this patient was to describe a nontrivial scenario of (extensive) trauma, in which rehabilitation was lengthy and challenging. However, despite the fact that nerve

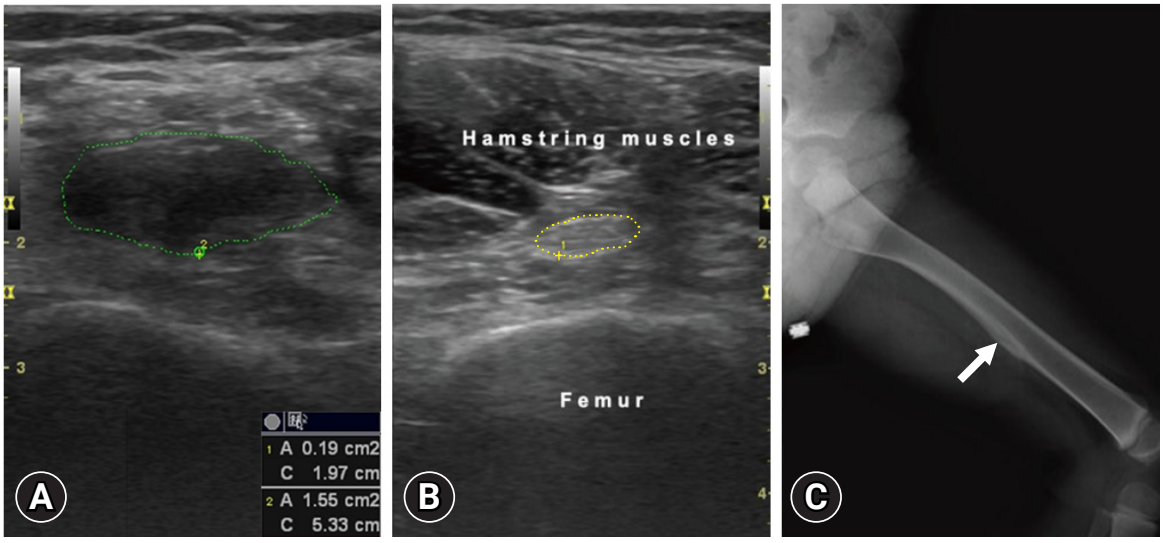

Fig. 1. (A) Axial imaging for cross-sectional area measurement (1.55 cm^2) shows the edematous, irregular, and anechoic sciatic nerve (green tracing) on the left side. (B) Axial imaging for cross-sectional area measurement (0.19 cm^2) shows the normal sciatic nerve (yellow tracing) on the right side. (C) Anteroposterior radiograph of the left femur (frog leg position) shows the periosteal lesion (arrow).

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and soft tissue healing is better in children than in adults, compliance with orthotic use during daily life or electrical stimulation during physical therapy may be significantly lower in children. Nonetheless, the patient's favorable progress with conservative treatment precluded additional surgery.

To the best of our knowledge, a direct/complete sciatic nerve cut due to a traumatic glass injury has not been reported in the relevant literature. Therefore, in this rare (but otherwise possible) case, we call attention to the need for prompt and thorough imaging during the acute care and long-term follow-up of extensive traumatic lesions. Last but not least, for children, ultrasound examinations might be the "sous chef" while "baking."

Supplementary materials

Supplementary Videos 1 and 2 can be found via https://doi.org/10.12701/jyms.2023.01018.

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Case report

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DaVinci SP-based simultaneous bilateral partial nephrectomy from the midline transperitoneal approach: a case report

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While simultaneous bilateral partial nephrectomy with a conventional multiport robot has been consistently reported since the 2010s, the introduction of the DaVinci SP system (Intuitive Surgical, Sunnyvale, CA, USA) could provide a novel way to perform surgery on bilateral kidneys while innovatively reducing the number of incisions. In our first report worldwide, the patient with bilateral small renal mass (2.0 cm for the left and 1.5 cm for the right side) and preoperative normal renal function was placed in the lateral decubitus position on an inverted bed. After tilting the bed to be as horizontal as possible, a 4-cm incision was made in the lower part of the umbilicus for the floating trocar technique. The partial nephrectomy was performed reliably as with the conventional transperitoneal approach, and then the patient could be repositioned to the contralateral side for the same procedure, maintaining all trocars. Total operation time (skin to skin), total console time, and the left- and right-side warm ischemic times were 260, 164, 27, and 23 minutes, respectively, without applying the early declamping technique. The estimated blood loss was 200 mL. The serum creatinine right after the operation, on the first day, 3 days, and 90 days after surgery were 0.92, 0.77, 0.79, and 0.81 mg/dL, respectively. For 90 days after the procedure, no complications or radiologic recurrence were observed. Further clinical studies will reveal the advantages of using the DaVinci SP device for this procedure over traditional multiport surgery, maximizing the benefit of a single port-based approach.

Keywords: Partial nephrectomy; Renal cell carcinoma; Robotics

Introduction

The minimally invasive approach to intraabdominal surgery in urology has been revolutionized by introducing the DaVinci SP (Intuitive Surgical, Sunnyvale, CA, USA), whose benefits can be maximized in bilateral renal masses, where conventional multiport requires too many holes to insert trocars for the robotic instrument. Bilateral renal tumors account for approximately 3% of renal tumors [1], and a simultaneous bilateral partial nephrectomy with a conventional multiport robot has been consistently reported since the 2010s. However, applying the DaVinci SP device by the transperitoneal approach through a median small incision for the floating trocar technique could provide an alternative surgical option that allows a bilateral approach to the kidney under a single anesthesia session. Here, we present the surgical technique and literature review.

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Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC-2023-08-019). Written informed consent was obtained from the patient for the publication of this report including all clinical images.

A 52-year-old man presents to the outpatient urology department with an incidentally discovered bilateral kidney mass by ultrasound. On the abdominal computed tomography (CT), the masses measured 1.5 cm on the right and 2.0 cm on the left. The RENAL (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines) nephrometry score was 5 for both sides the PADUA (preoperative aspects and dimensions used for an anatomical) score was 7 for the left and 8 for the right sides (Fig. 1). The patient had no previous history of surgery or trauma and no history of comorbidities or medications. Preoperatively, serum creatinine and estimated glomerular filtration rate (eGFR) were 0.81 mg/dL and 86.7 mL/min/1.73 m^2, respectively. All other preoperative laboratory findings were within normal limits. His body mass index was 24.3 kg/m^2. Given the relatively small size of the masses, a preoperative biopsy was not performed.

Given the larger mass in the left kidney and two renal arteries on the CT image, a left-side procedure was attempted first. The patient was placed on the right-side lateral decubitus position on an inverted bed. After tilting the bed to be as horizontal as possible, a 4 cm incision was made in the lower part of the umbilicus. Then, an SP Access Kit (manufactured by Intuitive Surgical) was installed for the floating trocar technique. An additional port for the assistant manipulating the laparoscopic device was made on the midline above 5 cm from the umbilicus, with a blind supporting the peritoneum with fingers through the previously made midline incision (Fig. 2A).

The surgical procedure involved robotic instruments, specifically monopolar curved scissors, Fenestrated bipolar forceps, Cadiere forceps, and needle drivers. Robotic partial nephrectomy was performed using the same procedure as the usual transperitoneal approach. In brief, the double renal artery was isolated, and two separate vessel loops were placed around them. The location and depth of the tumor were confirmed by intraoperative ultrasound, then the surface of the kidney was scored using a monopolar curved scissor. After clamping the arteries, indocyanine green was administrated to confirm complete ischemic status utilizing the firefly function. After careful resection of the tumor surrounding the pseudo capsule of the tumor, the baseline bleeding was secured with 15 cm of 3-0 observable suture, then resected renal parenchyma were closed with interrupted fashion utilizing the same suture material embedded with a large-sized surgical clip at the distal end. The procedures were performed without applying the early-declamping technique to minimize potential bleeding. The

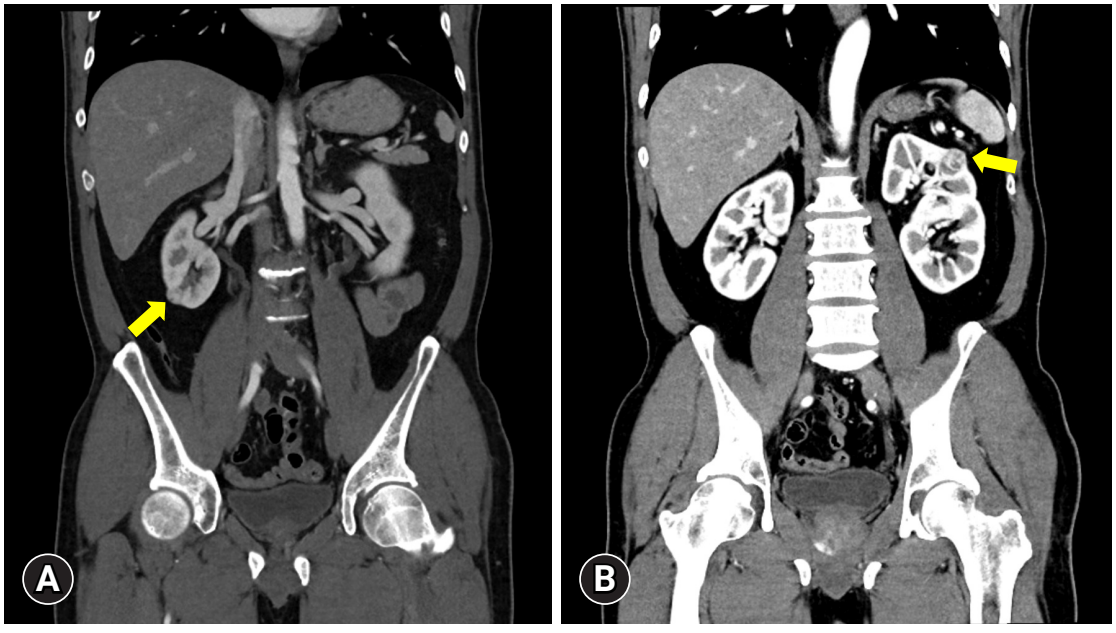

Fig. 1. The coronary images on preoperative computed tomography show (A) a 1.5-cm right and (B) a 2.0-cm left endophytic mass (arrows).

specimen was removed through the midline port without a laparoscopic sac device. The robot was undocked, and an Ioban 2 antimicrobial incise drape (3M Company, St. Paul, MS, USA) was applied, maintaining all the trocars inserted into the peritoneum (Fig. 3A). The patient's position was changed to the left decubitus, and the robot was re-docked to the same port (Fig. 3B). The operation on the right kidney was performed similarly, with the drain installed through the assist port site in the center, just like the already inserted left (Fig. 2A).

Total operation time (skin to skin) was 260 minutes, including the console time of 164 minutes. Among the console time, the left-side procedure was taken 109 minutes, with a warm ischemic time (WIT) of 27 minutes. The console and WIT were 55 minutes and 23 minutes for the right-side procedure, respectively. The estimated blood loss was 200 mL. The patient started a diet the next day and was discharged from the hospital on the third day according to the terms of his insurance (Fig. 2B). No perioperative complication, including blood transfusion, occurred.

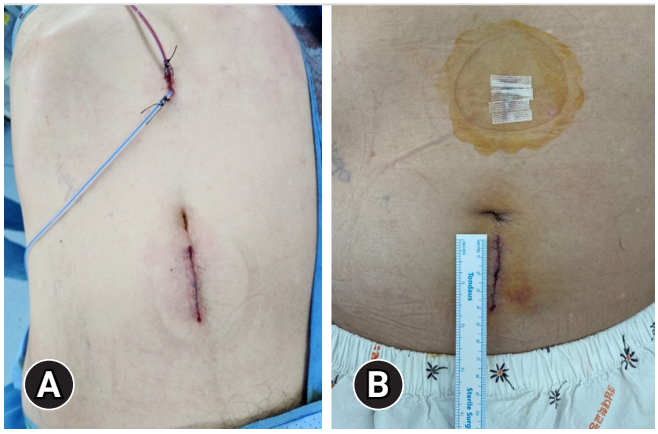

Fig. 2. The configuration for the robotic assessment port and additional laparoscopic port is designed to (A) the bilateral access to the renal mass and (B) postoperative status 3 days after surgery at the time of discharge. Note that the drain for both sides was inserted via a single midline port for the assistant.

Pathologic reports confirm a clear-cell type of renal cell carcinoma with margin negativity for both sides. Fuhrman grade was 2/4 for both sides. The serum creatinine right after the operation, on the first day, the day of discharge, and 90 days after surgery were 0.92, 0.77, 0.79, and 0.81 mg/dL, respectively. There were no adverse events such as hematuria, flank pain, or readmission requiring further management for 90 days after the procedure, and no abnormalities such as surgical site recurrence, anastomotic leakage, or local inflammation were observed on the abdominal CT at 3 months (Fig. 4).

Discussion

In the case of simultaneously detected kidney cancer, the kidney cancer on one side is often too large to be preserved. Though it could be found in the form of synchronous metastasis on the contralateral side from the large-sized tumor [2], kidney preservation is increasingly possible if detected early with the ubiquity of imaging diagnostics [3]. Nevertheless, the optimal treatment strategies for patients with synchronous bilateral renal tumors have not been established yet.

Given the potential risk of high-grade kidney cancer and the pa-

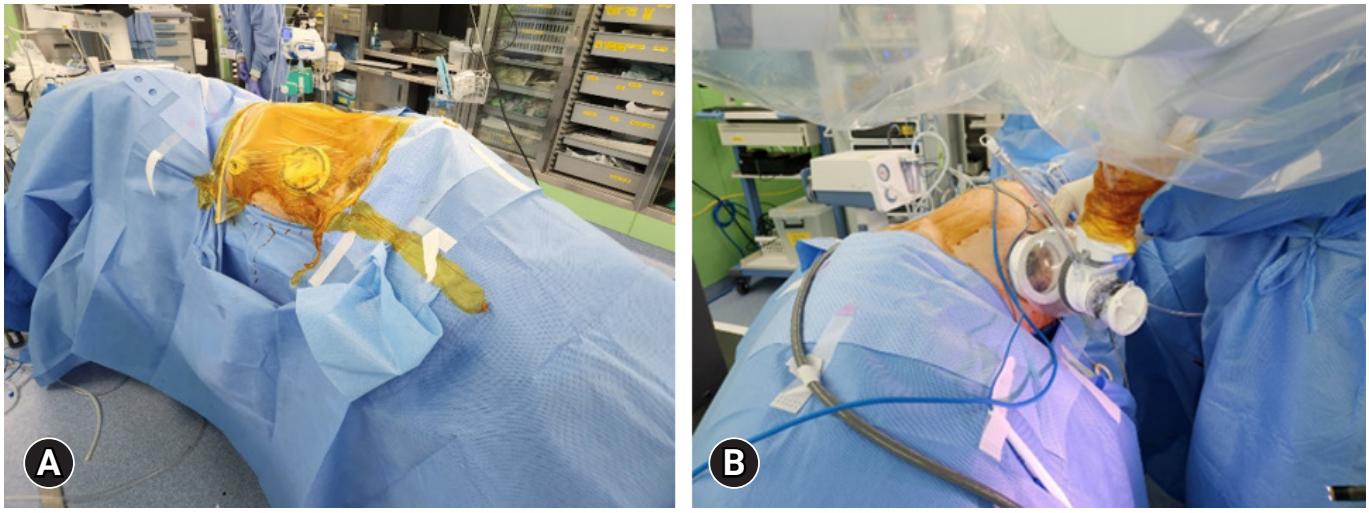

Fig. 3. (A) Preparation for the right-side procedure after undocking the robotic instrument for the left-side procedure. (B) Note that all the trocars inserted into the peritoneum were maintained utilizing surgical drape material.

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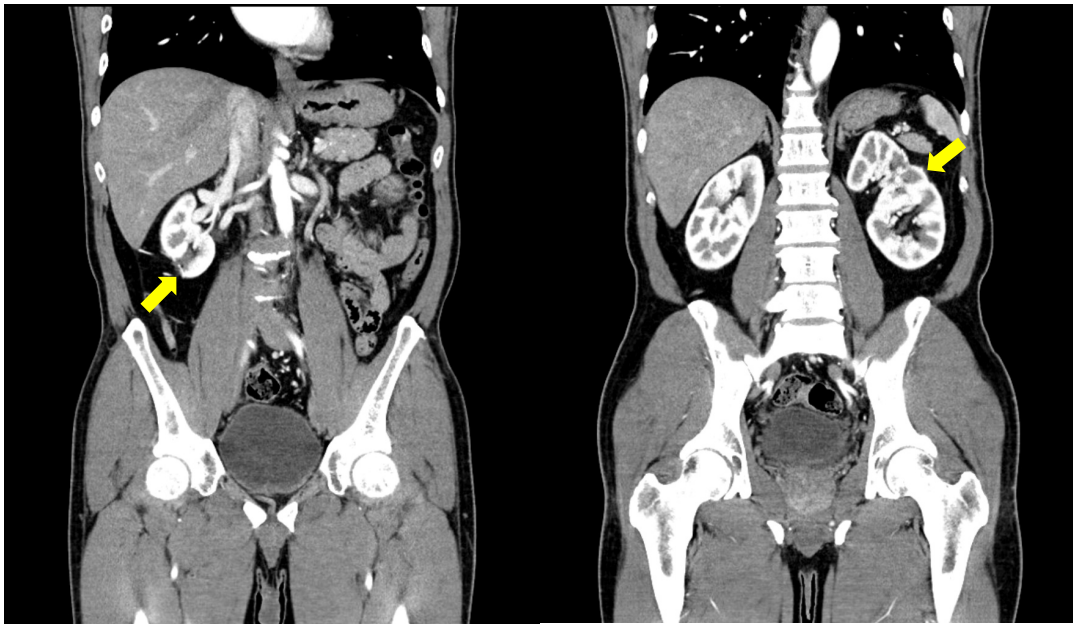

Fig. 4. The coronary images on postoperative computed tomography taken 3 months after surgery demonstrate no evidence of recurrence or urine leakage (arrows).

tient has already clinically progressed to synchronous metastasis, systemic treatment may be considered, but surgical removal is the most commonly attempted treatment for kidney cancer detected in the absence of distant metastases. Previously, the main treatment options for bilateral renal tumors were unilateral nephrectomy combined with partial resection for the contralateral side or bilateral partial nephrectomy [4-6]. Because bilateral nephrectomy could have a devastating impact on quality of life and loss of renal function could potentially shorten a patient's life expectancy, the renal-sparing approach has become the preferred option when feasible. Non-surgical removal options such as cryoablation, radiofrequency ablation, or irreversible electroporation may be performed as alternative methods of kidney preservation but have not been reported to perform as well as partial nephrectomy in long-term follow-up.

Regarding the timing of partial nephrectomy for bilateral masses, there has been controversy over whether it should be performed simultaneously or sequentially. In the absence of guideline statements, partial nephrectomy for bilateral kidney cancer has been tried as a staged operation in many cases and has been accepted traditionally as the standard approach. Lowrance et al. [6] reported that the staged procedure could minimize the decline in renal function, and patients could avoid dialysis treatment. However, the number of reports demonstrating no significant elevated risk in the requirement for dialysis after the simultaneous procedure has increased. In a report from the Mayo Clinic of 75 simultaneous bilateral cases, including most cases by open series performed from 1974 to 2013, eight patients suffered acute renal failure during the perioperative period, but none progressed to dialysis [3]. The eGFR values exhibited a median decrease of –19 mL/min/1.73 m^2 before and after surgery; therefore, the authors recommended the staged procedure for patients with preoperative impaired renal function. From the retrospective data accumulated over a decade (2009–2018), Di Maida et al. [7] compared the perioperative outcomes from the simultaneous procedure with the staged one. Among 41 patients included, a simultaneous approach was chosen in 17 patients (42%). Patients treated with a staged strategy showed significantly higher median cumulative operative time (310 minutes vs. 240 minutes, $p=0.01$), WIC (18 minutes vs. 10 minutes, $p=0.03$), and length of stay (10 days vs. 6 days, $p=0.01$) than patients receiving simultaneous surgery. No significant differences were found according to the median change of eGFR from the baseline to 3 months and disease-free survival in patients treated with simultaneous versus staged surgery.

Although retrospective, there are a growing number of reports of reliable simultaneous bilateral partial nephrectomy in the robotic era. Otoshi et al. [8] first reported their simultaneous robotic partial nephrectomy series for eight patients, with the tumors' median size of 1.4 cm (range, 0.9–9.0 cm). The eGFR 30 days after surgery decreased slightly compared to before but recovered to the preoperative level with no significant differences. In the most extensive patient report to date, Gallo et al. [9] performed simultaneous robotic partial nephrectomy in 27 patients, with a median operative time of 250 minutes and a median WIT of 15 minutes. However,

the complications were reported in seven patients (25.9%), mainly represented by Clavien-Dindo grade II events (six blood transfusions), and positive surgical margins were assessed in two of them (3.7%).

The unique advantage of robotic partial nephrectomy is that it can be performed through a single port compared to conventional multiport robots. In a systematic review of five comparative articles comparing the perioperative outcomes from the conventional multiport performing robot-assisted partial nephrectomy published, a recent systemic review demonstrated similar effectiveness and safety, with a marginally shorter length of hospital stay and less blood loss by a single port-based approach [10]. Simultaneous partial nephrectomy via transperitoneal midline approach could be a novel surgical category that maximizes the benefits of these previously proposed robotic single port surgeries and the technological advances of the DaVinci SP device, maintaining acceptable surgical, oncological, and functional outcomes. Further clinical studies will reveal the advantages of using this device for this procedure over traditional multiport surgery, maximizing the benefit of a single port-based approach.

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Conflicts of interest

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Author contributions

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The applicability of noncontact sensors in the field of rehabilitation medicine

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A noncontact sensor field is an innovative device that can detect, measure, or monitor physical properties or conditions without direct physical contact with the subject or object under examination. These sensors use a variety of methods, including electromagnetic, optical, and acoustic technique, to collect information about the target without physical interaction. Noncontact sensors find wide-ranging applications in various fields such as manufacturing, robotics, automobiles, security, environmental monitoring, space industry, agriculture, and entertainment. In particular, they are used in the medical field, where they provide continuous monitoring of patient conditions and offer opportunities in rehabilitation medicine. This article introduces the potential of noncontact sensors in the field of rehabilitation medicine.

Keywords: Brain injuries; Musculoskeletal diseases; Noncontact sensor; Rehabilitation; Spinal cord injuries

Introduction

A noncontact sensor, also known as a contactless sensor, is a device that can detect, measure, or monitor physical properties or conditions without requiring direct physical contact with the human or object being analyzed [1]. These sensors are designed to operate from a distance, often using electromagnetic, optical, or acoustic principles to obtain information about the target without physically touching it. This noncontact approach is often used to minimize contamination, reduce the wear and tear of equipment, and enable measurement when contact is impractical or undesirable. The representative types of noncontact sensors are as follows: (1) Infrared thermometer: This measures temperature by detecting the infrared radiation emitted by an object, facilitating contactless temperature measurement. (2) Radar sensors: Radio waves are used to detect the presence, motion, or position of targets without direct contact. (3) Optical sensors: Light or laser beams are used to measure attributes, such as distance, position, and object detection, without physical contact.

These noncontact sensors are used in several fields such as manufacturing, robotics, automobiles, security, environmental monitoring, space industry, agriculture, and entertainment [2-4]. The advantage of noncontact sensors, which can obtain information about the state or condition of a target without direct contact, is that they are being applied in the medical field. In addition, noncontact sensors have the advantage of enabling continuous longitudinal monitoring of a patient's condition throughout the day [5]. We believe that noncontact sensors are likely to be useful in reha-

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bilitation medicine. Here, we describe some scenarios or cases in which noncontact sensors can be applied in the field of rehabilitation medicine (Fig. 1).

The applicability of noncontact sensors in the field of rehabilitation medicine

First, patients with a stroke, traumatic brain injury, or spinal cord injury who undergo rehabilitation often experience unstable vital signs (e.g., autonomic dysfunction in patients with brain lesions and autonomic hyperreflexia or orthostatic hypotension in spinal cord injury) [6]. However, it is often difficult to detect and respond promptly to unstable patient vital signs with the current practice of only checking vital signs by contact, when direct checks by healthcare providers at set intervals make it difficult to detect and respond promptly. By using noncontact sensors, vital signs, such as heart rate, blood pressure, respiratory rate, inspiratory to expiratory ratios, and body temperature can be continuously monitored throughout the day [1]. This enables the immediate detection of unstable vital signs, enabling medical staff to respond quickly. Furthermore, these continuous measurements enable a comprehensive assessment of a patient's condition.

Second, the quantification of body movements plays a vital role in the assessment of individuals with brain lesions. Seizures are frequent manifestations in patients afflicted by conditions such as stroke or traumatic brain injury. However, due to the impracticality of sustained visual surveillance by healthcare providers, seizures are often underestimated. The utilization of noncontact sensors enables continuous monitoring of patient movements, allowing for the detection of even subtle movements. Therefore, healthcare providers can promptly identify seizures and take appropriate action in patients with brain lesions. Moreover, physiatrists often encounter challenges in accurately assessing motor function in patients with apraxia following brain lesions. Noncontact sensors en-

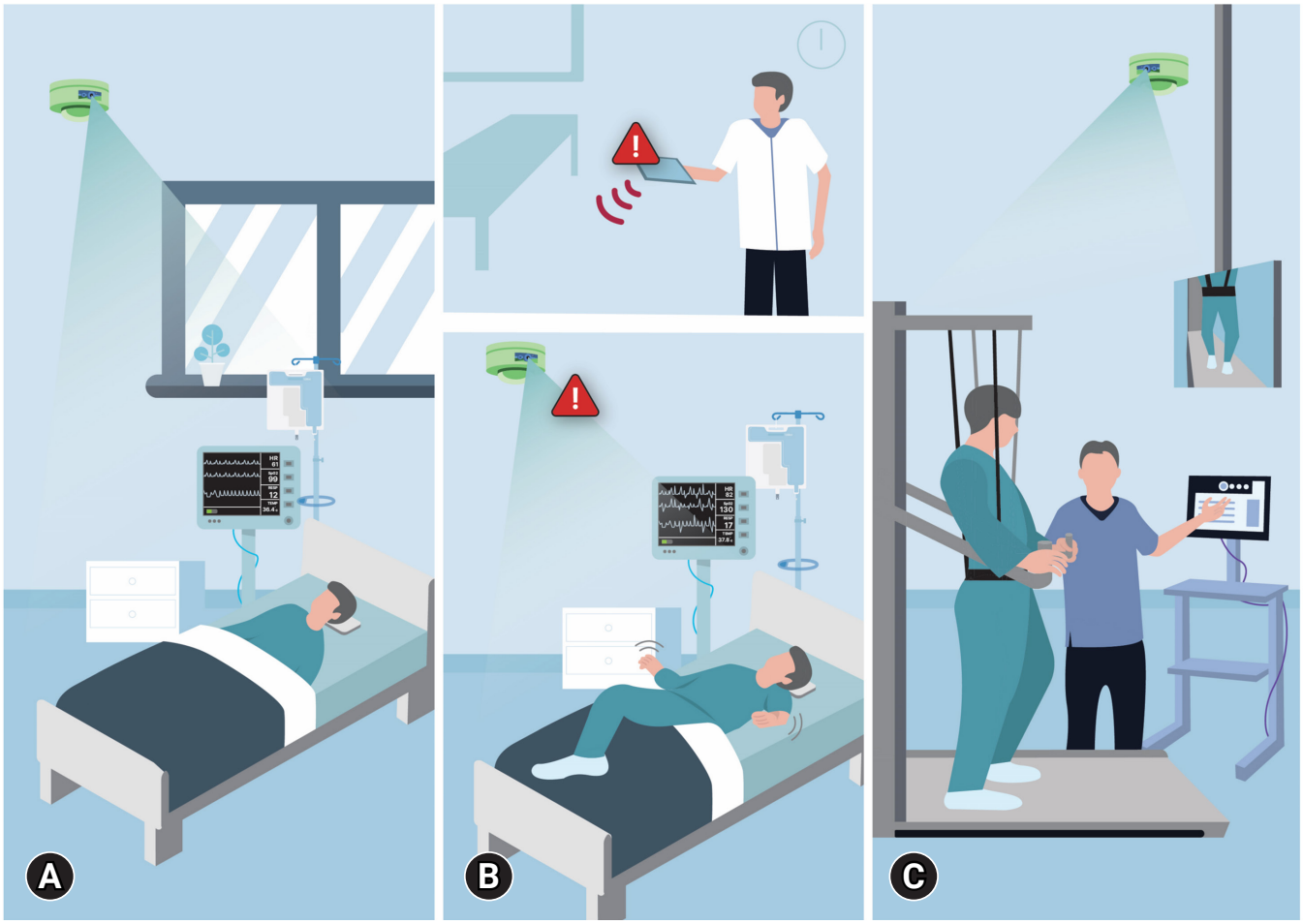

Fig. 1. Applications of noncontact sensors in the field of rehabilitation medicine. (A) Continuous vital sign monitoring. (B) Detection of patient movements such as seizures. (C) Posture analysis during exercise.

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able continuous monitoring of patient movements in everyday settings, enabling precise measurement of motor weakness.

Third, in patients with pain due to musculoskeletal disorders, exercise is important for pain management and the prevention of recurrence. However, exercising with poor posture not only compromises the effectiveness of exercise for the patients but can also worsen the severity of musculoskeletal disorders, potentially leading to pain even after recovery [7]. Noncontact sensors will provide accurate measurement and analysis of patients' motion during exercise. Through these measurements and analyses, physiatrists can measure patients' postures during exercise more accurately and in more detail, and patients can correct incorrect postures during exercise through feedback.

Conclusion

Noncontact sensors can be applied in many scenarios or cases in the field of rehabilitation medicine. Physiatrists can explore the potential of noncontact sensors, collaborate with engineering experts, and utilize these sensors for the rehabilitative management of patients. Thus, noncontact sensors can significantly assist in the care of patients in rehabilitation departments.

Article information

Conflicts of interest

Min Cheol Chang has been an associate editor of *Journal of Yeungnam Medical Science* since 2021. He was not involved in the review process of this manuscript. There are no other conflicts of interest to declare.

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Author contributions

Conceptualization, Methodology, Investigation: all authors; Formal analysis, Funding acquisition, Supervision, Validation: MCC; Visualization: YJC, MCC; Writing-original draft: all authors; Writing-review & editing: all authors.

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JOURNAL OF YEUNGNAM MEDICAL SCIENCE JYMS

Image vignette

Dynamic ultrasound examination of the median nerve during follow-up after wrist fracture/surgery

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Owing to its advantages, ultrasound examination of peripheral nerve injuries is paramount [1]. Herein, we present two cases of median nerve entrapment after internal fixation surgery for fractures of the wrist, one of the carpal bones, and the other of the distal radius.

A 51-year-old female presented with numbness/tingling of the thumb and index finger of her right hand. Her complaints ensued after a fracture of the carpal bones (and subsequent internal fixation surgery) 6 years prior. Her medical history was unremarkable. Ultrasonography revealed a mild swelling of the right median nerve, which was located close to the fixation material (Fig. 1). The median nerve was further impinged during wrist movements. During wrist extension/flexion, compression of the median nerve and the patient's symptoms became more apparent (Supplementary Video 1). Accordingly, the median nerve pathology was directly attributed to the internal fixation material. The results of previous electrodiagnostic evaluations were unremarkable. As the patient refused secondary corrective surgery, she was provided wrist splints and analgesics.

The second case involved a 54-year-old female with fractures of the distal radius and ulnar styloid process. She wore a cast for 5 weeks and then underwent internal fixation of the distal radius (Fig. 2). She later com-

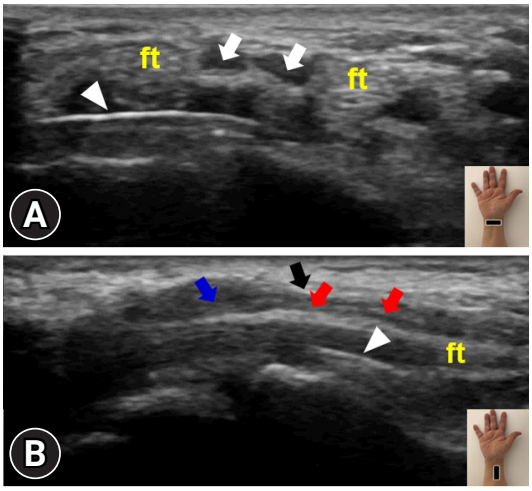

Fig. 1. Ultrasound imaging of the median nerve at the volar wrist. (A) Short-axis view depicts the close relationship between the bifid median nerve (white arrows) and the metal plate (arrowheads). (B) Long-axis view clearly shows the swollen median nerve (red vs. blue arrows) distal to compression (black arrow) by the underlying metal plate (arrowhead). Insets show the transducer's position. ft, flexor tendon.

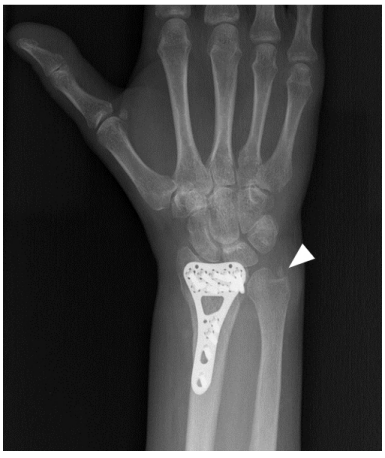

Fig. 2. Anteroposterior radiograph shows the metal plate in the radius and the fracture of the ulnar styloid (arrowhead).

plained of pain/dysesthesia in the first three fingers of the right hand. Upon ultrasound examination, the median nerve and metallic plate were located close to each other on both short- and long-axis imaging (Supplementary Fig. 1). On dynamic ultrasound examination (Supplementary Videos 2, 3), the median nerve appeared to be very close to and intermittently irritated by the underlying metallic plate on the distal radius. The median nerve was much more compressed during wrist flexion/extension movements. Furthermore, the patient described pain/dysesthesia during the dynamic, real-time ultrasound examination. Again, the metallic plate was thought to be the direct cause of median nerve irritation. The patient had not undergone electrodiagnostic testing before. She was prescribed physical therapy (whirlpool and exercise).

Median neuropathy can be observed after wrist fractures are treated with internal fixation [2]. In a cohort of 2,908 patients, distal radius fractures treated with open reduction and internal fixation surgery were associated with postoperative carpal tunnel syndrome [3]. In most relevant cases, diagnosis and follow-up were performed using physical and electrophysiological examinations. In this sense, calling attention to its numerous advantages—for example, patient/physician-friendly, convenient, radiation-free, and allowing dynamic evaluation—we highlight the paramount role of ultrasound examination in the prompt management of these cases. When ultrasound waves encounter highly reflective or absorbing surfaces such as bone, calcification, or metal plates, a hypoechoic area appears below the surface. This type of artifact is known as posterior acoustic shadowing [4]. One of the most important advantages of ultrasound is that it allows dynamic assessment of median nerve mobility [5]. Confirming the entrapment of the nerve(s) using different maneuvers, as well as sono-Tinel, cannot be performed with other imaging modalities, especially when the surgical materials are not compatible with imaging.

Supplementary materials

Supplementary Fig. 1 and Supplementary Videos 1–3 can be found at https://doi.org/10.12701/jyms.2023.01291.

Article information

Ethical statements

Informed patient consent was obtained from both patients included in the study.

Conflicts of interest

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

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Resident fellow section: Teaching images

Ultrasound assessment of a supraclavicular lipoma entrapping the brachial plexus: a diagnostic insight

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A 63-year-old woman presented with swelling in the left supraclavicular area that had persisted for 6 months. Initially, she experienced no pain in the swollen region, but over time she began to notice intermittent soreness (without any weakness) in her left upper extremity, particularly when carrying a backpack compressing the supraclavicular region.

During the examination, a bulging area in the supraclavicular region was observed without apparent skin color changes. Palpation revealed an elastic superficial mass with no sensory or motor deficits in the left upper extremity. Following ultrasound examination of her left suprascapular region, a well-demarcated hypoechoic mass measuring 7.1 × 3.5 × 3.6 cm was identified in the subcutaneous layer, exhibiting several hyperechoic strata. The mass was located over the brachial plexus. While talking, the omohyoid muscle glided under the mass over the suprascapular nerve (Fig. 1A). Rotation of the ultrasound transducer along the long axis of the brachial plexus revealed the anterior edge of the mass, which approximated the clavicle but did not extend to the infraclavicular region (Fig. 1B). Given the impression of a supraclavicular lipoma (with potential entrapment of the brachial plexus), the patient was referred for surgery.

Ultrasound imaging is highly effective in evaluating superficial mass lesions, with lipomas being the most prevalent type [1]. They display variable echogenicity, ranging from hypoechoic to isoechoic and hyperechoic, compared to adjacent muscles. A distinct linear internal echoic pattern resembling stripes is frequently observed. Lipomas are typically well-defined, often assuming an elongated fusiform shape, and generally lack intralesional vascularity. Although lipomas are usually not painful, they may become symptomatic if their size leads to a mass effect, causing compression of nearby neurovascular structures [2].

The supraclavicular region is vulnerable to compression of the brachial plexus owing to a lack of muscle coverage. In this region, the suprascapular nerve is separated from the brachial plexus and courses superficially. It travels alongside the omohyoid muscle where the suprascapular nerve may be entrapped [3]. When a lipoma is located in the subcutaneous tissue, there is usually sufficient space for expansion without direct compression of the brachial plexus. However, external factors such as tight clothing and carrying a heavy backpack can lead to a mass effect due to the lipoma initially irritating the suprascapular nerve and subsequently the brachial plexus. Furthermore, the lipoma may be partially squeezed into the costoclavicular space upon external compression, further increasing the risk of brachial plexus entrapment and causing symptoms resembling those of

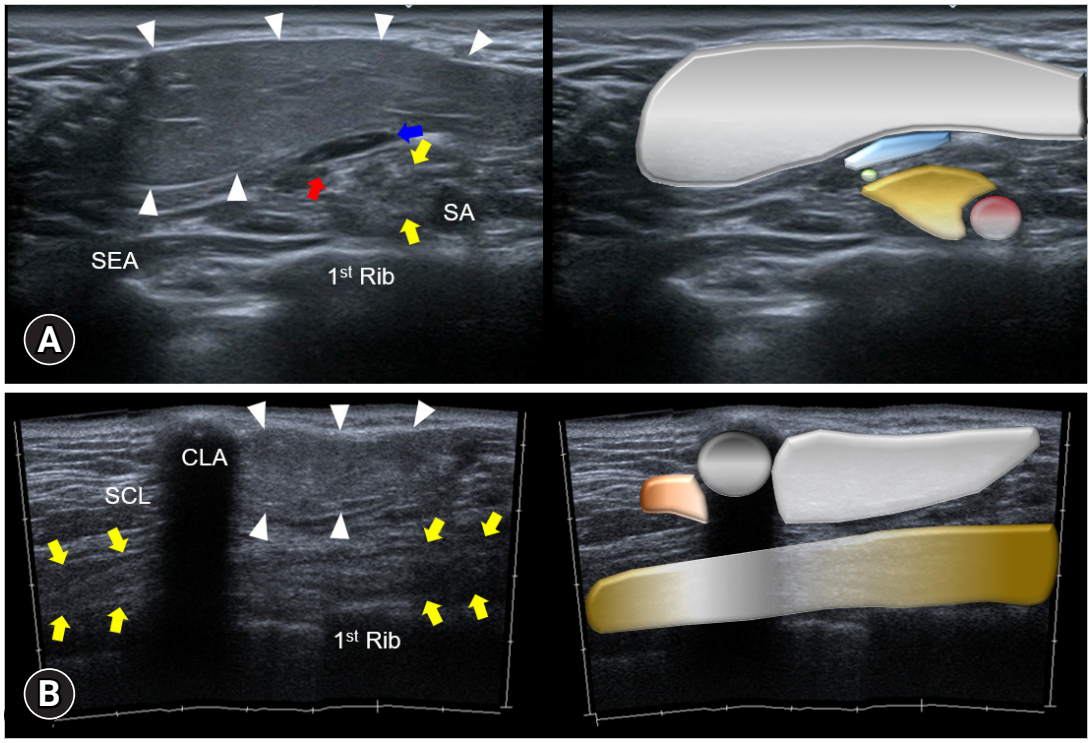

Fig. 1. Ultrasound imaging and schematic representation of a supraclavicular lipoma are depicted in both the (A) short axis and (B) long axis views of the brachial plexus. The supraclavicular lipoma (arrowheads) is a well-demarcated hypoechoic mass. The brachial plexus (yellow arrows), omohyoid muscle (blue arrow), and suprascapular nerve (red arrow) are present. SEA, serratus anterior muscle; SA, subclavian artery; SCL, subclavius muscle; CLA, clavicle.

thoracic outlet syndrome [4].

In summary, ultrasound is valuable for differentiating supraclavicular masses and identifying brachial plexus pathologies. When symptoms suggest the involvement of any neurovascular structure, elucidating the anatomical relationship between the mass, brachial plexus, and subclavian vessels is also helpful.

Learning points

- Ultrasound is highly effective in differentiating and characterizing superficial masses, particularly lipomas, offering insights into echogenicity, shape, and internal features.
- Supraclavicular lipomas, although typically non-painful, can become symptomatic, causing neurovascular compression, especially in the absence of muscle coverage. External factors, such as tight clothing and backpack use, can exacerbate symptoms.
- Anatomical considerations such as the vulnerability of the suprascapular nerve and the potential mass effect on the brachial plexus underscore the importance of ultrasound in delineating the relationship between masses, neurovascular structures, and subclavian vessels in the supraclavicular region.

Article information

Ethical statements

Written patient consent was obtained for the publication of this report.

Conflicts of interest

Ke-Vin Chang and Wei-Ting Wu have been editorial board members of *Journal of Yeungnam Medical Science* since 2021. They were not involved in the review process of this manuscript. There are no other conflicts of interest to declare.

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Author contributions

Conceptualization, Funding acquisition: KVC, WTW, LÖ; Investigation: KVC, KM, VR; Validation: WTW, LÖ; Writing-original draft: WTW; Writing-review & editing: KVC, KM, VR, LÖ.

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Instructions to authors

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The authors should express all measurements according to International System (SI) units with some exceptions such as seconds, mmHg, or °C.

Only standard abbreviations should be used. Abbreviations should be avoided in the title of the manuscript. Abbreviations should be spelled out when first used in the text—for example, extensible markup language (XML)—and the use of abbreviations should be kept to a minimum.

The names and locations (city, state, and country only) of manufacturers should be given.

When quoting from other sources, a reference number should be cited after the author's name or at the end of the quotation.
Manuscript preparation is different according to the publication type, including editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery.

Review article

All review articles will undergo peer review. An abstract is required whereas Methods section and a Results section are not required (no more than 250 words). The length of review articles is limited to 6,000 words with a maximum of 100 references.

Original article

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

1) Title page

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

2) Abstract

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) Keywords

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) Text

The text of manuscripts must have the following sections: Introduction, Methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

Introduction

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

Methods

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer's name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the re-

ported results. Define statistical terms, abbreviations, and most symbols.

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

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This should include a concise textual description of the data presented in tables and figures.

Discussion

This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References

References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading "References," and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed." (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles

- List all authors when six or less; when seven or more, list the first six and add et al. Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.
- Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.

Book

- Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.
- Luzikov VN. Mitochondrial biogenesis and breakdown. Galkin AV, translator; Roodyn DB, editor. New York: Consultants Bureau; 1985. p. 362

Book chapter

- Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Web resources

- Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.
- Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process.

5) Tables

Tables should fit within a single page. The Table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

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Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient's photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the *JYMS* website (https://e-jyms.org/authors/ethics.php) including each patient's signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations

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Authors should limit the use of abbreviations to an absolute minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report

Case reports should consist of an Abstract (no more than 250 words), Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors and follow the CARE guidelines.

Image vignette

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

Communications

Although communication articles are not limited in the format, they should contain a self-standing abstract and references. The abstract should be concisely written and not exceed 250 words.

Resident fellow section

RFS is designed to provide clinical cases and images that are informative for resident or fellow trainees. We encourage article submissions where the primary author(s) are prepared by trainees under the supervision of their attending physicians. We require a statement to be provided within the cover letter of any article submitted to this section that confirms the primary author(s) are residents or fellows. The following categories of articles will be included in the RFS:

1) Clinical vignette

Interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees. Authors should follow the CARE guidelines.

Cases may focus on either diagnosis or management. Vignettes should progress logically and be divided into the following sections:

- Brief history and physical exam. Include pertinent history of present illness, medical history, and physical exam findings.
- Differential diagnosis or potential approaches to management. Include discussion regarding reasons for selected differential or potential management approaches.
- Diagnostic results including lab results/imaging (if relevant).
- Diagnosis and discussion of management and outcomes. Include a discussion of the relevant literature related to the vignette.

Clinical vignette should be maximum of 1,500 words, 1-2 tables or 1-2 figures and maximum of 10 references.

2) Teaching images

Previously unpublished magnetic resonance images, computed tomography scans, ultrasound images, X-rays, patient photographs/videos, or other pictorial/videographic material. These pictorials should clearly demonstrate distinct examples of either rare, conventionally common, or uniquely pathognomic observations, techniques, or findings intended to further the education of the trainee audience. The title of the article should be brief and include the patient's age and sex, accompanied by a succinct 5-10 words description of the patient's presentation. Up to two labeled images or figures should be provided with a short description and/or legend. The case description should be written in 500 words or less and directly address the image provided while detailing the clinical significance of the presented findings and correlation with the patient's symptoms. Intended for trainees, teaching images should progress through a patient's history and physical exam while focusing on differential diagnoses, the clinical reasoning for selecting the particular diagnostic study, and the appropriate interpretation, subsequent treatment strategies, and achieved outcome. Finally, 2-3 bulleted learning points should accompany the submission to advance trainee knowledge (will not count toward word limit).

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This is a regular section of *JYMS*, featured at the beginning of issue and devoted to the artistic and imaginative qualities of the readers. *JYMS* invites your drawings, illustrations, or photographs with a brief explanation. Please send electronic images via e-mail to: jyms@yu.ac.kr. These contributions will not be returned.

Final preparation for publication

Final version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Color images must be created as CMYK files. The electronic original should be sent with appropriate labeling and arrows. The JPEG, TIFF, and PPT/PPTX formats are preferred for submission of digital files of photographic images. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All of the symbols must be defined in the figure caption. If the symbols are too complex to appear in the caption, they should appear on the illustration itself, within the area of the graph or diagram, not to the side. If references, tables, or figures are moved, added, or deleted during the revision process, they should be renumbered to reflect such changes so that all tables, references, and figures are cited in numeric order.

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Before publication, the manuscript editor may correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

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Research and publication ethics

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Enactment May 22, 2012

Research ethics

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Authorship credit should be based on (1) substantial contributions to the conception and design, acquisition of data, and/or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript, any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. A copyright assignment must also be completed by every author.

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The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

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