eISSN: 2234-0653

Annals of Rehabilitation Medicine

Official Journal of Korean Academy of Rehabilitation Medicine

Endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM)
and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM)

Volume 48, Number 3, June 2024

Review Articles

171 Robot-Assisted Gait Training in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

192 Effects of Botulinum Toxin-A for Spasticity and Nociceptive Pain in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis

Original Articles

203 Measurement of Knee Extensor Torque During Repetitive Peripheral Magnetic Stimulation: Comparison of the Forces Induced by Different Stimulators

211 Changes in Health-Related Quality of Life by Patient Education and Rehabilitation Based on a Behavior Change Program in Knee Osteoarthritis

220 Predictors for Failed Removal of Nasogastric Tube in Patients With Brain Insult

www.e-arm.org

arm
Annals of Rehabilitation Medicine
Volume 48, Number 3, June 2024
pages 171-228
www.e-arm.org

arm
Annals of Rehabilitation Medicine
www.e-arm.org

eISSN: 2234-0653

Annals of Rehabilitation Medicine

Volume 48, Number 3, June 2024

Aims and Scope

Annals of Rehabilitation Medicine (*ARM*) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, more than 3,500 physiatrists regularly receive this journal's table of contents via email, and the number is continually increasing. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM). International members comprise approximately half the editorial board, conducting peer-reviews of submitted manuscripts or acting as handling editors by assigning peer-review tasks to other reviewers.

The journal encompasses all aspects of physical medicine and rehabilitation, including basic, translational, clinical, and policy research, as well as rehabilitation education. Research areas covered by this journal include rehabilitation for brain disorders, spinal cord injuries, neuromuscular diseases. and dysphagia; cancer, cardiopulmonary, geriatric, pain & musculoskeletal, and pediatric rehabilitation; electrodiagnosis, orthosis & prosthesis, physical therapy, and sports medicine; and other emerging fields in rehabilitation medicine.

General Information

Annals of Rehabilitation Medicine is published in English bi-monthly on the last days of February, April, June, August, October, and December. Publication type includes original research, reviews, and other types of articles that reflect the depth and breadth of this specialty. Review board consists of members in 13 different countries. Articles are welcome for submission from all over the world. Full text is available from: http://www.e-arm.org/. All or part of the journal articles is indexed/tracked/covered by SCOPUS, EBSCO, PubMed Central/PubMed, KoreaMed, KoMCI, DOI/Crossref, Google Scholar, and Web of Science Core Collection as Emerging Sources Citation Index (ESCI) journal.

This journal is supported by the Korean Academy of Rehabilitation Medicine as well as the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

Open Access

Annals of Rehabilitation Medicine is available freely in electronic form at http://www.e-arm.org

Annals of Rehabilitation Medicine is an Open Access Journal. All articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

©2024 The Korean Academy of Rehabilitation Medicine.

Contacting the Annals of Rehabilitation Medicine

All manuscripts must be submitted online through the ARM e-submission system at http://e-arm.org. Items pertaining to manuscripts submitted for publication, as well as letters or other forms of communication regarding the editorial management of the journal, should be sent to:

Editor-in-Chief
Byung-Mo Oh, MD, PhD (Seoul National University, Korea)

Associate Editors
Han Gil Seo, MD, PhD (Seoul National University, Korea)
Hyun Iee Shin, MD (Chung-Ang University, Korea)
Sung Hwa Ko, MD, PhD (Pusan National University, Korea)

Editorial Office
Department of Rehabilitation Medicine, Seoul National University Hospital
101 Daehak-ro, Jongno-gu, Seoul, Korea
Tel +82-10-8678-2671 Fax +82-2-6072-5244 E-mail edit@e-arm.org; edit.karm@gmail.com

Editorial Board

Editor-in-Chief

Byung-Mo Oh *Seoul National University, Korea*

Associate Editors

Han Gil Seo *Seoul National University, Korea*
Hyun Iee Shin *Chung-Ang University, Korea*
Sung Hwa Ko *Pusan National University, Korea*

Section Editors

Neurological Rehabilitation
Sung-Rae Cho *Yonsei University, Korea*
Pain and Musculoskeletal Rehabilitation
Sun Jae Won *The Catholic University of Korea, Korea*
Electrodiagnosis and Neuromuscular Diseases
Dong Hwee Kim *Korea University, Korea*
Pediatric Rehabilitation
Jeong-Yi Kwon *Sungkyunkwan University, Korea*
Geriatric Rehabilitation
Jae-Young Lim *Seoul National University, Korea*
Cancer Rehabilitation
Jae Yong Jeon *University of Ulsan, Korea*
Orthosis and Prosthesis
Soo-Kyung Bok *Chungnam National University, Korea*

Editorial Board Members

Moon Suk Bang *Seoul National University, Korea*
Min Cheol Chang *Yeungnam University, Korea*
Won Hyuk Chang *Sungkyunkwan University, Korea*
Ian Cameron *University of Sydney, Australia*
Alberto Esquenazi *MossRehab, USA*
Michael Fredericson *Stanford University, USA*
Felipe Fregni *Harvard Medical School, USA*
Walter Frontera *University of Puerto Rico School of Medicine, Puerto Rico*
Abderrazak Hajjioui *Abdelmalek Essaâdi University, Morocco*
Der-Sheng Han *National Taiwan University, Taiwan*
Jae-Young Han *Chonnam National University, Korea*
Bo Young Hong *The Catholic University of Korea, Korea*
Ming-Yen Hsiao *National Taiwan University, Taiwan*
Shin-Ichi Izumi *Tohoku University, Japan*
Se Hee Jung *Seoul National University, Korea*
Na Young Kim *Yonsei University, Korea*
Jung Yoon Kim *Ewha Womans University, Korea*
Myoung-Hwan Ko *Chonbuk National University, Korea*
Ho Jun Lee *Dongguk University, Korea*
Jong Hwa Lee *Dong-A University, Korea*
Sang Yoon Lee *Seoul National University, Korea*
Seung Hak Lee *University of Ulsan, Korea*
Shi-Uk Lee *Seoul National University, Korea*
Jan Lexell *Lund University, Sweden*
Jianan Li *Nanjing Medical University, China*
Leonard S W Li *University of Hong Kong, China*
Peter Lim *Baylor College of Medicine in Houston, USA*
Reynaldo Rey-Matias *St Luke's Medical Center, Philippines*
William Micheo *University of Puerto Rico, Puerto Rico*
Masahiko Mukaino *Hokkaido University Hospital, Japan*
Min-Kyun Oh *Gyeongsang National University, Korea*
Chul-Hyun Park *Sungkyunkwan University, Korea*
Jae Hyeon Park *Hanyang University, Korea*
Mooyeon Oh-Park *Albert Einstein College of Medicine, USA*
Mohamad Yatim Saari *Serdang Hospital, Malaysia*
Joon-Ho Shin *National Rehabilitation Center, Korea*
Gerold Stucki *University of Lucerne, Switzerland*
Simon Fuk Tan Tang *Chang Gung University, Taiwan*
Shaun Xianghu Xiong *St George's Hospital, New Zealand*
Jin A Yoon *Pusan National University, Korea*

Statistical Editor

Joongyub Lee *Seoul National University, Korea*

Ethics Editor

Ock-Joo Kim *Seoul National University, Korea*

Manuscript Editors

Yeonjin Lee *Korean Academy of Rehabilitation Medicine, Korea*
Munju Lee *MEDrang Inc., Korea*

arm
Annals of Rehabilitation Medicine

This journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

eISSN: 2234-0653

Volume 48, Number 3, June 2024

Annals of Rehabilitation Medicine

Review Articles

171 Robot-Assisted Gait Training in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Jong Mi Park, Yong Wook Kim, Su Ji Lee, Ji Cheol Shin

192 Effects of Botulinum Toxin-A for Spasticity and Nociceptive Pain in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis
Dewan Md. Sumsuzzman, Zeeshan Ahmad Khan, Irin Sultana Nila, Vanina Myuriel Villagra Moran, Madhuvilakku Rajesh, Won Jong Yang, Yonggeun Hong

Original Articles

203 Measurement of Knee Extensor Torque During Repetitive Peripheral Magnetic Stimulation: Comparison of the Forces Induced by Different Stimulators
Masanori Kamiue, Akio Tsubahara, Tomotaka Ito, Yasuhiro Koike

211 Changes in Health-Related Quality of Life by Patient Education and Rehabilitation Based on a Behavior Change Program in Knee Osteoarthritis
Takako Nagai, Hiroshi Uei, Kazuyoshi Nakanishi

220 Predictors for Failed Removal of Nasogastric Tube in Patients With Brain Insult
Shih-Ting Huang, Tyng-Guey Wang, Mei-Chih Peng, Wan-Ming Chen, An-Tzu Jao, Fuk Tan Tang, Yu-Ting Hsieh, Chun Sheng Ho, Shu-Ming Yeh

©2024 The Korean Academy of Rehabilitation Medicine

Review Article

Ann Rehabil Med 2024;48(3):171-191
eISSN: 2234-0653
https://doi.org/10.5535/arm.230039

arm
Annals of Rehabilitation Medicine

Robot-Assisted Gait Training in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Jong Mi Park, MD[1], Yong Wook Kim, MD, PhD[2], Su Ji Lee, MD[2], Ji Cheol Shin, MD, PhD[2]

[1]*Department of Physical Medicine and Rehabilitation, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea*
[2]*Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea*

Spinal cord injury (SCI) rehabilitation emphasizes locomotion. Robotic-assisted gait training (RAGT) is widely used in clinical settings because of its benefits; however, its efficacy remains controversial. We conducted a systematic review and meta-analysis to investigate the efficacy of RAGT in patients with SCI. We searched international and domestic databases for articles published until April 18, 2024. The meta-analysis employed a random effects model to determine the effect size as either mean difference (MD) or standardized MD (SMD). Evidence quality was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Twenty-three studies with a total of 690 participants were included in the final analysis. The overall pooled effect size for improvement in activities of daily living was 0.24, with SMD (95% confidence interval [95% CI], 0.04–0.43; GRADE: high) favoring RAGT over conventional rehabilitation. Muscular strength (MD, 0.23; 95% CI, 0.02–0.44; GRADE: high), walking index for SCI (MD, 0.31; 95% CI, 0.07–0.55; GRADE: moderate) and 6 min walk test distance (MD, 0.38; 95% CI, 0.14–0.63; GRADE: moderate) showed significant improvement in the robot group. Subgroup analysis revealed that subacute patients and intervention periods >2 months were more effective. This meta-analysis revealed that RAGT significantly improved activities of daily living, muscular strength, and walking abilities. Additional studies are needed to identify the optimal treatment protocol and specific patient groups for which the protocol is most effective.

Keywords: Spinal cord injuries, Robotics, Locomotion, Gait, Recovery of function

Received: December 28, 2023
Revised: April 19, 2024
Accepted: May 22, 2024

Correspondence:
Ji Cheol Shin
Department of Rehabilitation Medicine, Yonsei University Medical Center, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: +82-2-2228-3713
Fax: +82-2-2228-3710
E-mail: jcsevrm@yuhs.ac

INTRODUCTION

Spinal cord injury (SCI) can cause various impairments in sensory, motor, and autonomic functions below the level of injury. This results in muscle weakness and atrophy, gait disturbances, sensory dysfunctions, and autonomic dysfunction [1]. Rehabilitation has focused on locomotion, especially for individuals with incomplete SCI classified as C or D on the American Spinal Injury Association (ASIA) Impairment Scale, because they are more likely to regain functional gait [2]. Early gait rehabilitation programs used manually assisted overground training with manual contact by a therapist, which later evolved into body weight-supported treadmill training. Since the introduction of the Lokomat (Hocoma AG) in the late 1990s, gait training with

© 2024 by Korean Academy of Rehabilitation Medicine

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

robots has gained traction, and is increasingly being used clinically because of its ability to perform high-intensity, repetitive movements for consistent periods of time, and is less demanding on the therapist [3].

With advancements in robotic technology, various types of robots are being utilized clinically, which can be broadly divided into three categories: exoskeleton treadmill training, wearable exoskeleton, and end-effector robots. Grounded exoskeleton robots have two programmable robotic joints in each leg, and are designed to support hip and knee movement when walking on a treadmill while supporting the body weight with a harness, with Lokomat being a prime example [3]. Wearable exoskeleton robots are ground walking systems that use a rigid external frame to support the lower limbs and torso while assisting movements at the hip and knee joints. They can be trained across a range of environments, including indoor and outdoor settings, as well as with obstacles and stairs. Examples include Ekso (Ekso Bionics), HANK (Gogoa Mobility), AIDER (Buffalo Robot Technology), and ReWalk (ReWalk Robotics) [4,5]. The end effector robot has a footplate attached with a walking trajectory only for the patient's feet, allowing the knees and hips to move freely. Examples include Morning Walk (Curexo) and G-EO systems (Reha Technology) [6,7].

In 2021, the Korea Institute of Health and Medical Research analyzed the clinical utility of robotic-assisted gait training (RAGT) compared to that of conventional rehabilitation in patients with SCI. No statistically significant differences were observed in walking ability, muscle strength, functional performance, spasticity, balance, and quality of life [8]. As the number of relevant studies has grown, subsequent meta-analyses of the international literature have shown that RAGT significantly improves spasticity, walking ability, distance, speed, function, and peak oxygen consumption [9-11]. However, no studies have analyzed the effects of the type of robot, intervention duration, or onset period. We aimed to obtain data from randomized clinical trials conducted so far and dissect them based on robot classification, intervention duration, and onset period, with the aim of offering a comprehensive overview of the efficacy of RAGT in patients with SCI. We also hope that this study will support future policy decisions in the medical technology sector and contribute to adequate health insurance coverage.

METHODS

This meta-analysis adhered to the guidelines outlined in the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. Supplementary Material S1 includes the PRISMA checklist. Additionally, the review protocol was registered and assigned the registration number CRD42023475357 in the International Prospective Register of Systematic Reviews.

Search strategy

The systematic search was conducted in six international (PubMed, Embase, Cochrane library, Scopus, Web of Science, and Google Scholar) and five domestic (KoreaMed, KMBase, KISS, RISS, and NDSL) databases until October 5, 2023, and we updated our search on April 18, 2024. The search formula was as follows: (Gait OR "Gait disorder" OR walking OR "Lower Extremity" OR leg or foot or ankle or tibia or fibula or femur or thigh or lower limb) AND (paresis OR paralysis or hemiplegia or paraplegia) AND (Robotics OR automation OR computer-assisted) AND (rehabilitation OR "Physical Therapy Modalities" OR "Exercise Therapy" OR physical therapy or physiotherapy or kinesitherapy or exercise) AND ("spinal cord injury" OR SCI) (Supplementary Material S2). We selected all published randomized controlled trials (RCTs) that compare RAGT with conventional rehabilitation methods. No data or language restrictions were applied. Two reviewers (JMP and JCS) independently reviewed titles and abstracts.

Study selection and data extraction

The study inclusion criteria adhered to the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework. The target population comprised patients with SCI and gait impairment. The intended intervention involved RAGT. For comparison, we established a control group of patients who received standard physical therapy with a therapist or non-robotic device therapy as traditional rehabilitation treatment. Designated outcomes comprised several primary outcomes encompassing activities of daily living (functional independence measure [FIM], spinal cord independence measurement [SCIM], and modified Barthel index [MBI]), muscular strength (lower extremity motor score, LEMS), spasticity (modified Ashworth scale, MAS), and balance (Berg balance scale, BBS), and walking ability (walking index for SCI [WISCI], 10 meter walk test [10MWT] speed, 6 min walk test [6MWT] distance, and step length). Secondary outcomes included body composition (body mass, lean tissue, and fat tissue) and cardiopulmonary function (forced expiratory volume in the first second [FEV1],

forced vital capacity [FVC], heart rate, and peak cough flow [PCF]). The study design specifically included RCTs, excluding non-human studies, cohort studies, case reports, and studies that did not conform to the PICOS framework.

Two reviewers (JMP and YWK) independently extracted relevant data, including the name of the first author, year of publication, patient demographic data, mean age, sample size, type of intervention (robot type), intervention protocol, control protocol, and outcomes. Information extraction was facilitated by ImageJ software version 1.53 (ImageJ software; National Institutes of Health, https://imagej.nih.gov) in instances where the study estimates were solely presented graphically without numerical reporting.

Quality assessment and GRADE evaluation

The quality of studies was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2), which identified potential bias risks. The RoB2 comprises five elements: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each element was appraised for low risk of bias, concerns of bias, high risk of bias, or lack of information [13]. Two reviewers (JMP and YWK) independently assessed the risk of bias, and disagreements regarding the quality assessment were resolved through discussion with a third reviewer (JCS).

The certainty of evidence in the included meta-analyses was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, which comprises five domains: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and (5) publication bias. Ratings for certainty of evidence were high, moderate, low, and very low [14].

Statistical analysis

In this meta-analysis, we conducted a statistical standardization of the effect sizes related to RAGT in patients with SCI. Initially, we calculated the mean and standard deviation (SD) of the change-from-baseline values for intervention and control groups. For studies lacking complete data, the mean and SD values of the change-from-baseline were computed, according to the guidelines outlined in Section 6 of the Cochrane Handbook (version 6.3). Effect sizes were calculated as mean difference (MD) and standardized MD (SMD), with 95% confidence interval (95% CI) within a random effects model. The included studies were from different countries and populations with different medical backgrounds; therefore, we conducted a restricted maximum likelihood random effects meta-analysis to account for an expected high level of heterogeneity [15]. Heterogeneity between studies was evaluated using the I^2 metric for inconsistency and Cochrane Q test p-values. As suggested in previous studies [16,17] we assessed publication bias only in meta-analyses of ≥3 studies using funnel plots and Egger's test. All statistical analyses were performed using Stata version 18 (StataCorp LP). Two-sided statistical tests were used, and significance was set at $p<0.05$. Subgroup analyses were performed according to robot type (treadmill training robot [Lokomat], wearable gait robot [Ekso, HANK, AIDER], end effector gait robot [morning walk]), intervention period, and onset period.

RESULTS

Study identification and characteristics

We screened 980 studies from international databases and 5,485 studies from domestic databases, excluding 102 and 334 duplicate records, respectively. After screening the titles and abstracts, 51 studies were selected from international and domestic databases, and their full texts were screened. Of these, 35 studies were excluded for various reasons (study protocol, observational study, review article, insufficient detail in the data, inappropriate intervention, and inappropriate control), and seven articles found through citation searches were combined, resulting in 23 studies that were finally included in the meta-analysis. Fig. 1 shows a flowchart outlining the study selection process. This meta-analysis included 690 patients with SCI: 346 and 344 in the intervention and control groups, respectively. The number of participants included in a single study ranged between 7 [18] and 88 [19]. The average age of the participants was between 8.4 [20] and 59.6 years [21]. The average onset duration of the participants was between 20 [22] and 7,665 days [23]. Overall characteristics of the included studies are summarized in Table 1 [18-40].

Assessment of risk and publication biases

Of the 23 RCTs, two showed high risk [24,25], but the rest showed some risk of concern. In all but one study [25], the randomization process and allocation were well described. Because the comparison was between RAGT and conventional standard physical treatment, all participants were aware of the intervention; therefore, bias due to deviations from the intended intervention was of some concern in all the studies. Approximately

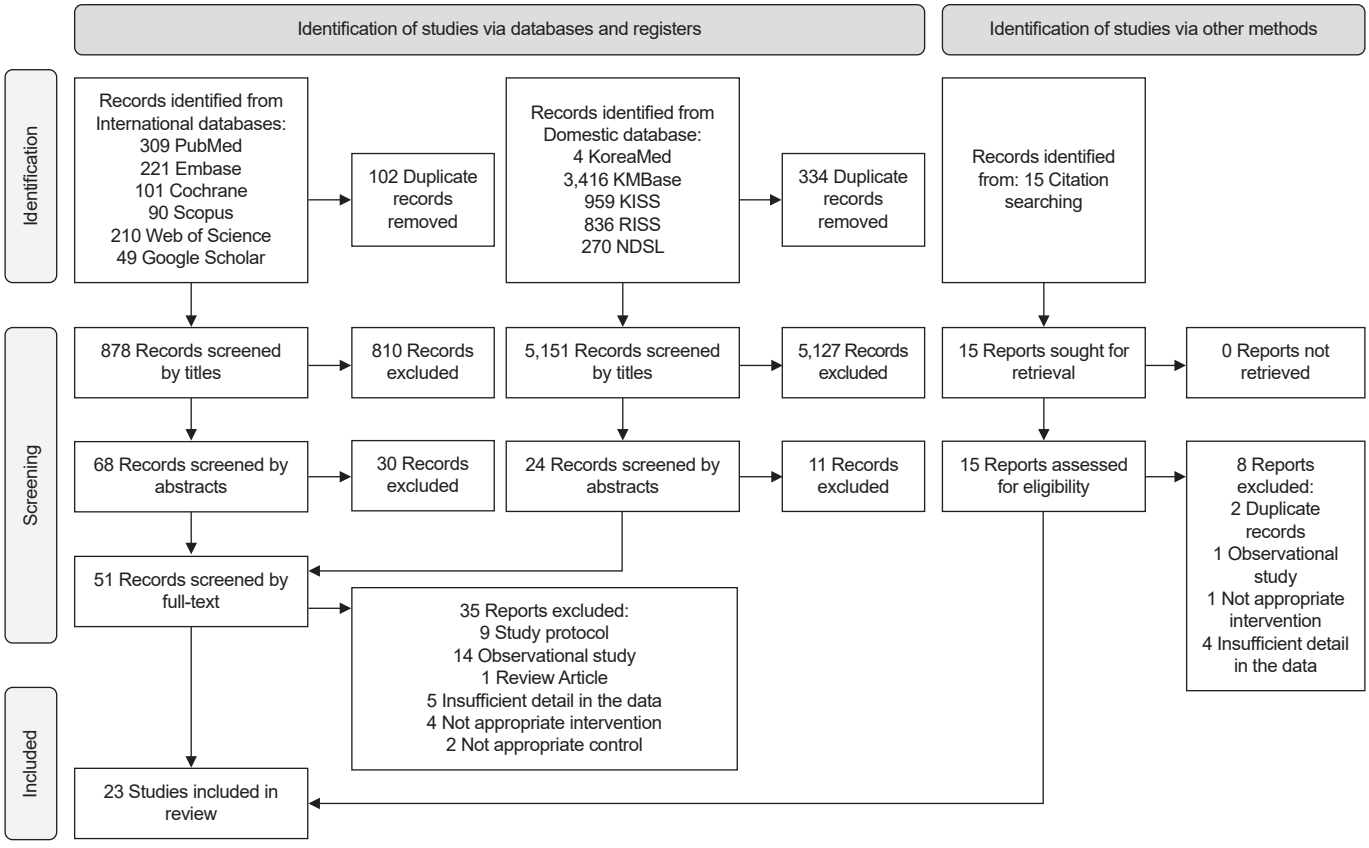

Fig. 1. Screening and selecting studies using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

half of the studies (12 studies) showed a low risk of bias due to missing outcome data. In 11 studies (just under half of the included studies), outcome measure assessments were blinded to the intervention type, suggesting a low risk of outcome measure bias. Fourteen studies (more than half) pre-registered their study protocols and no data were duplicated, resulting in a low risk of bias in the selection of the reported results. Fig. 2 presents a traffic light diagram for each study included in the evaluation.

In Supplementary Fig. S1 illustrates the funnel plot, which displays the publication bias for each meta-analysis. We also checked for publication bias using the Eager test, as shown in Table 2. All analyses showed no significant publication bias, except for the step length and peak expiratory flow.

Effects of RAGT on activities of daily living

Activities of daily living, as measured using the FIM, SCIM, and MBI assessment tools, were reported in 11 studies. The overall meta-analysis showed significant improvement in the robot groups (SMD, 0.24; 95% CI, 0.04–0.43; I^2=0%; p=0.02). When we analyzed the subgroups according to robot type, we found no significant difference in end-effector and wearable robots, but there was a statistically significant improvement in the Lokomat, a treadmill training robot (SMD, 0.29; 95% CI, 0.09–0.50; I^2=0%; p=0.01; Fig. 3A). Activities of daily living quality of evidence was estimated to be high, according to the GRADE system (Table 2).

Effects of RAGT on muscular strength

Muscular strength measured using LEMS has been reported in 12 studies. The overall meta-analysis showed significant improvement in the robot groups (MD, 0.23; 95% CI, 0.02–0.44; I^2=0%; p=0.03). Subgroup analysis according to robot type showed no significant difference in the end-effector and wearable robots, but a statistically significant improvement was observed in the Lokomat one (MD, 0.26; 95% CI, 0.03–0.49; I^2=0%; p=0.03; Fig. 3B). The quality of evidence for muscular strength was estimated to be high using the GRADE system (Table 2).

Table 1. Characteristics of the included studies

Study	No. of participants (experimental/control)	Age, years[2] (experimental/control)	ASIA grade (experimental/control)	Onset duration (experimental/control) (day)	Tetraplegia/paraplegia (experimental/control)	Initial WISCI (experimental/control)	Intervention protocol	Control protocol	Outcome measure	Main findings
Treadmill training exoskeleton robot-Lokomat										
Alcobendas-Maestro et al., 2012 [35]	37/38	45.2±15.5/49.5±12.8	C 68/71 D 32/29	117.4±43.3/136.3±64.9	Tetraplegia 59/61 Paraplegia 41/39	5.1±3.8/4.1±2.8	-Lokomat 30-min 40 sessions (8 wk) -Body weight support was initially set at 60% of each individual's weight and then decreased in accordance with load tolerance, but not <25% support	Standard physical treatment 40 walking training sessions of 1 h duration (8 wk)	1. Speed (m/s) 2. WISCI II 3. Walk distance (m) 4. FIM-Locomotor 5. LEMS 6. Ashworth 7. VAS	No significant differences were found at entry between treatment groups The WISCI II for the Lokomat group (16 [8.5–19]) was better than that for overground therapy (9 [8–16]) The 6MWT and LEMS displayed significant differences in favor of Lokomat therapy, but were not corrected for multiple comparisons
Cheung et al., 2019 [26]	8/8	55.6±4.9/53.0±12.9	C 7/4 D 1/4	510.0±210.3/312.0±189.3	Tetraplegia 8/8	14.6±4.3/17.0±2.8	-Lokomat 30-min 24 sessions (3 times per week for 8 weeks) -Body weight support was set at 40% of body weight to minimize individual difference	Standard physical treatment 30-min 24 sessions (3 times per week for 8 weeks)	1. Speed (cm/s) 2. WISCI II 3. SCIM III 4. LEMS 5. Maximal oxygen consumption (L/kg/min) 6. PEF (L/s) 7. FEV1 (L) 8. FVC (L)	The Lokomat group improved walking ability and cardiopulmonary function in patients with SCI However, there were no significant differences in the control group
Duffell et al., 2015 [36]	27/29	46.6±12.6/47.8±13.1	C N/R D N/R	3394.5±3942.0/2956.5±2956.5	N/R	14.7±5.2/13.8±5.8	-Lokomat 30–45 min 12 sessions (3 times per week for 4 weeks)	Standard physical treatment	1. Speed (m/s) 2. Distance (m) 3. Time (s) 4. WISCI II 5. MAS	Walking speed and endurance improved, with no difference between interventions
Esclarín-Ruz et al., 2014 [37]	21/21	43.6±12.0/44.9±7.0	C 14/16 D 7/5	125.6±65.2/140.3±45.5	Tetraplegia 16/16 Paraplegia 5/5	5.9±4.5/4.9±4.1	-Lokomat 30-min 40 sessions (8 wk) -Body weight support was initially set at 60% of each individual's weight and then decreased in accordance with load tolerance, but not <25% support	Standard physical treatment 30-min 40 sessions (8 wk)	1. 10MWT (m/s) 2. 6MWT (m) 3. FIM-Locomotor 4. LEMS	RAGT yielded better results in the 6MWT and LEMS in patients
Field-Fote and Roach, 2011 [38]	14/17	45.0±8.0/42.2±15.7	N/R	>365	N/R	LEMS 12.7±6.9/12.9±5.3	- Lokomat 60 sessions (12 wk) -Guidance forces were set at 100% to provide maximal assistance throughout the step cycle	Standard physical treatment Manual assistance for stepping	1. Speed (m/s) 2. Distance walked (m) 3. LEMS	In chronic motor incomplete SCI, there were no significant between-group differences

(Continued to the next page)

Table 1. Continued

Study	No. of participants (experimental/control)	Age, years[2] (experimental/control)	ASIA grade (experimental/control)	Onset duration (experimental/control) (day)	Tetraplegia/paraplegia (experimental/control)	Initial WISCI (experimental/control)	Intervention protocol	Control protocol	Outcome measure	Main findings
Gorman et al., 2016 [31]	12/6	51.5±12.7/52.0±15.4	C 2/0 D 10/6	>365	Tetraplegia 8/6 Paraplegia 4/0	LEMS 34.2±11.5/36.2±8.4	-Lokomat 25–45-min 36 sessions (12 wk) -Ultimately, partial body weight support was set between 70%–80% if the participant was able to support his or her weight	Standard physical treatment	1. Body mass (kg) 2. Tissue fat (%) 3. Lean tissue (kg) 4. Bone mineral content (kg) 5. VO2 peak (ml/kg/min)	Robot group improved peak VO2 than control group
Labruyère and van Hedel, 2014 [27]	9/9	59±11	N/R	1500.0±1680.0	Tetraplegia 6 Paraplegia 3	14.0±3.0	-Lokomat 45 min 16 sessions (4wk) -30% bodyweight support and a speed of 1–2 km/h	Strength training 45-min 16 sessions (4 wk)	1. 10MWT (m/s) 2. WISCI 3. SCIM 4. BBS 5. LEMS 6. Figure eight test 7. Gait symmetry 8. PCI 9. BBS	Chronic incomplete SCI dependent on walking assistance, robot group was not more effective in improving walking-related outcome compared to lower extremity strength training
Ma et al., 2022 [20]	10/10	8.4±1.1/8.6±1.2	N/R	400.8±147.0/468.0±158.1	N/R	16.2±1.3/15.9±2.2	-Lokomat 30-min 40 sessions (8 wk) -70%–40% bodyweight support	Standard physical treatment 60-min 40 sessions (8 wk)	1. 10MWT (m/s) 2. 6MWT (m) 3. LEMS 4. PCI 5. WISCI 6. Centre of pressure (cm^2)	RAGT may significantly improve the immediate motor function and walking ability of children with thoracolumbar incomplete SCI
Mıdık et al., 2020 [39]	15/15	35.4±12.1/37.9±10.0	C 6/10 D 9/5	411.4±637.9/861.6±662.5	Tetraplegia 0/0 Paraplegia 15/15	9.8±1.4/11.0±1.1	-Lokomat 30-min 15 sessions (5 wk) -In addition to standard physical treatment -50% bodyweight support and a speed of 1.5 km/h	Standard physical treatment 30-min 25 sessions (5 wk)	1. WISCI 2. SCIM 3. LEMS	Conventional rehabilitation is useful in terms of the improvement in the lower extremity motor function, walking, and functional status in men with incomplete SCI. Additional RAGT provides a better improvement in the lower extremity motor function and functional independence
Nooijen et al., 2009 [40]	12/13	44.3±8.9/38.2±14.6	N/R	3327.5±3214.8/1569.2±1545.4	Tetraplegia 0/11 Paraplegia 15/2	N/R	-Lokomat 60-min 60 sessions (12 wk) -30% bodyweight support	Standard physical treatment 60-min 60 sessions (12 wk)	1. Cadence (steps/min) 2. Symmetry index (%) 3. Step length (m) 4. Stride length (m) 5. Intralimb coordination 6. Timing of onset knee	No significant differences were found among training groups; however, there was an interaction effect, indicating that step and stride length improved least in the robot-assisted gait training group

(Continued to the next page)

Table 1. Continued

Study	No. of participants (experimental/control)	Age, years[2] (experimental/control)	ASIA grade (experimental/control)	Onset duration (experimental/control) (day)	Tetraplegia/paraplegia (experimental/control)	Initial WISCI (experimental/control)	Intervention protocol	Control protocol	Outcome measure	Main findings
Piira et al., 2019 [23]	7/12	55.0±8.0/ 46.0±15.0	C 1/5 D 6/7	7665.0±839.0/ 5475.0±6570.0	Tetraplegia 4/6 Paraplegia 3/6	LEMS 26.6±22.0/ 27.8±31.9	-Lokomat 20–30 min 60 sessions (24 wk) -<40% bodyweight support	Standard physical treatment 60 sessions (24 wk)	1. 10MWT (m/s) 2. 6MWT (m) 3. LEMS 4. BBS 5. Modified functional reach test	In chronic SCI, robot-assisted gait training did not restore independent walking function A modest, but non-significant, effect was seen on muscle strength and balance
Shin et al., 2014 [24]	27/26	43.2±14.4/ 48.2±11.5	N/R	99.9±90.6/ 81.9±59.1	Tetraplegia 15/16 Paraplegia 12/10	5.9±10.9/ 6.9±12.6	-Lokomat 40-min 12 sessions (4 wk) -In addition to standard physical treatment -50% bodyweight support and a speed of 1.5 km/h	Standard physical treatment 30-min 40 sessions (4 wk)	1. WISCI 2. SCIM 3. LEMS 4. Ambulatory motor index (AMI)	RAGT combined with conventional physiotherapy could yield more improvement in ambulatory function than conventional therapy alone
Tang et al., 2014 [25]	15/15	38.1±7.1/ 39.2±8.1	D 15/15	Median 189	Tetraplegia 0/0 Paraplegia 15/15	N/R	-Lokomat 40 min 1 session -35%–70% bodyweight support and a speed of 1.5–1.8 km/h	40 min 1 session Ergo_bike rate of 45 rpm with a work load of 60 W	1. 10MWT (m/s) 2. Probe reaction time	RAGT not only decreased reaction time, but also improved the walking ability
Wirz et al., 2017 [32]	9/9	35.56±13.8/ 34.3±16.0	B 3/6 C 6/3	35.1±18.6/ 43.2±25.7	Tetraplegia 7/6 Paraplegia 2/3	N/R	-Lokomat 50-min 34 sessions (8 wk) -Speed of 1.6–3.5 km/h	Standard physical treatment 25-min 34 sessions (8 wk)	1. SCIM 2. Spasticity (MAS)	No significant differences were found among training groups
Yıldırım et al., 2019 [19]	44/44	32±5.2/ 36.5±5.5	A 21/18 BCD 23/26	90±13.7/ 90±13.7	Tetraplegia 9/7 Paraplegia 35/37	5.0±6.9/ 5.0±5.1	-Lokomat 30-min 16 sessions (8 wk) -Standard physical treatment 30-min 40 sessions (twice a day) (8 weeks)	Standard physical treatment 30-min 40 sessions (twice a day) (8 wk)	1. WISCI 2. FIM	RAGT combined with conventional therapy was found to be superior to the conventional therapy in terms of gait function and level of disability
Song et al., 2012 [22]	11/11	53.7±8.8/ 53.3±6.0	N/R	20.2±5.0/ 20±4.8	Tetraplegia 9/10 Paraplegia 2/1	N/R	-Lokomat 20-min 20 sessions (4 wk) -Standard physical treatment 20-min 20 sessions (4 wk)	Standard physical treatment 20-min 20 sessions (4 wk)	1. Balance (TETRAX fall risk) 2. 10MWT (m/s) 3. 6MWT (m) 4. MBI	RAGT significantly improved in walking ability and lower fall risk
Wearable gait robot-Ekso, HANK, AIDER										
Chang et al., 2018 [18]	4/3	56.0±17.0/ 60.0±2.0	C 1/1 D 3/2	5475.0±5110.0/ 2555.0±1095.0	Tetraplegia 2/1 Paraplegia 2/2	N/R	-Ekso 60-min 15 sessions (3 wk)	Standard physical treatment 60-min 15 sessions (3 wk)	1. 10MWT (m/s) 2. 6MWT (m) 3. TUG (s) 4. Step length (m)	RAGT could be applied to individuals with incomplete SCI to facilitate gait recovery

(Continued to the next page)

Table 1. Continued

Study	No. of participants (experimental/control)	Age, years[2] (experimental/control)	ASIA grade (experimental/control)	Onset duration (experimental/control) (day)	Tetraplegia/paraplegia (experimental/control)	Initial WISCI (experimental/control)	Intervention protocol	Control protocol	Outcome measure	Main findings
Edwards et al., 2022 [33]	9/10	41.7±8.5/ 51.9±14.5	C 6/3 D 3/7	3066.0±3134.2/ 2568.3±1594.1	Tetraplegia 7/8 Paraplegia 2/2	12.1±4.4/ 13.8±4.5	-Ekso GT 45-min 36 sessions (12 wk)	Body weight support treadmill training 45-min 36 sessions (12 wk)	1. Gait speed (m/s)	RAGT not statistically significant in gait speed
Evans et al., 2021 [28]	8/8	41.0±11.0/ 38.0±14.0	C 4/5 D 4/3	4745.0±2920.0/ 2555.0±2190.0	Tetraplegia 8/8 Paraplegia 0/0	N/R	-Ekso GT 60-min 72 sessions (24 wk) Warm-up and mobility (5 min) Resistance training (20–30 min) Cardiovascular training (20–30 min)	60-min 72 sessions (24 wk)	1. Heart rate 2. Heart rate variability 3. Systolic blood pressure (mmHg) 4. Diastolic blood pressure (mmHg) 5. Ankle brachial pressure index (ABPI) 6. Distance (m) 7. Rating of perceived exertion (Borg)	Cardiovascular efficiency of exoskeleton walking improved, particularly over the first 6 weeks
Gil-Agudo et al., 2023 [34]	11/10	41.0±12.4/ 51.8±11.9	C 8/4 D 3/6	144.6±39/ 166.5±69	Tetraplegia 4/2 Paraplegia 7/8	11.9±4.3/ 11.7±3.8	-HANK 30-min 15 sessions (5 wk)	Standard physical treatment 30-min 15 sessions (5 wk)	1. LEMS 2. 10MWT (m/s) 3. TUG (s) 4. 6MWT (m) 5. WISCI 6. SCIM	Exoskeleton improved their walking independence as measured by the WISCI-II after the treatment
Shackleton et al., 2022 [29]	8/8	40.5±11.2/ 38.4±14.3	C 4/5 D 4/3	5037.0±3029.5/ 2664.5±2336.0	Tetraplegia 8/8 Paraplegia 0/0	N/R	-Ekso Bionics 60-min 72 sessions (24 wk)	Standard physical treatment 60-min 72 sessions (24 wk)	1.Bone mineral density (g/cm^2) 2. Fat mass (kg, %) 3. Fat-free soft tissue mass (kg)	Twenty-four weeks of robot locomotor training is possibly a sufficient duration to prevent the progressive decline of bone mineral density
Xiang et al., 2021 [30]	9/9	39.8±12.2/ 36.6±11.8	A 8/4 B 0/3 C 1/3	60.0±118.5/ 60.0±13.1	Tetraplegia 5/4 Paraplegia 4/5	N/R	-AIDER 60-min 16 sessions (4 wk) -40%–60% maximal heart rate	Standard physical treatment 60-min 16 sessions (4 wk)	1. FVC (L) 2. FEV1 (L) 3. PEF (L/s) 4. Maximal voluntary ventilation (MVV) (L) 5. Distance (m) 6. Heart rate 7. Rating of Perceived Exertion 8. SpO2 9. LEMS	Exoskeleton-assisted walking has potential benefits to facilitate pulmonary function parameters among individuals with lower thoracic neurological level of SCI compared with conventional therapy

(Continued to the next page)

Table 1. Continued

Study	No. of participants (experimental/control)	Age, years[2] (experimental/control)	ASIA grade (experimental/control)	Onset duration (experimental/control) (day)	Tetraplegia/paraplegia (experimental/control)	Initial WISCI (experimental/control)	Intervention protocol	Control protocol	Outcome measure	Main findings
End effector gait robot-Morning walk										
Shin et al., 2023 [21]	16/13	49.5±27.0/59.6±7.5	C 2/4 D 14/9	61.7±44.9/58.2±50.7	Tetraplegia 14/10 Paraplegia 2/2	WISCI II 3.6±4.6/3.7±6.6	-Morning walk 30-min 20 sessions (4 wk) -20% body weight support -Standard physical treatment 60-min 20 sessions (4 wk)	Standard physical treatment 90-min 20 sessions (4 wk)	1. WISCI 2. SCIM 3. LEMS 4. Proprioception 5. BBS 6. WISCI II 7. SCIM III	End-effector robot gait training could improve balance and gait abilities substantially better than conventional therapy

ASIA, American Spinal Injury Association; WISCI, walking index for spinal cord injury; N/R, not recorded; LEMS, lower extremity motor score; FIM, functional independence measure; VAS, visual analogue scale; SCIM, spinal cord independence measurement; PEF, peak expiratory flow; FEV1, forced expiratory volume in the first second; MAS, modified Ashworth scale; 10MWT, 10 meter walk test; 6MWT, 6 min walk test; BBS, Berg balance scale; PCI, Physiological Cost Index; TETRAX, Tetrax (Sunlight Medical Ltd.); MBI, modified Barthel index; TUG, Timed Up and Go Test; FVC, forced vital capacity; RAGT, robotic-assisted gait training.

Effects of RAGT on spasticity

Spasticity measured using the MAS was reported in three studies. The overall meta-analysis showed no significant difference (MD, -0.05; 95% CI, -0.37 to 0.28; I^2=0%; p=0.77; Fig. 3C). The spasticity quality of evidence was estimated as low performing using the GRADE system (based on risk of bias and imprecision) (Table 2).

Effects of RAGT on balance

Balance, measured using the BBS, was reported in three studies. The overall meta-analysis showed no significant difference (MD, 0.44; 95% CI, -0.18 to 1.06; I^2=33.42%; p=0.16). Subgroup analysis by robot type showed no significant difference in the Lokomat, but a statistically significant improvement was observed for end-effector robot (MD, 0.95; 95% CI, 0.17–1.72; I^2=uncheckable; p=0.02; Fig. 3D). The balance quality of evidence was estimated as low performing using the GRADE system (based on inconsistency and imprecision) (Table 2).

Effects of RAGT on walking ability

Ten studies reported the WISCI, and the overall meta-analysis showed significant improvement in the robot group (MD, 0.31; 95% CI, 0.07–0.55; I^2=30.67%; p=0.01). Subgroup analysis according to robot type showed no significant difference in the Lokomat, but there was statistically significant improvement in the end-effector and wearable robots, with a larger effect size for wearable robots (MD, 1.30; 95% CI, 0.35–2.25; I^2=uncheckable; p=0.01; Fig. 4A). The WISCI quality of evidence was estimated to be moderate, according to the GRADE system (based on risk of bias) (Table 2).

Thirteen studies reported 10MWT Speed, and the overall meta-analysis showed no significant difference (MD, -0.02; 95% CI, -0.46 to 0.42; I^2=73.44%; p=0.91). Subgroup analysis according to robot type showed no significant differences between the end-effector, Lokomat, and wearable robots (Fig. 4B). The 10MWT Speed quality of evidence was estimated to be very low when the GRADE system was used (based on risk of bias, inconsistency, indirectness, and imprecision) (Table 2).

Ten studies reported 6MWT distance, and the overall meta-analysis showed significant improvement in the robot group (MD, 0.38; 95% CI, 0.14–0.63; I^2=0%; p=0.00). Subgroup analysis according to robot type showed no significant difference in the end-effector and wearable robots, but a statistically significant improvement was observed in the Lokomat (MD, 0.40; 95% CI, 0.10–0.70; I^2=0%; p=0.01; Fig. 5A). The 6MWT

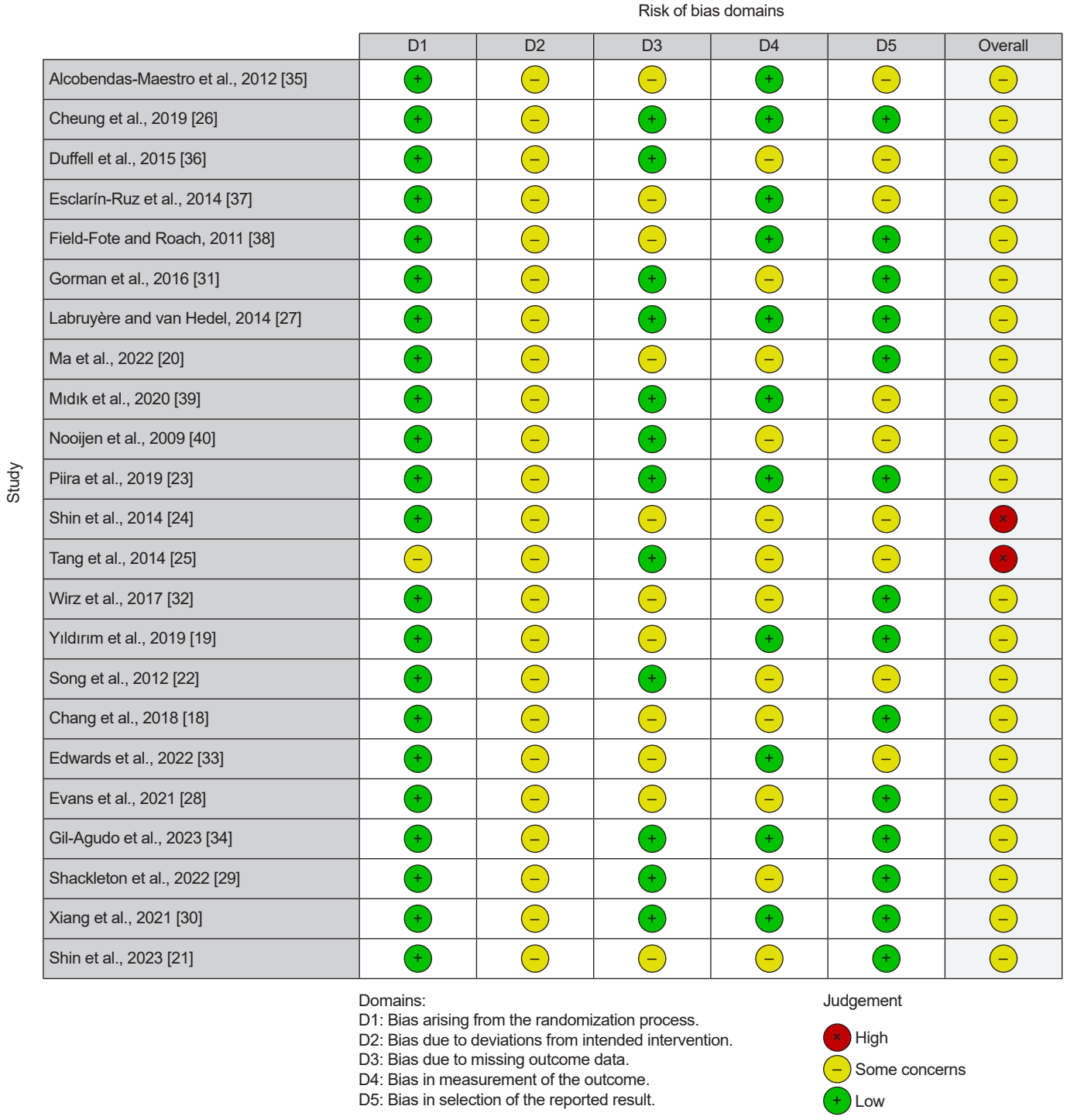

Fig. 2. Traffic light diagram for the risk of bias of included studies as assessed using the Cochrane Risk of Bias 2.0 tool.

distance quality of evidence was estimated to be moderate, according to the GRADE system (based on risk of bias) (Table 2).

Two studies reported step length, and the overall meta-analysis showed no significant difference (MD, -0.15; 95% CI, -0.84 to 0.55; I^2=0%; p=0.68). Subgroup analysis according to robot type showed no significant differences between the Lokomat

Table 2. Summary of the findings and quality of evidence assessment using the GRADE approach

Outcome measure		Summary of findings		Heterogeneity	Publication bias	Quality of evidence assessment (GRADE)					
		No. of patients Experimental/ control (trials)	Effect size (95% confidence interval)	I^2 (%)	Egger's test	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence[f]
Activities of daily living	FIM, SCIM, MBI	208/203 (11)	SMD 0.24 (0.04–0.43)**	0	0.950	Not serious	Not serious	Not serious	Not serious	None	High
Muscular strength	LEMS	184/187 (12)	MD 0.23 (0.02–044)**	0	0.592	Not serious	Not serious	Not serious	Not serious	None	High
Spasticity	MAS	73/75 (3)	MD -0.05 (-0.37 to 0.28)	0	0.952	Serious	Not serious	Not serious	Serious	None	Low
Balance	BBS	32/34 (3)	MD 0.44 (-0.18 to 1.06)	33.42	0.269	Not serious	Serious	Not serious	Serious	None	Low
Walking ability	WISCI	215/212 (10)	MD 0.31 (0.07–0.55)**	30.67	0.260	Serious	Not serious	Not serious	Not serious	None	Moderate
	10MWT speed (m/s)	172/176 (13)	MD -0.02 (-0.46 to 0.42)	73.44	0.521	Serious	Very serious	Not serious	Serious	None	Very low
	6MWT distance (m)	134/134 (10)	MD 0.38 (0.14–0.63)**	0	0.256	Serious	Not serious	Not serious	Not serious	None	Moderate
	Step length (m)	16/16 (2)	MD -0.15 (-0.84o 0.55)	0	N/A	Not serious	Not serious	Not serious	Serious	Suspected	Low
Body composition	Body mass (kg)	20/14 (2)	MD 0.02 (-0.67 to 0.71)	0	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
	Lean tissue (kg)	20/14 (2)	MD 0.02 (-0.67 to 0.72)	0	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
	Tissue fat (%)	20/14 (2)	MD 0.09 (-0.60 to 0.79)	0	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
Cardiopulmonary Function	FEV1 (L)	17/17 (2)	MD 0.49 (-0.20 to 1.18)	0	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
	Forced vital capacity (L)	17/17 (2)	MD 0.33 (-0.35 to 1.02)	0	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
	Heart rate (beats/min)	17/17 (2)	MD 0.56 (-0.71 to 1.30)	10.09	N/A	Not serious	Not serious	Not serious	Serious	None	Moderate
	Peak expiratory flow (L/s)	17/17 (2)	MD 0.26 (-0.41 to 0.94)	0	N/A	Not serious	Not serious	Not serious	Serious	Suspected	Low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; FIM, functional independence measure; SCIM, spinal cord independence measurement; MBI, modified Barthel index; LEMS, lower extremity motor score; MAS, modified Ashworth scale; BBS, Berg balance scale; WISCI, walking index for spinal cord injury; 10MWT, 10 meter walk test; 6MWT, 6 min walk test; FEV1, forced expiratory volume in first second; SMD, standardized mean difference; MD, mean difference; N/A, not applicable.

[a]Risk of bias based on the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2).

[b]Downgraded if significant and unexplained heterogeneity (I2>50%, p<0.10) was not explained by the meta-regression or subgroup analysis results.

[c]Downgraded if there were any factors related to the participants, interventions, or results that limited the generalizability of the results.

[d]Downgraded if the 95% confidence interval crossed the benefit-or-harm boundary.

[e]Downgraded if there was evidence of publication bias using Egger's test or suspecting publication bias when visualizing with funnel plots.

[f]Because all included studies were meta-analyses of randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded according to pre-specified criteria. The quality was graded as high, medium, low, or very low.

**p<0.05.

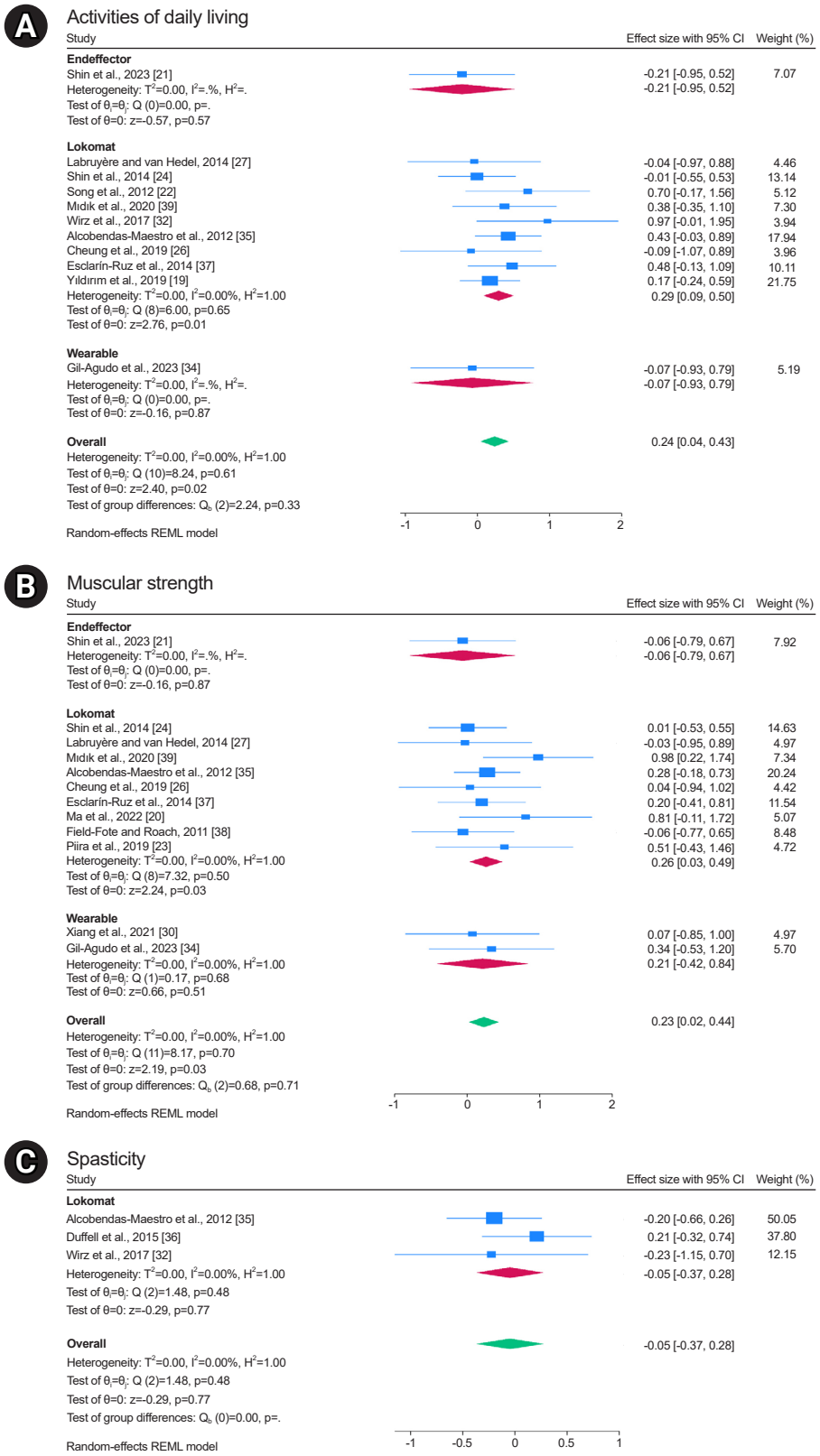

Fig. 3. Meta-analysis of the effects of RAGT in patients with spinal cord injury (SCI). (A) Activities of daily living. (B) Muscular strength. (C) Spasticity. (D) Balance.

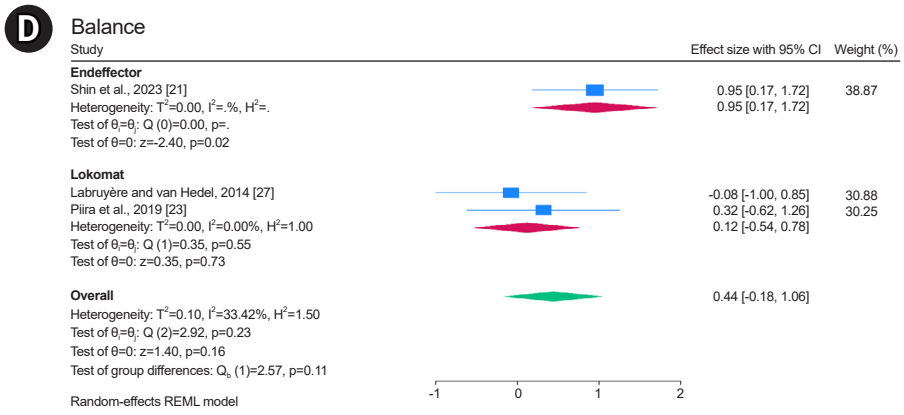

Fig. 3. Continued.

and wearable robots (Fig. 5B). The step length quality of evidence was estimated to be low when using the GRADE system (based on imprecision and publication bias) (Table 2).

Effects of RAGT on body composition

Two studies reported body mass, and the overall meta-analysis showed no significant difference (MD, 0.02; 95% CI, -0.67 to 0.71; I^2=0%; p=0.96). Two studies reported lean mass, and the overall meta-analysis showed no significant difference (MD, 0.02; 95% CI, -0.67 to 0.72; I^2=0%; p=0.95). Two studies reported fat tissue percentage, and the overall meta-analysis showed no significant difference (MD, 0.09; 95% CI, -0.60 to 0.79; I^2=0%; p=0.79). The quality of evidence for each sub-analysis of body composition was rated as moderate (based on imprecision) using the GRADE system (Fig. 6A, Table 2).

Effects of RAGT on cardiopulmonary function

Two studies reported FEV1, and the overall meta-analysis showed no significant difference (MD, 0.49; 95% CI, -0.20 to 1.18; I^2=0%; p=0.17). Two studies reported FVC, and the overall meta-analysis showed no significant difference (MD, 0.33; 95% CI, -0.35 to 1.02; I^2=0%; p=0.34). Two studies reported heart rate, and the overall meta-analysis showed no significant difference (MD, 0.56; 95% CI, -0.17 to 1.30; I^2=10.09%; p=0.13). Two studies reported PCF, and the overall meta-analysis showed no significant difference (MD, 0.26; 95% CI, -0.41 to 0.94; I^2=0%; p=0.44). In the sub-analysis of cardiopulmonary function, the quality of evidence was assessed using the GRADE system, with only peak expiratory flow rated low (based on imprecision and publication bias) and the rest rated moderate (based on imprecision) (Fig. 6B, Table 2).

Subgroup analysis

Subgroup analyses were performed based on intervention period and onset duration (Supplementary Fig. S2, Table 3). Subgroup analysis according to intervention duration showed significant improvements in activities of daily living difference (SMD, 0.34; 95% CI, 0.09–0.60; I^2=0%; p=0.01; Supplementary Fig. S2A) and WISCI (MD, 0.33; 95% CI, 0.07–0.60; I^2=0%; p=0.01; Supplementary Fig. S2E) in the group that intervened for >2 months. The 6MWT distance showed significant improvement in intervention periods of <1 month (MD, 0.59; 95% CI, 0.10–1.07; I^2=23.92%; p=0.02) and >2 months (MD, 0.38; 95% CI, 0.04–0.72; I^2=0%; p=0.03; Supplementary Fig. S2I).

Onset duration was categorized as acute (0–3 months), subacute (4–12 months), and chronic (>12 months). When sub-analyzed according to onset duration, patients in the subacute phase had significant improvements in activities of daily living (MD, 0.37; 95% CI, 0.03–0.70; I^2=0%; p=0.03; Supplementary Fig. S2B) and WISCI (MD, 0.51; 95% CI, 0.06–0.96; I^2=35.72%; p=0.03; Supplementary Fig. S2F). The 6MWT distance showed significant improvement in acute patients (MD, 0.69; 95% CI, 0.06–1.32; I^2=38.51%; p=0.03; Supplementary Fig. S2J).

Adverse events

Six [18,26-30] of the 23 studies reported no adverse events. A variety of adverse events were reported in five studies [23,31-34], of which four [23,31,33,34] reported skin abrasions at the site of the robot, which improved with the application of pads at the time of treatment. Additionally, three studies [32-34] reported musculoskeletal pain, particularly knee and neck pain; one study [33] reported possibly related numbness; and one study [34] reported fatigue. The remaining 12 studies did not

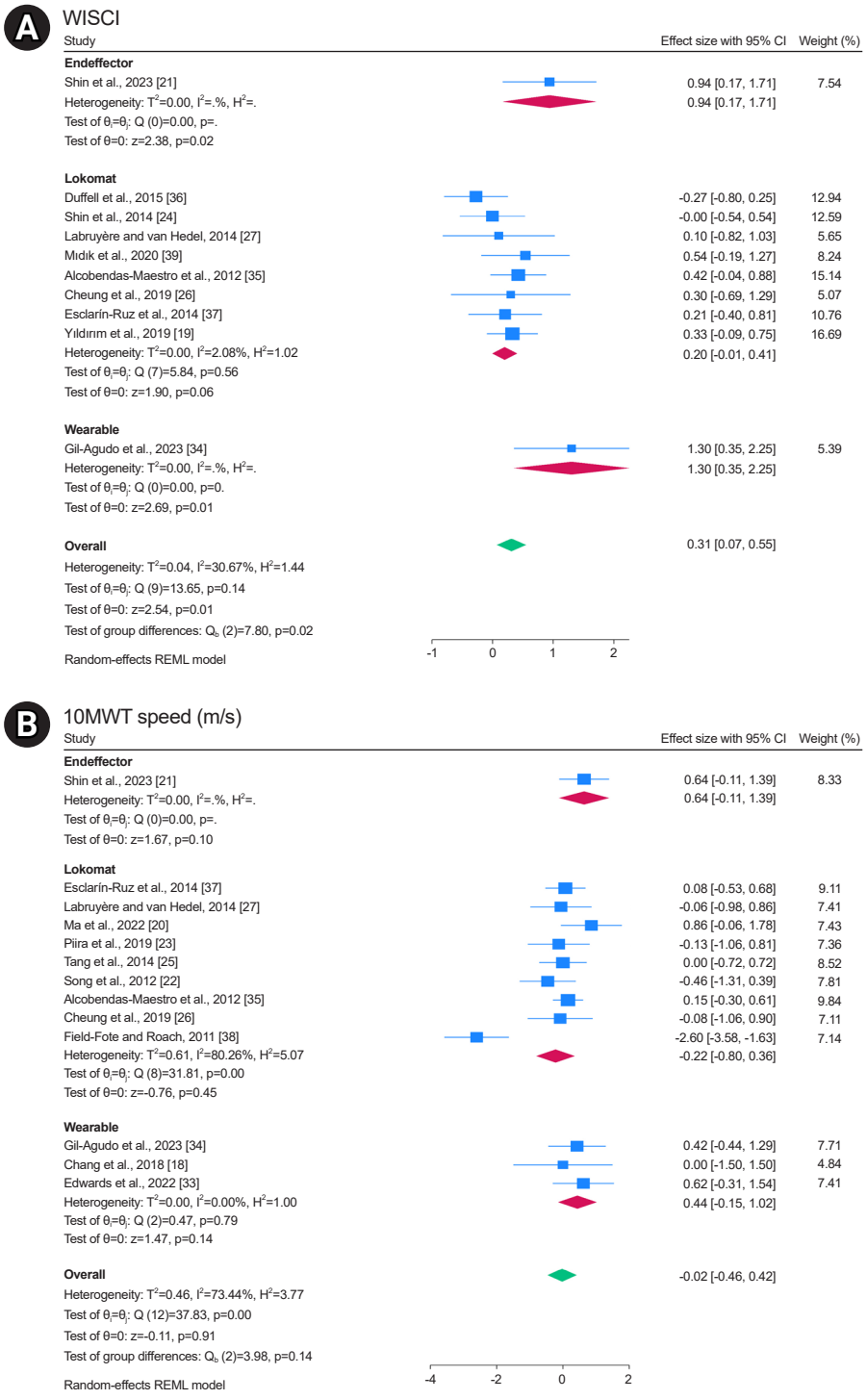

Fig. 4. Meta-analysis of the effects of RAGT on walking ability in patients with spinal cord injury (SCI). (A) Walking index for spinal cord injury (WISCI). (B) 10-min walk test (10MWT) speed (m/s).

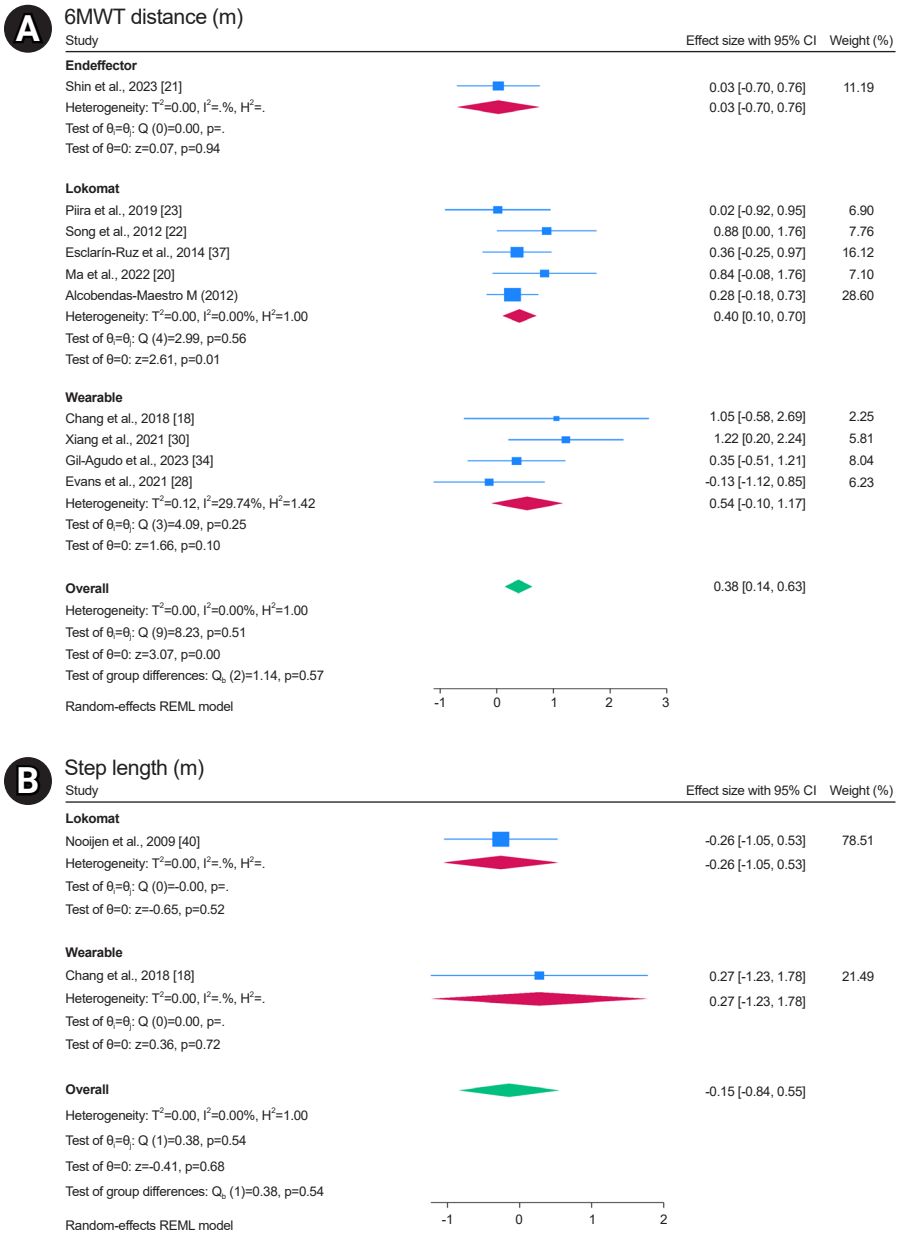

Fig. 5. Meta-analysis of the effects of the RAGT on walking ability in patients with spinal cord injury (SCI). (A) 6-min walk test (6MWT) distance (m). (B) Step length (m).

mention safety or side effects.

DISCUSSION

This systematic review investigated the efficacy of RAGT in patients with SCI. A study showed a high level of evidence that RAGT significantly improves activities of daily living and muscle strength. RAGT has been shown to significantly improve walking ability, specifically WISCI and 6MWT distances. Spasticity, balance, body composition, and cardiopulmonary function did not differ significantly between RAGT and conventional rehabilitation groups. Subgroup analyses showed significant improvements in activities of daily living and WISCI in subacute patients with onset duration of 4–12 months and intervention duration of ≥2 months.

The mechanism by which RAGT improves functionality in

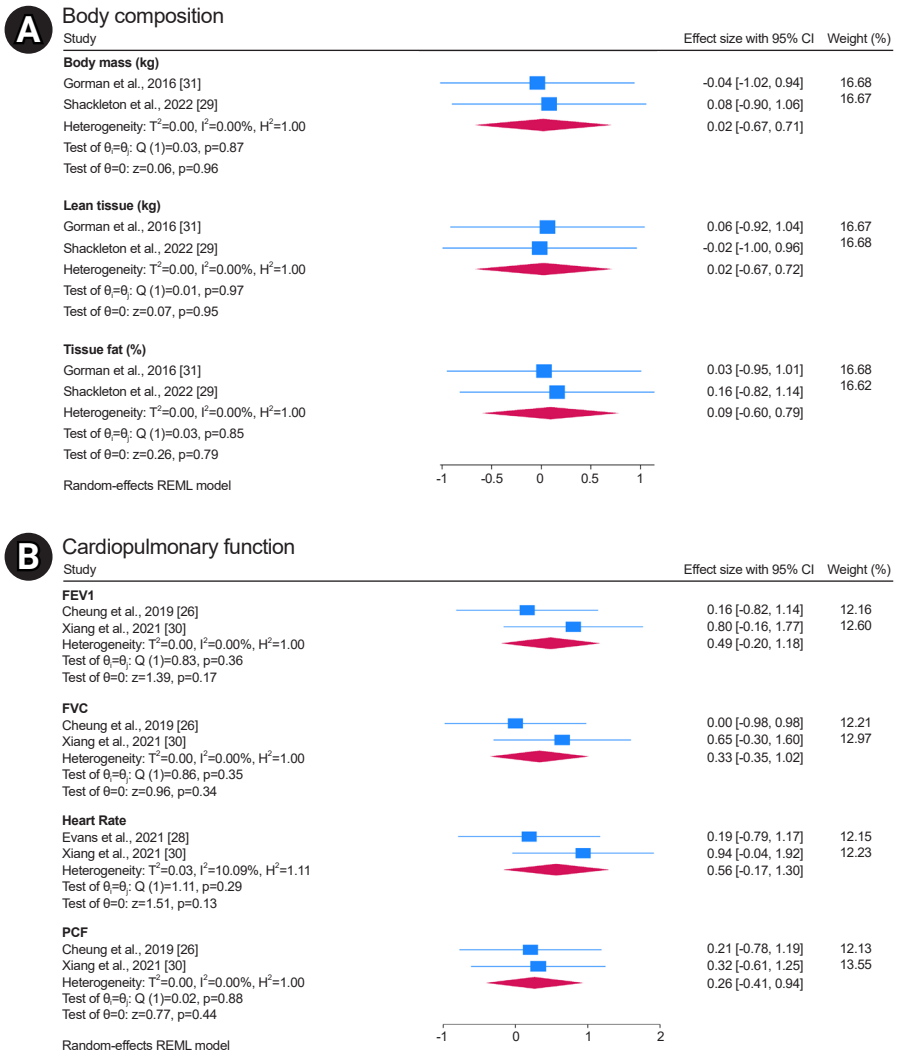

Fig. 6. Meta-analysis of the effects of the RAGT in patients with spinal cord injury (SCI). (A) Body composition. (B) Cardiopulmonary function.

patients with SCI involves reinforcing proprioceptive input to the spinal cord through walking-related rhythmic movements facilitated by robots. This process activates the central pattern generator embedded within the lumbosacral spinal cord and can induce plastic changes at the spinal cord level and within the sensorimotor cortex (S1 and S2) and cerebellar regions of the brain [41-44].

When analyzing the effects of robot type, the results were heterogeneous. For activities of daily living and muscular strength, the Lokomat had the largest effect size; for the WISCI, the wearable robot had the largest effect size; and for balance, the end effector had the largest effect size. Among existing studies, none compared the effects of the three types of robots simultaneously; however, studies comparing the Lokomat and wearable robots have shown that wearable robots show greater improvement in walking speed [10]. In previous studies, the difference has been explained between wearable robots and stationary treadmill systems, such as the Lokomat, because the former is an overground walking system that requires patients to exert greater effort on their trunk and arms while engaging in higher cognitive and cardiovascular efforts [45]. This increased effort results in elevated muscle activity in the torso and pelvic floor [46], significantly enhancing motor and sensory functions [47]. Additionally, wearable robots provide more proprioceptive stimulation and adaptability to real-world environments through overground walking programs, thereby promoting

Table 3. Subgroup analysis

Outcome measure		No. of patients Experimental/control (trials)	Effect size (95% confidence interval)	I^2 (%)
Activities of daily living	Intervention ≤1 month	89/84 (6)	SMD 0.10 (-0.20 to 0.40)	0
	Intervention >2 months	119/119 (5)	S MD 0.34 (0.09–0.60)**	0
	Acute	107/103 (5)	SMD 0.19 (-0.09 to 0.46)	0
	Subacute	69/68 (3)	SMD 0.37 (0.03–0.70)**	0
	Chronic	32/32 (3)	SMD 0.14 (-0.35 to 0.63)	0
Muscular strength	Intervention ≤1 month	87/82 (6)	MD 0.20 (-0.13 to 0.53)	12.97
	Intervention >2 months	76/76 (4)	MD 0.29 (-0.03 to 0.62)	0
	Intervention >3 months	21/29 (2)	MD 0.15 (-0.42 to 0.71)	0
	Acute	52/48 (3)	MD 0.00 (-0.39 to 0.3)	0
	Subacute	69/68 (3)	MD 0.26 (-0.07 to 0.60)	0
	Chronic	63/71 (3)	MD 0.38 (-0.02 to 0.78)	22.67
WISCI	Intervention ≤1 month	105/102 (6)	MD 0.37 (-0.11 to 0.84)	62.54
	Intervention >2 months	110/110 (4)	MD 0.33 (0.07–0.60)**	0
	Acute	87/83 (3)	MD 0.35 (-0.09 to 0.78)	45.65
	Subacute	69/68 (3)	MD 0.51 (0.06–0.96)**	35.72
	Chronic	59/61 (4)	MD 0.10 (-0.34 to 0.54)	26.96
10MWT speed (m/s)	Intervention ≤1 month	66/61 (6)	MD 0.12 (-0.24 to 0.48)	2.52
	Intervention >2 months	76/76 (4)	MD 0.19 (-0.13 to 0.51)	0
	Intervention >3 months	30/39 (3)	MD -0.70 (-2.60 to 1.20)	91.81
	Acute	31/27 (3)	MD 0.10 (-0.67 to 0.87)	47.35
	Subacute	84/83 (4)	MD 0.14 (-0.16 to 0.44)	0
	Chronic	57/66 (6)	MD -0.23 (-1.21 to 0.75)	84.61
6MWT distance (m)	Intervention ≤1 month	51/46 (5)	MD 0.59 (0.10–1.07)**	23.92
	Intervention >2 months	68/68 (3)	MD 0.38 (0.04–0.72)**	0
	Intervention >3 months	15/20 (2)	MD -0.04 (-0.72 to 0.64)	0
	Acute	40/36 (4)	MD 0.69 (0.06–1.32)**	38.51
	Subacute	69/68 (3)	MD 0.31 (-0.02 to 0.65)	0
	Chronic	25/30 (3)	MD 0.26 (-0.35 to 0.86)	18.50

Acute (0–3 months), subacute (4–12 months), and chronic (>12 months).
WISCI, walking index for spinal cord injury; 10MWT, 10 meter walk test; 6MWT, 6 min walk test; SMD, standardized mean difference; MD, mean difference.
**p<0.05.

greater neuroplasticity and facilitating connectivity remodulation [48]. The findings suggest that caution is needed in generalizing the efficacy of end-effector robots in improving balance, owing to limited studies. However, unlike exoskeleton-type robots, end-effector robots allow the knee and hip joints of participants to move freely, while their feet remain attached to the robot's footplates. Previous studies have shown that this unrestricted movement of the hip and knee joints encourages destabilization training and promotes the coordination of postural control through feedback and feed-forward mechanisms, ultimately improving overall postural control [49].

Typically, approximately half of the recovery occurs within the initial 2 months following an injury, with a declining recovery rate over the subsequent 4 months. According to the 1-year mark post-injury, neurological recovery is generally close to completion [50]. Engaging in repetitive functional gait training during the acute phase aids in restoring muscle activation and relearning proper gait patterns. However, individuals with chronic SCI face challenges due to a slower rate of neuroplasticity, making motor relearning and reducing dependence on walking aids more challenging. The sub-analysis results of this study can also be said to support the above hypothesis because there was a significant improvement in the activities of daily living and WISCI in subacute patients with an onset period of 4–12 months. However, in this analysis, RAGT was more effective in the subacute phase than in the acute phase because, firstly, in the acute phase, there is a lack of medical stability and a higher complication rate [51], which may reduce the effectiveness of RAGT, which is a high-intensity repetitive exercise, and, secondly, because of the difference in treatment duration be-

tween the two groups. Previous subgroup analyses have shown that RAGT is more effective when the treatment duration is 2 months or more, but 71.4% of the trials in the acute phase had a treatment duration of less than 1 month, and only 25% of the trials in the subacute phase had a treatment duration of less than 1 month, which may explain the smaller effect analyzed in the acute phase. Future studies comparing treatment effects in groups of patients with the same treatment duration and protocol but different onset times are needed.

Strengths and limitations

The strength of this meta-analysis is that it provided the most up-to-date and comprehensive information on the efficacy of RAGT in individuals with SCI. Additionally, we sub-analyzed the effects of robot type, duration of intervention, and onset of SCI.

This meta-analysis has several limitations. First, there was a limited pool of involved articles, with the majority having small sample sizes. The included papers varied according to robot type: 16 Lokomat papers, 6 wearable robot papers, and 1 end-effector robot paper. The largest sample size of the included papers was 88, and the remaining papers all had small sample sizes of less than 100. Previous research has shown that pilot studies or studies with small sample sizes can inflate pooled effect sizes, even in meta-analyses [52], so this study should be interpreted with this in mind. Second, heterogeneity was observed among the included studies. For the primary outcome, the 10MWT speed meta-analysis was highly heterogeneous, with an I^2 value of 73.44%. This was because the study protocols varied according to robot type, intervention duration, treatment time, robot body weight support percentage, guidance force, and speed, and the injury level, severity, and onset time of the included patients varied. To address this heterogeneity, we performed subgroup analyses based on the duration of intervention and onset. Third, it does not take into account initial ASIA assessment results, level of injury, and patient age. Studies have shown that recovery and ambulation in SCI patients are associated with initial ASIA assessment results and age, and the applicability of RAGT varies depending on whether the patient is a paraplegia or tetraplegia [53]. However, none of the RCTs published to date compared patients according to ASIA grades and level of injury, so a meta-analysis could not be performed. Further studies are needed to address this issue.

CONCLUSION

The meta-analysis findings indicated that RAGT resulted in beneficial enhancements in the activities of daily living, muscular strength, and walking ability. Notably, these improvements were more prominent in interventions lasting >2 months and among subacute patients. Consequently, RAGT appears to be a viable option for individuals with SCI, with positive outcomes without significant adverse events.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

This study was supported by the Special Research Fund for ARM Development of the Korean Academy of Rehabilitation Medicine in 2023.

AUTHOR CONTRIBUTION

Conceptualization: Park JM, Shin JC. Methodology: Park JM. Formal analysis: Park JM. Funding acquisition: Shin JC. Project administration: Park JM. Visualization: Park JM. Writing – original draft: Park JM. Writing – review and editing: Park JM, Kim YW, Lee SJ, Shin JC. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.5535/arm.230039.

ORCID

Jong Mi Park, https://orcid.org/0000-0003-4272-7489
Yong Wook Kim, https://orcid.org/0000-0002-5234-2454
Su Ji Lee, https://orcid.org/0000-0002-6376-0125
Ji Cheol Shin, https://orcid.org/0000-0002-1133-1361

REFERENCES

1. Mehrholz J, Kugler J, Pohl M. Locomotor training for walking after

spinal cord injury. Cochrane Database Syst Rev 2012;11:CD006676.
2. Edgerton VR, Kim SJ, Ichiyama RM, Gerasimenko YP, Roy RR. Rehabilitative therapies after spinal cord injury. J Neurotrauma 2006;23:560-70.
3. Lünenburger L, Colombo G, Riener R, Dietz V. Biofeedback in gait training with the robotic orthosis Lokomat. Conf Proc IEEE Eng Med Biol Soc 2004;2004:4888-91.
4. Tan K, Koyama S, Sakurai H, Teranishi T, Kanada Y, Tanabe S. Wearable robotic exoskeleton for gait reconstruction in patients with spinal cord injury: a literature review. J Orthop Translat 2021;28:55-64.
5. Rodríguez-Fernández A, Lobo-Prat J, Font-Llagunes JM. Systematic review on wearable lower-limb exoskeletons for gait training in neuromuscular impairments. J Neuroeng Rehabil 2021;18:22.
6. Shin JC, Jeon HR, Kim D, Cho SI, Min WK, Lee JS, et al. Effects on the motor function, proprioception, balance, and gait ability of the end-effector robot-assisted gait training for spinal cord injury patients. Brain Sci 2021;11:1281.
7. Hesse S, Waldner A, Tomelleri C. Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. J Neuroeng Rehabil 2010;7:30.
8. National Evidence-based Healthcare Collaborating Agency (NECA). Gait therapy using lower limb rehabilitation robots in spinal cord injury patients. NECA; 2021. p.1-12.
9. Li R, Ding M, Wang J, Pan H, Sun X, Huang L, et al. Effectiveness of robotic-assisted gait training on cardiopulmonary fitness and exercise capacity for incomplete spinal cord injury: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil 2023;37:312-29.
10. Zhang L, Lin F, Sun L, Chen C. Comparison of efficacy of Lokomat and wearable exoskeleton-assisted gait training in people with spinal cord injury: a systematic review and network meta-analysis. Front Neurol 2022;13:772660.
11. Wardhana DPW, Maliawan S, Mahadewa TGB, Rosyidi RM, Wiranata S. The impact of machine learning and robot-assisted gait training on spinal cord injury: a systematic review and meta-analysis. J Clin Med 2023;12:7230.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89.
13. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
14. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
15. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 1999;18:2693-708.
16. Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol 2011;64:1187-97.
17. Sterne JA, Egger M, Moher D. Addressing reporting biases. In: Higgins JPT, Green S, editor. Cochrane handbook for systematic reviews of interventions: Cochrane book series. The Cochrane Collaboration; 2008. p.297-333.
18. Chang SH, Afzal T, TIRR SCI Clinical Exoskeleton Group; Berliner J, Francisco GE. Exoskeleton-assisted gait training to improve gait in individuals with spinal cord injury: a pilot randomized study. Pilot Feasibility Stud 2018;4:62.
19. Yıldırım MA, Öneş K, Gökşenoğlu G. Early term effects of robotic assisted gait training on ambulation and functional capacity in patients with spinal cord injury. Turk J Med Sci 2019;49:838-43.
20. Ma TT, Zhang Q, Zhou TT, Zhang YQ, He Y, Li SJ, et al. Effects of robotic-assisted gait training on motor function and walking ability in children with thoracolumbar incomplete spinal cord injury. NeuroRehabilitation 2022;51:499-508.
21. Shin JC, Jeon HR, Kim D, Min WK, Lee JS, Cho SI, et al. Effects of end-effector robot-assisted gait training on gait ability, muscle strength, and balance in patients with spinal cord injury. NeuroRehabilitation 2023;53:335-46.
22. Song MS, Kang TW, Noh HJ, Bang DH. Effects of robot-assist training using virtual reality program on gait ability in patient with acute spinal cord injury. J Spec Educ Rehabil Sci 2012;51:347-62.
23. Piira A, Lannem AM, Sørensen M, Glott T, Knutsen R, Jørgensen L, et al. Robot-assisted locomotor training did not improve walking function in patients with chronic incomplete spinal cord injury: a randomized clinical trial. J Rehabil Med 2019;51:385-9.
24. Shin JC, Kim JY, Park HK, Kim NY. Effect of robotic-assisted gait training in patients with incomplete spinal cord injury. Ann Rehabil Med 2014;38:719-25.
25. Tang Q, Huang Q, Hu C. Research on design theory and compliant control for underactuated lower-extremity rehabilitation robotic systems code: (51175368); 2012.01-2015.12. J Phys Ther Sci 2014;26:1597-9.
26. Cheung EYY, Yu KKK, Kwan RLC, Ng CKM, Chau RMW, Cheing GLY. Effect of EMG-biofeedback robotic-assisted body weight supported treadmill training on walking ability and cardiopulmonary function on people with subacute spinal cord injuries - a randomized controlled trial. BMC Neurol 2019;19:140.

27. Labruyère R, van Hedel HJ. Strength training versus robot-assisted gait training after incomplete spinal cord injury: a randomized pilot study in patients depending on walking assistance. J Neuroeng Rehabil 2014;11:4.
28. Evans RW, Shackleton CL, West S, Derman W, Laurie Rauch HG, Baalbergen E, et al. Robotic locomotor training leads to cardiovascular changes in individuals with incomplete spinal cord injury over a 24-week rehabilitation period: a randomized controlled pilot study. Arch Phys Med Rehabil 2021;102:1447-56.
29. Shackleton C, Evans R, West S, Derman W, Albertus Y. Robotic walking to mitigate bone mineral density decline and adverse body composition in individuals with incomplete spinal cord injury: a pilot randomized clinical trial. Am J Phys Med Rehabil 2022;101:931-6.
30. Xiang XN, Zong HY, Ou Y, Yu X, Cheng H, Du CP, et al. Exoskeleton-assisted walking improves pulmonary function and walking parameters among individuals with spinal cord injury: a randomized controlled pilot study. J Neuroeng Rehabil 2021;18:86.
31. Gorman PH, Scott W, York H, Theyagaraj M, Price-Miller N, McQuaid J, et al. Robotically assisted treadmill exercise training for improving peak fitness in chronic motor incomplete spinal cord injury: a randomized controlled trial. J Spinal Cord Med 2016;39:32-44.
32. Wirz M, Mach O, Maier D, Benito-Penalva J, Taylor J, Esclarin A, et al. Effectiveness of automated locomotor training in patients with acute incomplete spinal cord injury: a randomized, controlled, multicenter trial. J Neurotrauma 2017;34:1891-6.
33. Edwards DJ, Forrest G, Cortes M, Weightman MM, Sadowsky C, Chang SH, et al. Walking improvement in chronic incomplete spinal cord injury with exoskeleton robotic training (WISE): a randomized controlled trial. Spinal Cord 2022;60:522-32.
34. Gil-Agudo Á, Megía-García Á, Pons JL, Sinovas-Alonso I, Comino-Suárez N, Lozano-Berrio V, et al. Exoskeleton-based training improves walking independence in incomplete spinal cord injury patients: results from a randomized controlled trial. J Neuroeng Rehabil 2023;20:36. Erratum in: J Neuroeng Rehabil 2023;20:160.
35. Alcobendas-Maestro M, Esclarín-Ruz A, Casado-López RM, Muñoz-González A, Pérez-Mateos G, González-Valdizán E, et al. Lokomat robotic-assisted versus overground training within 3 to 6 months of incomplete spinal cord lesion: randomized controlled trial. Neurorehabil Neural Repair 2012;26:1058-63.
36. Duffell LD, Brown GL, Mirbagheri MM. Interventions to Reduce Spasticity and Improve Function in People With Chronic Incomplete Spinal Cord Injury: Distinctions Revealed by Different Analytical Methods. Neurorehabil Neural Repair 2015;29:566-76.
37. Esclarín-Ruz A, Alcobendas-Maestro M, Casado-Lopez R, Perez-Mateos G, Florido-Sanchez MA, Gonzalez-Valdizan E, et al. A comparison of robotic walking therapy and conventional walking therapy in individuals with upper versus lower motor neuron lesions: a randomized controlled trial. Arch Phys Med Rehabil 2014;95:1023-31.
38. Field-Fote EC, Roach KE. Influence of a locomotor training approach on walking speed and distance in people with chronic spinal cord injury: a randomized clinical trial. Phys Ther 2011;91:48-60.
39. Mıdık M, Paker N, Buğdaycı D, Mıdık AC. Effects of robot-assisted gait training on lower extremity strength, functional independence, and walking function in men with incomplete traumatic spinal cord injury. Turk J Phys Med Rehabil 2020;66:54-9.
40. Nooijen CF, Ter Hoeve N, Field-Fote EC. Gait quality is improved by locomotor training in individuals with SCI regardless of training approach. J Neuroeng Rehabil 2009;6:36.
41. Hubli M, Dietz V. The physiological basis of neurorehabilitation--locomotor training after spinal cord injury. J Neuroeng Rehabil 2013;10:5.
42. Calancie B, Needham-Shropshire B, Jacobs P, Willer K, Zych G, Green BA. Involuntary stepping after chronic spinal cord injury. Evidence for a central rhythm generator for locomotion in man. Brain 1994;117(Pt 5):1143-59.
43. Scivoletto G, Ivanenko Y, Morganti B, Grasso R, Zago M, Lacquaniti F, et al. Plasticity of spinal centers in spinal cord injury patients: new concepts for gait evaluation and training. Neurorehabil Neural Repair 2007;21:358-65.
44. Winchester P, McColl R, Querry R, Foreman N, Mosby J, Tansey K, et al. Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury. Neurorehabil Neural Repair 2005;19:313-24.
45. Corbianco S, Cavallini G, Dini M, Franzoni F, D'Avino C, Gerini A, et al. Energy cost and psychological impact of robotic-assisted gait training in people with spinal cord injury: effect of two different types of devices. Neurol Sci 2021;42:3357-66.
46. Chisholm AE, Alamro RA, Williams AM, Lam T. Overground vs. treadmill-based robotic gait training to improve seated balance in people with motor-complete spinal cord injury: a case report. J Neuroeng Rehabil 2017;14:27.
47. Khan AS, Livingstone DC, Hurd CL, Duchcherer J, Misiaszek JE, Gorassini MA, et al. Retraining walking over ground in a powered exoskeleton after spinal cord injury: a prospective cohort study to examine functional gains and neuroplasticity. J Neuroeng Rehabil 2019;16:145.
48. Brown AR, Martinez M. From cortex to cord: motor circuit plastici-

ty after spinal cord injury. Neural Regen Res 2019;14:2054-62.
49. Gandolfi M, Valè N, Dimitrova E, Zanolin ME, Mattiuz N, Battistuzzi E, et al. Robot-assisted stair climbing training on postural control and sensory integration processes in chronic post-stroke patients: a randomized controlled clinical trial. Front Neurosci 2019;13:1143.
50. Piepmeier JM, Jenkins NR. Late neurological changes following traumatic spinal cord injury. J Neurosurg 1988;69:399-402.
51. Burns AS, Marino RJ, Kalsi-Ryan S, Middleton JW, Tetreault LA, Dettori JR, et al. Type and timing of rehabilitation following acute and subacute spinal cord injury: a systematic review. Global Spine J 2017;7(3 Suppl):175S-94S.
52. Beets MW, Weaver RG, Ioannidis JPA, Pfledderer CD, Jones A, von Klinggraeff L, et al. Influence of pilot and small trials in meta-analyses of behavioral interventions: a meta-epidemiological study. Syst Rev 2023;12:21.
53. Burns SP, Golding DG, Rolle WA Jr, Graziani V, Ditunno JF Jr. Recovery of ambulation in motor-incomplete tetraplegia. Arch Phys Med Rehabil 1997;78:1169-72.

Review Article

Ann Rehabil Med 2024;48(3):192-202
eISSN: 2234-0653
https://doi.org/10.5535/arm.240034

arm
Annals of Rehabilitation Medicine

Effects of Botulinum Toxin-A for Spasticity and Nociceptive Pain in Individuals With Spinal Cord Injury: A Systematic Review and Meta-Analysis

Dewan Md. Sumsuzzman, PhD[1,2,3], Zeeshan Ahmad Khan, PhD[2,3,4], Irin Sultana Nila, PhD[2,3,5], Vanina Myuriel Villagra Moran, BPT[2,3,6], Madhuvilakku Rajesh, PhD[2,3,4], Won Jong Yang, MD, PhD[7], Yonggeun Hong, PhD[1,2,3,4,5,6]

[1]*Department of Rehabilitation Science, Graduate School of Inje University, Gimhae, Korea*
[2]*Biohealth Products Research Center (BPRC), Inje University, Gimhae, Korea*
[3]*Research Center for Aged-life Redesign (RCAR), Inje University, Gimhae, Korea*
[4]*Department of Physical Therapy, College of Healthcare Medical Science & Engineering, Gimhae, Korea*
[5]*Department of Digital Anti-aging Healthcare, Graduate School of Inje University, Gimhae, Korea*
[6]*Department of Physical Therapy, Graduate School of Inje University, Gimhae, Korea*
[7]*Department of Rehabilitation Medicine, Medical Corporation, Daegu Medical Foundation The K Hospital, Daegu, Korea*

We conducted a systematic review and meta-analysis to examine the protective effects of botulinum toxin-A (Botox-A) on spasticity and nociceptive pain in individuals with spinal cord injuries (SCIs). PubMed, Embase, and Cochrane Library databases were searched from inception to July 2023. The primary outcome of interest was spasticity and nociceptive pain. We pooled the available data using the generic inverse variance method, and we used a fixed-effect/ random-effects model. We then calculated standardized mean difference (SMD) and 95% confidence intervals (95% CIs) to estimate the effect size. A total of fourteen studies meeting the inclusion criteria comprised two randomized controlled trials, five pre-post studies, and seven case reports. Across the various study designs, the majority of trials were assessed to have fair to high quality. The meta-analysis shows that Botox-A significantly decreased spasticity (SMD, -1.73; 95% CI, -2.51 to -0.95; p<0.0001, I^2=48%) and nociceptive pain (SMD, -1.79; 95% CI, -2.67 to -0.91; p<0.0001, I^2=0%) in SCI patients. Furthermore, Botox-A intervention improved motor function, activities of daily living (ADL), and quality of life. Our study suggests that Botox-A may alleviate spasticity and nociceptive pain in SCI patients. Moreover, the observed improvements in motor function, ADL, and overall quality of life following Botox-A intervention underscore its pivotal role in enhancing patient outcomes.

Keywords: Botulinum toxins type A, Muscle spasticity, Nociceptive pain, Spinal cord injuries, Systematic review

Received: March 19, 2024
Revised: May 26, 2024
Accepted: June 12, 2024

Correspondence:
Yonggeun Hong
Department of Rehabilitation Science, Graduate School of Inje University, 197 Inje-ro, Gimhae 50834, Korea.
Tel: +82-55-320-3681
Fax: +82-55-329-1678
E-mail: yonghong@inje.ac.kr

INTRODUCTION

Spasticity and pain frequently emerge as secondary sequelae following spinal cord injury (SCI), affecting around 60%–80% of cases [1]. Spasticity is also associated with a decline in quality of life (QoL) and increased mortality rates in SCI patients [2]. Pain

© 2024 by Korean Academy of Rehabilitation Medicine

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

following SCI, whether nociceptive or neuropathic [3], is equally prevalent and severe, adversely affecting physical, psychological, and social well-being, often worsening alongside other pain types. In the latest systematic review, nociceptive pain was found in 45% of cases, while neuropathic pain occurred in 58% of cases [4].

Despite significant advancements in managing spasticity and pain, addressing the fundamental barriers to QoL in individuals with SCI remains challenging. The management of spasticity often necessitates a multidisciplinary approach involving anti-spasticity medications, physical therapy, and, in some cases, surgical interventions [5]. However, oral anti-spasticity medications commonly prescribed to SCI patients are associated with various systemic adverse effects, such as sedation, confusion, hallucinations, nausea, and liver toxicity [6]. Compounding the issue, a significant portion of spasticity patients, around 40%, cannot tolerate the side effects of oral anti-spasticity agents [7], and physiotherapy frequently yields inconsistent outcomes in this population [8]. Local injections of botulinum toxin-A (Botox-A) offer a promising alternative to mitigate the side effects of oral anti-spasticity drugs and address the limitations of physiotherapies in SCI patients [9,10].

Botox-A, derived from the *Clostridium botulinum* bacterium, exerts its potent action by proteolytically cleaving synaptosomal associated protein-25 at nerve endings, thus impeding the release of acetylcholine neurotransmitter from axon terminals, resulting in muscle relaxation [11]. Numerous studies have demonstrated the safety and efficacy of Botox-A in managing spasticity across various neurological conditions including stroke, and traumatic brain injury [12,13]. Nearly a decade ago, a systematic review assessed the efficacy of Botox-A in managing spasticity among SCI patients [14]; however, given the dynamic nature of this field and the increasing number of published studies, the findings from this review may be outdated, reflecting the evolving landscape and highlighting the need for updated evidence to inform current clinical practice. Notably, recent randomized controlled trials (RCTs), such as the study by Yan et al. [15], have begun to evaluate the safety and efficacy of Botox-A specifically in SCI patients. Botox-A has been used to reduce spasticity in the rehabilitation setting, and its potential to manage pain is increasingly popular in the last decades [16,17]. A recent clinical review was conducted to evaluate the therapeutic efficacy of Botox-A for neuropathic pain in individuals with SCI [17]. Nonetheless, the therapeutic potential of Botox-A on nociceptive pain in SCI patients remains uncertain.

This systematic review and meta-analysis explore existing evidence on the protective role of Botox-A against spasticity and nociceptive pain in SCI patients. The evidence presented underscores the therapeutic potential of alleviating spasticity and nociceptive pain to enhance QoL in individuals with SCI.

METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The PRISMA checklist is provided in Supplementary Material.

Search strategy and data sources

We searched PubMed, Embase, and Cochrane Library electronic databases to identify all relevant trials up to July 2023. The reference lists of the included studies and of relevant reviews were examined for additional relevant trials. An electronic search of three databases was conducted, using the following search terms: "spinal cord injuries," "botulinum toxin," and "muscle spasticity." No limits (e.g., on language or publication date) were used. The in-depth search strategy performed in major electronic databases is given in Supplementary Table S1.

Inclusion criteria and outcomes of interest

Population

Any SCI patients who were diagnosed with spasticity will be included.

Interventions

Trials that evaluated the effects of Botox-A on spasticity in patients with SCI. The combined therapy of Botox-A with other interventions will be excluded. In terms of RCT, all participants in the control group underwent any therapies for spasticity, but not any types of Botox-A. In pre-post design studies, before Botox-A injection were categorized as "pre" (control arm), and after Botox-A treatment were deemed "post" (experimental).

Outcomes

The primary outcome encompasses spasticity, assessed through validated scales including the modified Ashworth scale (MAS), modified Tardieu scale (MTS), Ashworth scale (AS), and spasm frequency score (SFS), as well as nociceptive pain measured by the visual analogue scale (VAS) and numerical rating scale (NRS). Nociceptive pain being defined by the diagnostic crite-

ria proposed by the international SCI pain classification [18]. The secondary outcome includes the evaluation of activities of daily living (ADL) through tools such as the Barthel index (BI), Functional Independence Measure (FIM), or goal attainment scale (GAS). Additionally, motor function is assessed using the modified Rivermead mobility index or other pertinent tools, and QoL is measured using the disability assessment scale (DAS).

Study design

This study includes RCTs, before and after studies (pre-post design), or case report studies that assess the efficacy of Botox-A for the treatment of spasticity in patients with SCI. Any other studies, such as animal studies, conference abstracts, observational studies, letters, and reviews were removed.

Selection of studies

We used reference management software (Mendeley) to organize and manage a large number of citations, as well as remove duplicate articles. The remaining unique articles were then imported into a Rayyan web application to allocate the references randomly (https://www.rayyan.ai/). Based on titles and abstracts screening, two independent reviewers identified all of the pertinent articles, and trials that did not meet the inclusion criteria were eliminated. The same reviewers who were responsible for the primary screening had also evaluated the selected full-text articles for final inclusion. Any disagreements in study selection or data extraction were resolved by discussion between the reviewers, if consensus had not been reached, a third reviewer arbitrated.

Data extraction

Two reviewers individually extracted the following information: first author name and publication year, location, study design, sample size, patient characteristics, interventions, and outcomes measured. With regard to the pre-post study, the mean and standard deviation (SD) of final scores and the total number of participants before Botox-A treatment and after Botox-A treatment were extracted. Finally, we contacted the corresponding author via ResearchGate to retrieve any missing data. If efforts to obtain the raw data were unsuccessful, the article was removed from the meta-analysis. When the data were presented graphically, GetData Graph Digitizer [19] was used to extract numerical data from graphs or figures.

Quality assessment

Two reviewers individually evaluated the methodological quality of the selected trials. We applied the National Institutes of Health quality assessment tool for all pre-post design studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Additionally, the methodological quality of RCT was appraised by two authors using the Physiotherapy Reference Database (PEDro) scale, which has been designed to explore the reliability of data and provides a score out of 1–10 [20]. Studies with a PEDro score of 6–8, 4–5, and scoring below 4 are categorized as good quality, fair quality, and poor quality respectively [20]. Finally, the methodological quality of the selected case studies had evaluated utilizing the tool proposed by Murad et al. [21] to assess case series and case reports. This tool employs four domains for assessment: (1) selection, (2) ascertainment, (3) causality, and (4) reporting. If a trial has sufficient data in a domain, it was given one point. A total score of 4 out of 4 was considered high quality, 3 out of 4 was considered moderate quality, and a score ≤2 was considered low quality. Both the high and moderate-quality trials had considered having enough data to make inferences related to clinical practice. Finally, the Grading of Recommended Assessment, Development and Evaluation (GRADE) approach was used to determine the certainty of evidence for the primary outcomes (https://www.gradeworkinggroup.org/).

Data analysis

The variation of control groups between the included two RCTs, a formal meta-analysis was not possible. Furthermore, our included case reports were heterogeneous and did not include a control group. Hence, quantitatively synthesizing the results of each case study and estimating effect size is not possible either. Therefore, only descriptive and narrative results of qualitative analysis on the role of "Botox-A" described in each individual study were provided. However, statistical analysis was carried out by Review Manager software (RevMan 5.3; The Nordic Cochrane Centre) for pre-post design studies. We enumerated standardized mean differences (SMDs) for continuous data where trials used different scales for each outcome [22]. For each study and each comparison, we calculated the SMD, the pooled SD, and the standard error of the SMD. Where the correlation coefficient was unable to be extracted from publications or raw data, a conservative value of 0.5 was assumed [22]. This can be considered a conservative estimate when using the change scores from the baseline. When SD was not reported we

calculated SD from the t-value or the p-value [23], otherwise we inputted the highest SD from the existing meta-analysis. We pooled the available data using the generic inverse variance method, and we used a random-effects model. In the absence of clinical or statistical heterogeneity, we also applied a fixed-effect model for pooling. To assess the statistical heterogeneity, we performed a chi^2 test and calculated the I^2 value according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions. The I^2 test was utilized to assess heterogeneity among the studies (I^2=25%, low heterogeneity; I^2=50%, moderate heterogeneity; and I^2=75%, high heterogeneity) [24]. The fixed-effects model was used for the meta-analysis when I^2 was ≤50% and the random-effects model when I^2 was >50% [25,26]. Finally, we performed sensitivity analyses to evaluate the effect of the correlation coefficient; one assuming no correlation (when correlation coefficient=0.00) and one assuming a higher correlation (when correlation coefficient=0.80). And, p-value <0.05 is considered statistically significant. When conducting a meta-analysis, it's generally recommended to assess publication bias through funnel plot asymmetry only if there are at least 10 studies included. This is because with fewer studies, the tests lack sufficient power to differentiate chance from actual asymmetry. Since our study included fewer than 10 studies, evaluating publication bias through funnel plot asymmetry and Egger regression was not possible.

RESULTS

Search strategy

Our screening process is presented in Fig. 1. Initially, 914 potentially relevant articles were searched through the electronic databases, and one additional citation was identified by manual searching. After removing duplicates (n=356), 558 studies were screened in view of the title, abstract, or full text, and 498 were discarded. The remaining 60 studies were included for full-text evaluation. Finally, 14 articles met the eligibility criteria and included our review, and 46 studies were excluded with reasons (Supplementary Table S2).

Characteristics of included studies

Fourteen studies investigated the effect of Botox-A for the management of spasticity in SCI patients. The citation search identified two RCTs [15,27], five pre-post designs [16,28-31], and seven case report studies [32-38]. An overview of assessments of outcomes measured in the intervention is shown in Table 1. The MAS and VAS were the most common outcome measures for spasticity and pain assessment respectively. Regarding activity of daily living, the BI was adopted most, followed by GAS and FIM evaluation. The gait analysis was frequently adopted for the locomotion activity. Only one RCT evaluated the quality-of-life outcome by DAS scoring. A detailed characteristic of the selected studies is shown in Tables 2-4.

Quality assessment

The methodological quality of the included studies was presented in Supplementary Table S3 (RCTs), Supplementary Table S4 (pre-post studies), and Supplementary Table S5 (case reports). According to the results of quality of evidence, all RCTs had appraised of high quality [15,27], three out of five pre-post trials had appraised of good quality [19,29,30], and two studies rated

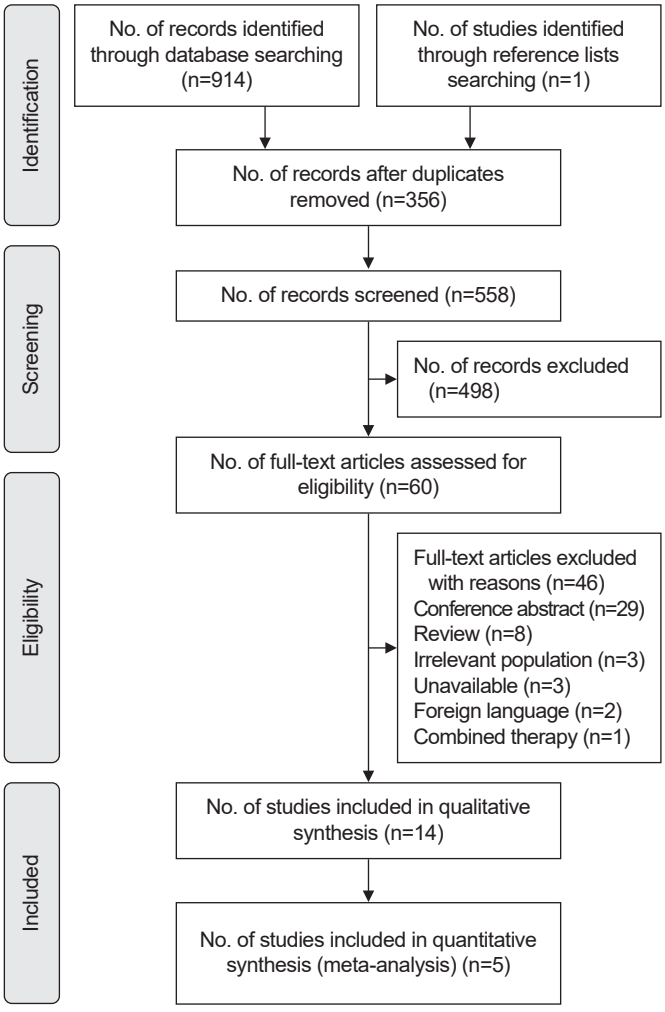

Fig. 1. Flow diagram of included and excluded studies.

Table 1. Description of outcome measures

Study design (level of evidence)	Outcome measure	Category	No. of studies
Pre-post studies (level-4)	Modified Ashworth scale	Spasticity	4
	Modified Tardieu scale	Spasticity	1
	Visual analogue scale	Pain	1
	Numerical rating scale	Pain	1
	Modified Rivermead mobility index	Motor function	1
	Functional Independence Measure	Activities of daily living	1
	Barthel index	Activities of daily living	1
Case-reports (level-5)	Modified Ashworth scale	Spasticity	4
	Ashworth scale	Spasticity	2
	Modified Tardieu scale	Spasticity	1
	Spasm frequency score	Spasticity	1
	Visual analogue scale	Pain	3
	Numerical rating scale	Pain	1
	Rivermead motor assessment	Motor function	1
	Barthel index	Activities of daily living	1
Randomized controlled trials (level-1)	Modified Ashworth scale	Spasticity	1
	Ashworth scale	Spasticity	1
	Rivermead motor assessment	Motor function	1
	Disability assessment scale	Quality of life	1
	Goal attainment scale	Activities of daily living	1
	Barthel index	Activities of daily living	1

Table 2. Characteristics of included studies in the systematic review: randomized controlled trials

Reference (country)	Study design	Participant	Inclusion criteria	Experimental group	Control group	Outcome measure
Yan et al., 2018 [15] (China)	Parallel-group	Total: n=224 (66 male, 158 female) Control group 1: n=112 (35.47±2.21 yr) Control group 2: n=112 (36.55±3.42 yr) BoNT-A group: n=112 (36.95±7.12 yr)	1. Duration since injury: more than 6 months 2. ≤2 MAS	BoNT-A 500 IU	Control group 1: locomotor training and intensive task-specific training for 6 weeks Control group 2: 5 mg of baclofen 3 times/day for 1 week, 10 mg of baclofen 3 times/day for 1 week in the second week, 15 mg of baclofen 3 times/day for 1 week in the third week, and 20 mg of baclofen 3 times/day for 1 week in the 4th week	MAS, DAS, BI
Richardson et al., 2000 [27] (UK)	Parallel-group	Total: n=6[a] Placebo group: n=2[a] BoNT group: n=4[a]	1. Duration since injury: more than 6 months 2. Moderate to severe spasticity	BoNT-A 100 IU	Placebo	AS, RMA, BI, GAS

Age presented as mean±standard deviation.
Control group 1=physical therapy; control group 2=baclofen.
BoNT-A, botulinum toxin-A; MAS, modified Ashworth scale; DAS, disability assessment scale; BI, Barthel index; AS, Ashworth scale; RMA, Rivermead motor assessment; GAS, goal attainment scale.
[a]Etiology specific data not reported.

as fair quality [28,31]; and three out of seven case report studies had appraised of high quality [32,36,37], and rest of four were moderate quality [33-35,38].

Meta-analysis

Effects of Botox-A in pre-post studies on the spasticity

Short-term (2–4 weeks) Botox-A treatment was effective as determined by the MAS and MTS scales. Taken together, four

Table 3. Characteristics of included studies in the systematic review: pre-post studies

Reference (country)	Population	ASIA impairment scale	N	Mean age (range), yr	Male (%)	Intervention	Outcome
Opara et al., 2007 [30] (Poland)	SCI patients with lower limb paresis and spasticity confirmed by MAS	NR	8	40.25 (23–62)	100	BoNT-A, 100–300 IU	MAS, VAS, MRMI
Bernuz et al., 2012 [28] (France)	SCI patients with lower limb spasticity and spasticity confirmed by Ely test as well as MAS	D	15	43 (28–58)	93	BoNT-A, 200 IU	MTS
Béseler et al., 2012 [29] (Spain)	SCI patients with lower limb spasticity and spasticity confirmed by MAS	NR	2	NR (mean) (>18)	50	BoNT-A, 100–300 IU	MAS
Spiegl et al., 2014 [31] (Germany)	SCI patients with lower limb spasticity and spasticity confirmed by MAS	A, C	9	40 (24–56)	100	BoNT-A, 100 IU	MAS
De Icco et al., 2019 [16] (Italy)	SCI patients with lower limb spasticity and spasticity confirmed by MAS as well as MRC	NR	5	39.5 (30.3–48.7)	100	BoNT-A, 50–200 IU	MAS, BI, FIM, NRS

ASIA, American Spinal Injury Association; SCI, spinal cord injury; MAS, modified Ashworth scale; NR, not reported; BoNT-A, botulinum toxin-A; VAS, visual analogue scale; MRMI, modified Rivermead mobility index; MTS, modified Tardieu scale; BI, Barthel index; FIM, Functional Independence Measure; NRS: numerical rating scale.

studies (24 patients) that used MAS and one study (15 patients) MTS to measure spasticity showed that short-term Botox-A treatment significantly decreased spasticity (SMD, -1.73; 95% CI, -2.51 to -0.95; p<0.0001, I^2=48%; Fig. 2). We imputed the 0.5 correlation coefficients to ascertain missing SDs. To reduce bias, we performed the sensitivity analysis and applied correlation coefficients of 0.8 and 0.0. Using a correlation coefficient of 0.8 (SMD, -1.86; 95% CI, -2.64 to -1.07; p<0.00001, I^2=80%; Supplementary Fig. S1), as well as 0.0 (SMD, -1.45; 95% CI, -2.11 to -0.78; p<0.0001, I^2=1%; Supplementary Fig. S2), the pooled difference between before Botox-A treatment and after Botox-A treatment remained statistically significant.

Effects of Botox-A in pre-post studies on the pain

Short-term (3–4 weeks) Botox-A treatment significantly reduced the pain as determined using the VAS and NRS scales. Altogether, one study (8 patients) that used VAS and one study (5 patients) NRS to measure pain showed that short-term Botox-A treatment significantly decreased pain (SMD, -1.79; 95% CI, -2.67 to -0.91; p<0.0001, I^2=0%; Fig. 3). We imputed the 0.5 correlation coefficients to ascertain missing SDs. As the sensitivity analysis, we applied correlation coefficients of 0.8 and 0.0. Using a correlation coefficient of 0.8 (SMD, -1.79; 95% CI, -2.34 to -1.24; p<0.00001, I^2=0%; Supplementary Fig. S3), as well as 0.0 (SMD, -1.79; 95% CI, -3.01 to -0.57; p=0.004, I^2=0%; Supplementary Fig. S4), the pooled difference between before Botox-A treatment and after Botox-A treatment remained statistically significant.

Systematic review

Effects of Botox-A on spasticity in RCTs

Two RCTs were included in our systematic review [15,27]. Both trials measured spasticity and found that Botox-A yielded a significant reduction of spasticity when compared with a comparator group. Yan et al. [15] compared the efficacy of Botox-A with baclofen and/or physical therapy at 2, 4, and 6 weeks of follow-up. Compared with the baseline score, at 2 weeks, physical therapies had no effect (p=0.063), baclofen (p=0.003), and Botox-A (p=0.0224) had decreased MAS scores. At 4 weeks, physical therapy (p<0.0001) baclofen (p<0.0001), and Botox-A (p<0.0001) had reduced MAS scores. Final follow-up after 6 weeks, baclofen (p=0.02) had not improved, and Botox-A (p=0.02) had decreased MAS score compared to physical therapy. In another study, Richardson et al. [27] compared the efficacy of Botox-A with placebo at 3, 6, 9, and 12 weeks follow-up. Across both groups, AS was significantly decreased at 3 weeks relative to baseline (p<0.0001) but when compared with subsequent successive time contrasts such as 6 weeks vs. 3 weeks; 9 weeks vs. 6 weeks; 12 weeks vs. 9 weeks were insignificant (p>0.2, in every case).

Effects of Botox-A on motor function, ADL, and QoL in RCTs

Richardson et al. [27] also assessed motor function and ADL by RMA and GAS scale respectively, but there was no group difference in aggregate outcome scores. Yan et al. [15] measured ADL by BI score and demonstrated that physical ther-

Table 4. Characteristics of included studies in the systematic review: case report studies

Reference (country)	Study population			Case definition	Intervention (dose)	Outcome	Author conclusion
	Age (yr)	Sex	n				
Richardson et al., 1997 [37] (UK)	23	Male	1	Incomplete C5/6 SCI with flaccid paralysis of all four limbs. Mild spastic paraparesis in the right leg, and mild hyperreflexia and clumsiness in the left arm and weakness in the right arm, most noticeable in the wrist, finger and thumb extensors	BoNT-A (210 IU)	RMA, VAS, AS	BoNT-A produced a temporary effect on muscle strength but may have a prolonged effect on function
Al-Khodairy et al., 1998 [32] (Switzerland)	50	Male	1	Incomplete T12 paraplegia (ASIA impairment scale=C) patient. presenting spasticity in his lower limbs with frequent painful spasms predominantly at night and with cold humid weather	BoNT-A (100–400 IU)	MAS, SFS, VAS	BoNT-A has its place in the treatment of spasticity in SCI. Although high doses of the product are well tolerated, the quantity should be tailored to the patient's needs
Tang et al., 2009 [38] (USA)	60	Male	1	C3-C4 SCI with right upper and lower limbs painful spasms. On the physical exam, he had right upper and lower limb hyperspasticity, hemiparesis, and poor positional and vibrational sense	BoNT-A (50–100 IU)	AS, NRS	BoNT-A can relief pain to biceps, flexor digitorum superficilais, brachialis, and pronator teres muscles
Naicker et al., 2009 [36] (Malaysia)	56	Male	1	C-5 SCI with spasticity in hips and knees. Patient had generalized pain in his legs, which was movement-related, dull, aching, and increased during spastic cramps	BoNT-A (NR)	MAS, BI, VAS	BoNT-A reduced spasticity and improved functional outcomes
Gross et al., 2012 [34] (France)	54	Male	1	The traumatic SCI pateint, AIS grade C spastic tetraplegia with right motor level C8, left motor level C5, right sensory level C6, and left sensory level C4. The initial ASIA upper limb motor score was 32 and the lower limb motor score 30	BoNT-A (100 IU)	MAS	The spastic activity of the rectus femoris and the abnormal knee motion totally reversed after BoNT-A injection
Htwe et al., 2016 [35] (Malaysia)	22	Female	1	T5 AIS A paraplegic patient, who presented with severe lower limb spasticity with unstable hips	BoNT-A (25–75 IU)	MAS, MTS	BoNT-A effective in a case of severe spasticity with unstable hips in SCI patient
Frost et al., 2021 [33] (Canada)	64	Female	1	The traumatic SCI patient, C6 AIS D with hip adductor spasticity that affecting her gait	BoNT-A (200 IU total)	MTS, pain	BoNT-A minimizing postoperative increase in spasticity, reduce pain, and no longer required a gait aid

C, cervical; SCI, spinal cord injury; ASIA, American Spinal Injury Association; AIS, ASIA impairment scale; T, thoracic; BoNT-A, botulinum toxin-A; NR, not reported; RMA, Rivermead motor assessment; VAS, visual analogue scale; AS, Ashworth scale; MAS, modified Ashworth scale; SFS, spasm frequency score; NRS, numerical rating scale; BI, Barthel index; MTS, modified Tardieu scale.

apy was required for at least 6 weeks for increasing the BI scores ($p<0.0001$). However, baclofen ($p<0.0001$) and Botox-A ($p=0.0015$) showed increased BI scores within 2 weeks. After 6 weeks, baclofen and Botox-A had the same effects on BI scores and consistently increased BI scores during the follow-up period. Besides, Yan et al. [15] also measured QoL by DAS score and showed that baclofen relatively improved DAS score than Botox-A at 4 weeks ($p=0.0496$) and 6 weeks ($p<0.0001$), as well.

Effects of Botox-A on spasticity and pain in case studies

The anti-spasticity effect of Botox on individuals with SCI was reported in seven case studies. The authors' conclusions and population characteristics from included case studies were presented in Tables 2-4. Among the seven case studies, five studies featured SCI patients with lower limb spasticity [32-36], while two studies included upper limb spasticity [37,38]. In addition, five case studies [32-36] also measured pain by different pain assessment scales, including VAS, and NRS. A study by Frost et

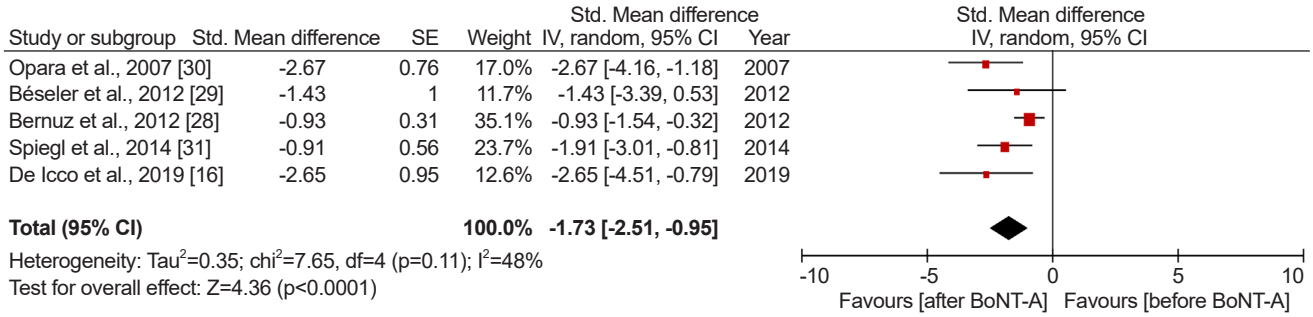

Fig. 2. Forest plot comparing the changes in the spasticity score between before botulinum toxin-A (Botox-A) and after Botox-A treatment in spinal cord injury. 95% CI, 95% confidence interval; SE, standard error; IV, independent variable.

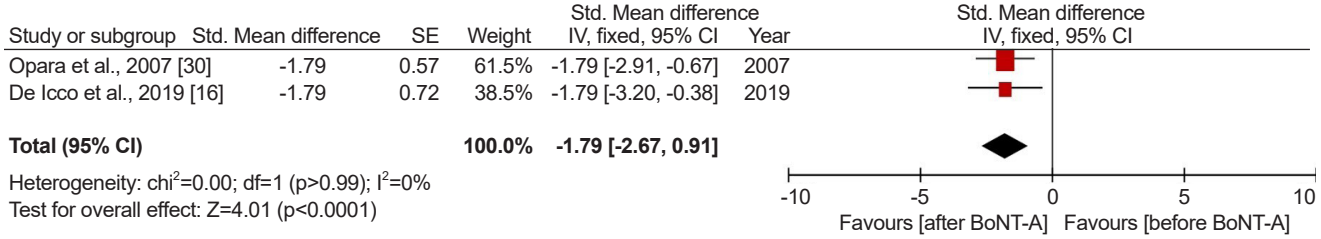

Fig. 3. Forest plot comparing the changes in the pain score between before botulinum toxin-A (Botox-A) and after Botox-A treatment in spinal cord injury. 95% CI, 95% confidence interval; SE, standard error; IV, independent variable.

al. [33] demonstrated that preoperative Botox-A reduces postoperative spasticity and pain, and eliminated the need for gait aids in patients with SCI-spasticity. Similarly, Botox-A treatment of spasticity in SCI patients reduced lower limb spasticity and spasticity-related pain after 24–72 hours [32]. Consistent with these findings, Al-Khodairy et al. [32] also reported that the clinical effects initiate within 24–72 hours after the Botox-A injection, peak in around 4–6 weeks, and are sustained for more than 3 months. The results, as shown by Htwe et al. [35], indicated that Botox-A response was very promising with a significant reduction in lower limb MAS score. Gross et al. [34] further disclosed that Botox-A markedly decreased spasticity of the rectus femoris. Naicker et al. [36] reported that Botox-A reversed the spasticity, spasticity- associated pain in the lower limb as indicated by SCI patient decreased MAS, VAS score, and sleep quality. In the upper limb, Botox-A treatment notably reduced AS (from 3 to 1) and maintain over 12 weeks [34]. Furthermore, the VAS score was significantly decreased by Botox-A injection, and the patient was able to shake hands during the 12-week study period [34]. Similarly, Tang et al. [38] found that Botox-A reduced spasticity and pain in upper limb muscles, including biceps, flexor digitorum superficilais, brachialis, and pronator teres muscles.

Certainty of the evidence

The certainty of evidence for the efficacy of Botox-A on spasticity and pain outcomes was assessed using the GRADE approach. Details of GRADE certainty of evidence for the spasticity outcomes are shown in Supplementary Table S6.

DISCUSSION

This systematic review of the literature summarized the available evidence on the effects of Botox-A for the management of spasticity in SCI patients. We identified two RCTs [15,27], five pre-post studies [18,28-31] and seven case reports [32-38], from three major electronic databases. The meta-analysis from pre-post studies suggested that patients with SCI could eventually show benefits regarding decreased spasticity (p<0.0001) within 2–4 weeks of Botox-A treatment. However, as depicted in Fig. 2, one study [29] approached the threshold of no effect, suggesting that Botox-A may not significantly improve spasticity outcomes. This study included two SCI patients: one female at 4 months post-onset and one male at 3 years post-onset [29], highlighting the potential impact of elapsed time between SCI onset and treatment administration on Botox-A effectiveness for spasticity. A further study is imperative to determine the op-

timal timing of Botox-A administration relative to SCI onset for achieving maximum efficacy in improving spasticity outcomes. Furthermore, Botox-A treatment may be also effective in SCI for the reduction of nociceptive pain ($p<0.0001$). Our quality assessment of included studies indicates the pre-post studies are fair to good quality. We rated all RCTs are high quality, and case reports are moderate to high quality. It is important to note that due to variation of the control group between two included RCTs, we did not perform the pairwise meta-analysis. In addition, case reports based on a single patient do not permit the estimation of effect size. Thus, the findings of RCTs and case reports were narratively described.

Despite our ample efforts, we were only able to include 14 studies in this review. Of these, two (RCTs) are level 1, five (pre-post) studies are level 4, and seven (case reports) are level 5 evidence [39]. The encouraging findings of our study that we are included two RCTs and performed for the first-time meta-analysis based on pre-post design studies in the SCI population. Consistent with other studies our meta-analysis has shown that Botox-A significantly reduced lower limb spasticity in SCI patients [40]. Recently, Yan et al. [15] performed one large RCTs to evaluate the efficacy of Botox-A in SCI patients. The results of this study also corroborated our findings that Botox-A notably decreased MAS score after a 2, 4, and 6 weeks follow-up period. Richardson et al. [37] compared the efficacy of Botox-A with the placebo up to 12 weeks follow-up period. This RCT only included 6 SCI patients (placebo group=2, and Botox-A group=4) and also concluded that Botox-A significantly decreased lower limb spasticity. In our systematic review, we only retrieved two RCTs and outcome measures estimated for short follow-up periods (2 to 12 weeks). In-future, long-term follow-up studies in RCT design are urgently required to establish the efficacy of Botox-A in spasticity caused by SCI. Our meta-analysis based on level 4 evidence in SCI showed very promising results for spasticity management through Botox-A, but meta-analysis based on level 1 evidence is required to confirm our findings before getting approval for this drug. In the future, a well-design, multicenter RCT on the current topic is therefore recommended. While we conducted searches across databases without restricting by language or publication date, we excluded non-English language articles and conference abstracts. This exclusion may introduce publication bias and result in an incomplete representation of the available evidence. Future studies should consider including non-English literature, grey literature like conference abstracts, and expanding search strategies to encompass country-specific databases such as CNKI and WANFANG, thus ensuring a comprehensive representation of available evidence.

Abnormal posture and soft tissue changes by spasticity can aggravate the risk of pain, in turn, pain may worsen spasticity [18]. Thus, patients with SCI-spasticity and spasticity-related pain can enter a vicious circle that can intensify both pain and spasticity. Most recently, a cross-sectional survey reported that spasticity and chronic pain commonly appears following SCI [41]. Tibbett et al. [1] also reported that spasticity and chronic pain are directly related, which significantly impact ADL in SCI patients. Our included case reports [32-38] also support the idea that spasticity and pain are interrelated. Interestingly, Botox-A treatment not only reduced the spasticity but also pain in SCI patients [27,32,33,35,36,38]. Our meta-analysis based on level 4 evidence demonstrated that Botox-A treatment markedly reduced nociceptive pain ($p<0.0001$) in the SCI population. Surprisingly, no RCTs yet evaluated the efficacy of Botox-A to reduce nociceptive pain in SCI subjects. However, our included RCTs reported other beneficial effects of Botox-A in SCI, including improvement of motor function, ADL, and QoL [15,27]. Further research should be undertaken to investigate the salutary effects of Botox-A for the management of spasticity and nociceptive pain in SCI are therefore recommended.

CONCLUSION

This systematic review and meta-analysis provide promising insights into the potential of Botox-A therapy in alleviating spasticity and nociceptive pain among individuals with SCI, supported by pre-post studies and case reports. Moving forward, there is a critical need for additional high-quality RCTs with extended follow-up periods to firmly establish the efficacy of Botox-A in managing SCI. Furthermore, our study underscores the complex relationship between spasticity and pain in SCI patients, suggesting the potential for Botox-A treatment to address both conditions simultaneously. Future research should explore the broader impact of Botox-A therapy on motor function, ADL, and overall QoL within this demographic, advancing our understanding of its clinical application in treating spinal cord injuries.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

This work was supported in part by grants from the National Research Foundation (2017R1D1A1B0302956514, 2020R1A2C201215511 to Y.H.), Korea.

AUTHOR CONTRIBUTION

Conceptualization: Sumsuzzman DM, Hong Y. Methodology: Sumsuzzman DM, Khan ZA, Nila IS, Moran VMV. Formal analysis: Sumsuzzman DM, Khan ZA, Nila IS, Moran VMV. Funding acquisition: Hong Y. Project administration: Sumsuzzman DM, Hong Y. Visualization: Sumsuzzman DM, Rajesh M, Yang WJ. Writing – original draft: Sumsuzzman DM, Hong Y. Writing – review and editing: Sumsuzzman DM, Khan ZA, Nila IS, Moran VMV, Rajesh M, Yang WJ, Hong Y. Approval of final manuscript: all authors.

ACKNOWLEDGMENTS

The authors would like to acknowledge the invaluable support and critical comments of members in the 'Biological Clock and Aging Control' laboratory. This study was completed as part of the doctoral dissertation by D.M.S.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.5535/arm.240034.

ORCID

Dewan Md. Sumsuzzman, https://orcid.org/0000-0002-4468-1202
Zeeshan Ahmad Khan, https://orcid.org/0000-0002-0737-0253
Irin Sultana Nila, https://orcid.org/0000-0003-2792-2139
Vanina Myuriel Villagra Moran, https://orcid.org/0000-0003-0680-757X
Madhuvilakku Rajesh, https://orcid.org/0000-0002-7636-3102
Won Jong Yang, https://orcid.org/0000-0002-2711-3318
Yonggeun Hong, https://orcid.org/0000-0003-1288-0546

REFERENCES

1. Tibbett JA, Field-Fote EC, Thomas CK, Widerström-Noga EG. Spasticity and pain after spinal cord injury: impact on daily life and the influence of psychological factors. PM R 2020;12:119-29.
2. McKay WB, Sweatman WM, Field-Fote EC. The experience of spasticity after spinal cord injury: perceived characteristics and impact on daily life. Spinal Cord 2018;56:478-86.
3. Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, et al. International spinal cord injury pain classification: part I. Background and description. March 6-7, 2009. Spinal Cord 2012;50:413-7.
4. Hunt C, Moman R, Peterson A, Wilson R, Covington S, Mustafa R, et al. Prevalence of chronic pain after spinal cord injury: a systematic review and meta-analysis. Reg Anesth Pain Med 2021;46:328-36.
5. Elbasiouny SM, Moroz D, Bakr MM, Mushahwar VK. Management of spasticity after spinal cord injury: current techniques and future directions. Neurorehabil Neural Repair 2010;24:23-33.
6. de Sousa N, Santos D, Monteiro S, Silva N, Barreiro-Iglesias A, Salgado AJ. Role of baclofen in modulating spasticity and neuroprotection in spinal cord injury. J Neurotrauma 2022;39:249-58.
7. Ward AB. Spasticity treatment with botulinum toxins. J Neural Transm (Vienna) 2008;115:607-16.
8. Harvey LA, Glinsky JV, Bowden JL. The effectiveness of 22 commonly administered physiotherapy interventions for people with spinal cord injury: a systematic review. Spinal Cord 2016;54:914-23.
9. Palazón-García R, Alcobendas-Maestro M, Esclarin-de Ruz A, Benavente-Valdepeñas AM. Treatment of spasticity in spinal cord injury with botulinum toxin. J Spinal Cord Med 2019;42:281-7.
10. Palazón-García R, Benavente-Valdepeñas AM. Botulinum toxin: from poison to possible treatment for spasticity in spinal cord injury. Int J Mol Sci 2021;22:4886.
11. Dressler D, Adib Saberi F. Botulinum toxin: mechanisms of action. Eur Neurol 2005;53:3-9.
12. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of botulinum toxin treatment for upper limb spasticity poststroke over different ICF domains: a systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100:1703-25.
13. Dong Y, Wu T, Hu X, Wang T. Efficacy and safety of botulinum toxin type A for upper limb spasticity after stroke or traumatic brain injury: a systematic review with meta-analysis and trial sequential analysis. Eur J Phys Rehabil Med 2017;53:256-67.
14. Lui J, Sarai M, Mills PB. Chemodenervation for treatment of limb spasticity following spinal cord injury: a systematic review. Spinal Cord 2015;53:252-64.
15. Yan X, Lan J, Liu Y, Miao J. Efficacy and safety of botulinum toxin type A in spasticity caused by spinal cord injury: a randomized, controlled trial. Med Sci Monit 2018;24:8160-71.
16. De Icco R, Perrotta A, Berra E, Allena M, Alfonsi E, Tamburin S, et al. OnabotulinumtoxinA reduces temporal pain processing at spinal

level in patients with lower limb spasticity. Toxins 2019;11:359.
17. Lakra C, Cohen H. A clinical review of the use of Botulinum Toxin type A in managing central neuropathic pain in patients with spinal cord injury. J Spinal Cord Med 2022;45:651-5.
18. Wissel J. Treatment of spasticity-related pain syndromes. In: Jost WH, editor. Botulinum toxin in painful diseases. Karger Publishers; 2003. p.126-39.
19. Taova S. GetData Digitizing Program Code: Description, Testing, Training. 2013.
20. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 2003;83:713-21.
21. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60-3.
22. Sumsuzzman DM, Choi J, Jin Y, Hong Y. Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: a systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev 2021;127:459-73.
23. Higgins JPT, Green S. 7.7.3.3 Obtaining standard deviations from standard errors, confidence intervals, t values and P values for differences in means [Internet]. The Cochrane Collaboration; 2011 [cited 2024 Mar 2]. Available from: https://handbook-5-1.cochrane.org/chapter_7/7_7_3_3_obtaining_standard_deviations_from_standard_errors.htm.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
25. Sumsuzzman DM, Khan ZA, Choi J, Hong Y. Differential role of melatonin in healthy brain aging: a systematic review and meta-analysis of the SAMP8 model. Aging (Albany NY) 2021;13:9373-97.
26. Sumsuzzman DM, Khan ZA, Choi J, Hong Y. Assessment of functional roles and therapeutic potential of integrin receptors in osteoarthritis: a systematic review and meta-analysis of preclinical studies. Ageing Res Rev 2022;81:101729.
27. Richardson D, Sheean G, Werring D, Desai M, Edwards S, Greenwood R, et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. J Neurol Neurosurg Psychiatry 2000;69:499-506.
28. Bernuz B, Genet F, Terrat P, Pradon D, Barbot F, Bussel B, et al. Botulinum toxin effect on voluntary and stretch reflex-related torque produced by the quadriceps: an isokinetic pilot study. Neurorehabil Neural Repair 2012;26:542-7.
29. Béseler MR, Grao CM, Gil A, Martínez Lozano MD. Walking assessment with instrumented insoles in patients with lower limb spasticity after botulinum toxin infiltration. Neurologia 2012;27:519-30.
30. Opara J, Hordyńska E, Swoboda A. Effectiveness of botulinum toxin A in the treatment of spasticity of the lower extremities in adults - preliminary report. Ortop Traumatol Rehabil 2007;9:277-85.
31. Spiegl UJ, Maier D, Gonschorek O, Heyde CE, Bühren V. Antispastic therapy with botulinum toxin type A in patients with traumatic spinal cord lesion. GMS Interdiscip Plast Reconstr Surg DGPW 2014;3:Doc14.
32. Al-Khodairy AT, Gobelet C, Rossier AB. Has botulinum toxin type A a place in the treatment of spasticity in spinal cord injury patients? Spinal Cord 1998;36:854-8.
33. Frost G, Finlayson H, Saeidiborojeni S, Lagnau P, Reebye R. Perioperative botulinum toxin injections to enhance surgical outcomes in patients with spasticity: preoperative, intraoperative, and postoperative case reports. Arch Rehabil Res Clin Transl 2021;3:100101.
34. Gross R, Leboeuf F, Rémy-Néris O, Perrouin-Verbe B. Unstable gait due to spasticity of the rectus femoris: gait analysis and motor nerve block. Ann Phys Rehabil Med 2012;55:609-22.
35. Htwe O, Hussain RI, Naicker AS. Challenges in managing severe lower limb spasticity associated with bilateral hip joints subluxation. Electron J Gen Med 2016;13:165-7.
36. Naicker AS, Roohi SA, Chan JL. Botulinum toxin type A for rehabilitation after a spinal cord injury: a case report. J Orthop Surg (Hong Kong) 2009;17:96-9.
37. Richardson D, Edwards S, Sheean GL, Greenwood RJ, Thompson AJ. The effect of botulinum toxin on hand function after incomplete spinal cord injury at the level of C5/6: a case report. Clin Rehabil 1997;11:288-92.
38. Tang N, Stickevers S, Awan G. Delayed onset of Brown-Sequard syndrome involving upper extremity pain. Pain Pract 2009;9:150-1.
39. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71-2.
40. Francisco GE, Bandari DS, Bavikatte G, Jost WH, McCusker E, Largent J, et al. High clinician- and patient-reported satisfaction with individualized onabotulinumtoxinA treatment for spasticity across several etiologies from the ASPIRE study. Toxicon X 2020;7:100040.
41. Andresen SR, Biering-Sørensen F, Hagen EM, Nielsen JF, Bach FW, Finnerup NB. Pain, spasticity and quality of life in individuals with traumatic spinal cord injury in Denmark. Spinal Cord 2016;54:973-9.

Original Article

Ann Rehabil Med 2024;48(3):203-210
eISSN: 2234-0653
https://doi.org/10.5535/arm.230025

Annals of Rehabilitation Medicine

Measurement of Knee Extensor Torque During Repetitive Peripheral Magnetic Stimulation: Comparison of the Forces Induced by Different Stimulators

Masanori Kamiue, MS[1], Akio Tsubahara, MD, DMSC[2], Tomotaka Ito, PhD[2], Yasuhiro Koike, MS[3]

[1]*Doctoral Program in Rehabilitation, Graduate School of Health Science and Technology, Kawasaki University of Medical Welfare, Kurashiki, Japan*
[2]*Department of Physical Therapy, Faculty of Rehabilitation, Kawasaki University of Medical Welfare, Kurashiki, Japan*
[3]*Department of Occupational Therapy, Faculty of Rehabilitation, Kawasaki University of Medical Welfare, Kurashiki, Japan*

Objective: To investigate the factors that induce strong contractions during repetitive peripheral magnetic stimulation (rPMS) and compare the muscle torque induced by two stimulators (Stim A and Stim B) with different coil properties.
Methods: rPMS was applied to the right vastus lateralis of 30 healthy young adults. Stim A contained a 10.1 cm^2 rectangular iron core coil, while Stim B contained a 191 cm^2 round coil. The knee extensor torque (KET) induced by rPMS at 30 Hz was measured isometrically and divided by the maximum voluntary contraction (MVC) to obtain a relative value of MVC (%MVC). KET at 100% intensity of Stim A (A100%, 1.08 T) was compared to those at 100% or 70% intensity of Stim B (B100%, 1.47 T vs. B70%, 1.07 T). Additionally, we conducted a comprehensive literature search for studies that measured the KET during rPMS.
Results: Both the mean values of %MVC using B100% and B70% were significantly greater than that using A100%. Furthermore, the KET induced by Stim B was found to be larger than that described in previous reports, unless booster units were used to directly stimulate the main trunk of the femoral nerve.
Conclusion: Stim B induced a stronger muscle contraction force than Stim A did. This may be because the larger the coil area, the wider the area that can be stimulated. Additionally, a circular coil allows for deeper stimulation.

Keywords: Muscle strength, Strengthening, Contraction force, Magnetic coil, Disuse atrophy

Received: November 21, 2023
Revised: February 9, 2024
Accepted: April 11, 2024

Correspondence:
Masanori Kamiue
Doctoral Program in Rehabilitation, Graduate School of Health Science and Technology, Kawasaki University of Medical Welfare, 288 Matsushima, Kurashiki 710-0193, Japan.
Tel: +81-86-462-1111
Fax: +81-86-462-1193
E-mail: p_reticulata_0229@yahoo.co.jp

INTRODUCTION

Resistance exercises at 40%–85% of maximum voluntary contraction (MVC) has been reported to be important for preventing age-related muscle weakness and physical dysfunction [1-5]. However, resistance exercises are often difficult to continue performing because they depend on individual motivation. Therefore, electrical stimulation, which has little relevance to motivation, is used to maintain and improve muscle strength. Recently, application of repetitive peripheral magnetic stimulation (rPMS), which can be stimulated over clothing, to skeletal muscles has been reported to be useful for muscle strengthening as an alternative to electrical stimulation [6,7]. Since rPMS induces skeletal muscle contraction without activating cutaneous

© 2024 by Korean Academy of Rehabilitation Medicine

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

nociceptors [7], it produces less pain than electrical stimulation does [8,9].

Several rPMS intervention studies have reported muscle strengthening effects in healthy participants, patients with stroke and chronic obstructive pulmonary disease, and after total hip replacement [10-14]. However, in other studies, rPMS did not produce any significant changes in muscle thickness or cross-sectional area after 4 weeks [12] or did not clearly increase muscle strength in the lower extremities [15]. Thus, rPMS intervention studies have inconsistent results and are limited in number compared with studies on electrical stimulation. We have previously examined the stimulation methods, such the intensity and application site, and confirmed that strong muscle contraction can be obtained by selecting the optimal stimulation intensity and application site [16,17]. Differences in the shape of the stimulating coil can have a large effect on muscle contraction. Stimulation of the femoral nerve with a figure-eight coil reportedly induces greater muscle contraction than stimulation with a circular coil does [18]. Additionally, the larger the coil size, the stronger the muscle contraction force induced by femoral nerve stimulation, when the shape of the coil is the same [19].

Although the effects of equipment differences and stimulation methods on muscle contraction have been clarified gradually in our study and previous studies, reports on the measurement of rPMS-induced muscle contraction are limited. Recently, magnetic stimulators that can induce stronger muscle contractions without generating excessive heat have been developed; however, reports on the actual measurement of muscle contraction force using such stimulators are scarce. Thus, in this study, the muscle torques induced by two stimulators with different coil properties were compared, and the factors that caused strong contractions were examined. Furthermore, we conducted a comprehensive search for previous studies that measured the muscle contraction force during rPMS and compared our study results with those of the previous studies. The results of this study could aid in the clinical application of rPMS-induced muscle contractions for the prevention of disuse atrophy or strengthening of lower extremity muscle in older adults.

METHODS

Participants

Thirty healthy young adults (mean age, 21.5±4.1 years; 15 females and 15 males) without any history of orthopedic, neuromuscular, or central nervous system diseases voluntarily participated in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki. The purpose of the study was explained in detail to all participants, both orally and in writing. Written informed consent was obtained from all the participants. This study was approved by the Ethics Committee of the Kawasaki University of Medical Welfare (No: 20-108; April 2021).

Equipment

Two types of magnetic stimulators manufactured by IFG Co. Ltd. (Stim A) and REMED Co. Ltd. (Stim B) were used for rPMS. Stim A and Stim B were air-cooled and oil-cooled magnetic stimulators, respectively (Fig. 1). Stim A contained a 10.1 cm^2 rectangular iron core coil with rounded corners, while Stim B contained a large round coil (radius 7.8 cm, area 191 cm^2). The maximum outputs of the magnetic stimulation just below the probe surface of Stim A and Stim B were 1.08 T and 1.47 T, respectively, at a frequency of 30 Hz.

Stimulation conditions

The right vastus lateralis (VL) was magnetically stimulated according to previous reports [17,20-23]. Participants were seated with their right knee and hip joints flexed at 75°. The trunk and pelvic girdle were strapped to the seat, and the distal end of the right lower extremity was strapped to a machine that measured the isometric contraction (Fig. 2).

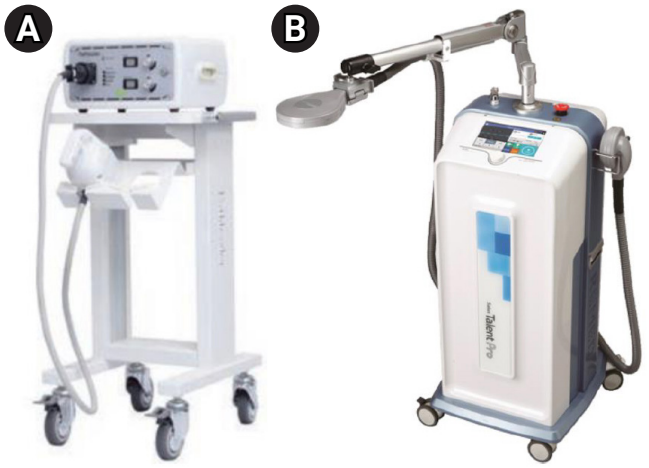

Fig. 1. Magnetic stimulators used for muscle contraction. (A) Air-cooled type stimulator manufactured by IFG Co. Ltd. (Stim A). (B) Oil-cooled type stimulator manufactured by REMED Co. Ltd. (Stim B).

First, we used Stim A to identify stimulation points that could induce the maximum right VL contraction. The area between the proximal and distal 1/3 of the line connecting the anterior superior iliac spine and the superolateral margin of the patella was examined to identify the stimulation points [12]. Five to ten stimulations were applied to find the optimal point that could induce a stable and strong muscle contraction force; the identified point was marked.

When measuring the rPMS-induced muscle contraction force, great care was taken to ensure that the central part of the probe with the built-in coil coincided with the optimal stimulation point and that the long axis of the coil was parallel to the long axis of the thigh. Magnetic stimulation pulse trains were gradually increased to the maximum output intensity. After habituation to the magnetic stimulation was acquired, the VL was stimulated three times at the maximum output intensity of each stimulator (A100% and B100%). Each stimulation lasted 3 seconds with a 2 seconds rest interval between stimulations. Subsequently, additional muscle contractions were induced with Stim B at 70% of the maximum output intensity (B70%), that is 1.07 T/sec, to produce a magnetic stimulation output equivalent to that of Stim A at A100%.

The participants were instructed to relax their entire body as much as possible to avoid voluntary contraction of the quadriceps femoris during rPMS. The isometric knee extensor torque (KET) was measured three times in each condition (A100%, B100%, and B70%). Immediately after each stimulation, the degree of pain during rPMS was evaluated using a visual analogue scale (VAS). The participants were instructed to place an "x" mark on a 100 mm straight line. The left end (0 mm) of the line was set as "no pain" and the right end (100 mm) as "pain too intense to be tolerated." The VAS values were recorded to one decimal place.

Fig. 2. Muscle contraction induced by repetitive peripheral magnetic stimulation and measurement of muscle torque. (A) Contraction induced by the stimulator manufactured by IFG Co. Ltd. (Stim A). (B) Contraction induced by the stimulator manufactured by REMED Co. Ltd. (Stim B).

Measurement of KET

The right-sided KET was measured using a dynamometer (BIODEX System 3®; Biodex Medical Systems, Inc.), at a frequency of 100 Hz. Before MVC measurement, four sets of 3 seconds isometric knee extension exercises were performed with approximately 90% MVC as a warm-up. A rest interval of 5 seconds was maintained between the sets. After a 5 minutes post-warm up break, the muscle torque during a MVC of 3 seconds was measured twice with a 5 seconds rest interval between measurements. The larger of the two measurements was used in the analysis.

After another 5 minutes break, the rPMS-induced KET was measured at A100%, B100%, and B70%. The mean torque value for 1 second from 500 to 1,500 ms before the waveform returned to baseline after contraction was used for the analysis (Fig. 3). To compare the rPMS-induced muscle torque under the three conditions, the mean of the three measurements in each condition was calculated. The relative value of MVC (%MVC) was obtained by dividing the rPMS-induced KET by the MVC.

Data analysis

The Shapiro–Wilk test was performed on all data obtained in this study to determine if they were normally distributed. To examine the effects of the stimulation conditions on the KET (%MVC) and pain level (VAS value), their mean values at A100%, B100%, and B70% were compared. The Friedman test

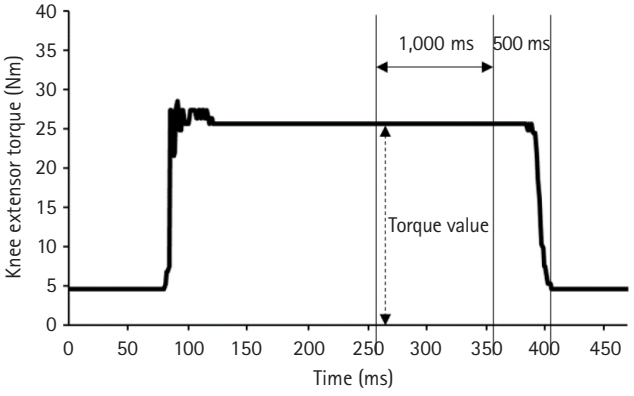

Fig. 3. Knee extensor torque waveform during repetitive peripheral magnetic stimulation. Torque value: mean torque for 1 second from 500 to 1,500 ms before the waveform returned to baseline after contraction.

was used for multiple comparisons, followed by the Bonferroni correction for post-hoc testing. IBM SPSS version 22.0 (IBM Corp.) was used for the statistical analysis, and the significance level was set at $p<0.05$.

Comprehensive literature search

A comprehensive literature search was conducted to compare our study's rPMS-induced KET with those of previous studies. PubMed was searched independently by two researchers. The titles, abstracts, and texts of studies published on rPMS in humans were searched without restrictions on publication date or methodological design.

First, an OR search was performed using "repetitive peripheral magnetic stimul*," "rPMS," "spinal magnetic stimul*," "magnetic nerve stimul*," "magnetic stimulation," and "electromagnetic stimulation." In the next OR search, the keywords used were "torque," "force," and "Nm." In the third OR search, the keywords used were "quadriceps," "vastus lateralis," and "rectus femoris." An AND search was then performed on the results of the three OR searches. The papers identified in the search were reviewed, and studies that actually measured the KET were selected. In addition, we manually searched for relevant studies among the references of the selected articles.

RESULTS

Comparison of the KETs in each stimulation condition

The Friedman test showed a statistically significant difference in %MVC between the different intensities ($p<0.001$). The mean MVC was 161.0±51.4 Nm (Table 1). The mean KETs induced by A100%, B100%, and B70% were 29.6±18.1 Nm (%MVC, 17.7%±8.3%), 66.1±24.5 Nm (%MVC, 41.1%±9.0%), and 54.9±23.4 Nm (%MVC, 33.8%±9.8%), respectively (Table 1). The mean %MVC at B100% was significantly greater than that at A70% and A100% ($p<0.001$). The mean %MVC at B70% was also significantly greater than that at A100% ($p<0.001$) (Fig. 4).

Table 1. MVC of the knee extensors and rPMS-induced KET induced under each stimulation condition

	Coil area (cm^2)	KET (Nm)	Output intensity (T)
MVC	-	161.0±51.4	-
A100%	10.1	29.6±18.1	1.08
B70%	191	54.9±23.4	1.07
B100%	191	66.1±24.5	1.47

Values are presented as number only or mean±standard deviation.
The output intensity of the magnetic stimulation immediately below the probe surface was equivalent between B70% and A100%.
MVC, maximum voluntary contraction; rPMS, repetitive peripheral magnetic stimulation; KET, knee extensor torque; A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B.

Comparison of the pain scores in each stimulation condition

The degree of pain evaluated using the VAS is shown in Fig. 5. The Friedman test showed a statistically significant difference in the VAS scores between the different intensities ($p<0.001$). The mean VAS score caused by A100% was lower than that caused by B70% ($p<0.05$) and B100% ($p<0.001$). The mean VAS score caused by B70% was also significantly lower than that caused by B100% ($p<0.01$). However, the pain caused by A100% was not uncomfortable.

Comprehensive literature search

The AND and OR searches identified 115 papers published prior to October 2022. However, a review of the selected papers revealed that only four studies actually measured the rPMS-induced KET in the quadriceps femoris muscle. The magnetic

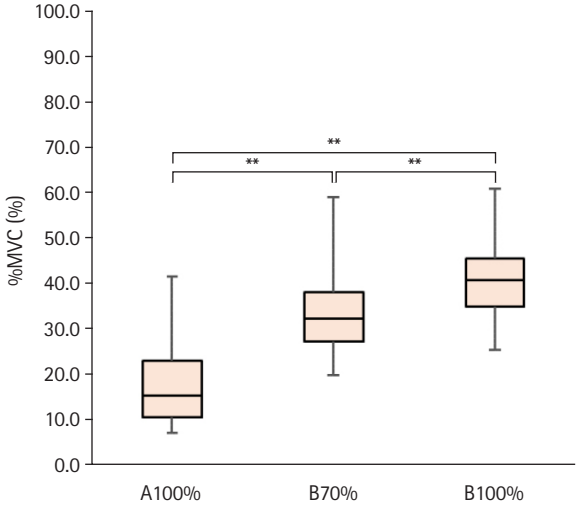

Fig. 4. Comparison of relative value of maximum voluntary contraction (%MVC) during repetitive peripheral magnetic stimulation between each stimulation condition. %MVC was calculated by dividing the knee extensor torque during stimulation by the MVC. A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B. **p<0.01.

stimulator used for transcranial magnetic stimulation (TMS), with stimulation intensities ranging from 1.8 to 2.0 T, was utilized in all four papers.

In a previous study in which the rectus femoris was stimulated, the maximum rPMS-induced KET did not exceed 20 Nm. In three other studies, in which the main trunk of the femoral nerve was directly stimulated with a stimulator equipped with booster units, the KET exceeded 20 Nm (Table 2). Among these three studies, in one study, the mean KET which was measured as the sum of four muscles, was greater than that of one muscle in our study. The other two studies using booster units reported a %MVC greater than 70%; however, the actual MVC values were not included in these papers.

None of the three studies that directly stimulated the main trunk of the femoral nerve reported on pain assessments. The study in which the rectus femoris was stimulated reported VAS scores of zero in all participants.

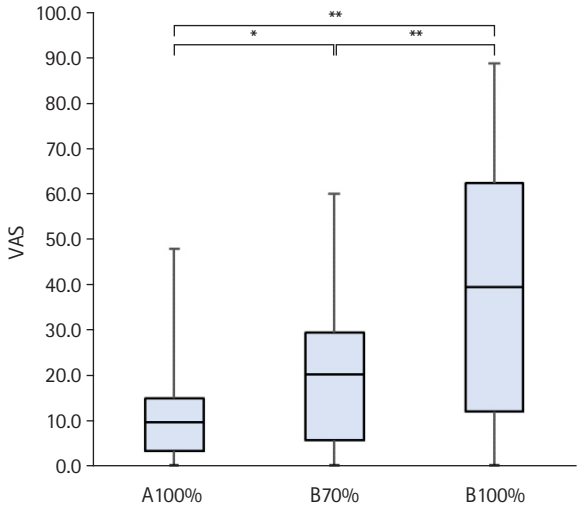

Fig. 5. Comparison of pain during repetitive peripheral magnetic stimulation in each stimulation condition. A100%, maximum output intensity of the stimulator manufactured by IFG Co. Ltd. (Stim A); B70%, 70% of maximum output intensity of the stimulator manufactured by REMED Co. Ltd. (Stim B); B100%, maximum output intensity of the Stim B; VAS, visual analogue scale. *p<0.05, **p<0.01.

DISCCUSION

The results of this study revealed that the rPMS-induced KET with Stim B was greater than that induced by Stim A, even when the output intensity of the magnetic stimulation just below the probe surface was adjusted to be equivalent. The output intensity was previously measured, and B70% was found to be equivalent to A100%. The muscle contraction force induced by A100% was weaker than that induced by B70%, so we did not measure the muscle contraction force induced by A70%. Although the rPMS-induced contraction force is related to the magnetic stimulation intensity [15,16,18,19], coil size [19], and coil shape [18], no studies have compared the contraction forces induced by different coils at the same stimulation intensity. In the present study, the KET was compared by equalizing the stimulation intensities of the two different stimulators. Our

Table 2. Details of the four studies extracted from a comprehensive literature search

Reference	Equipment	Coil properties	Stimulation frequency (Hz)	Output intensity (T)	Stimulation site	Duration of stimulation (s)	Pain assessment	Measured value of KET	Participants
Han et al., 2006 [27]	Biocon-1000	Circumferential	25	1.8	Rectus femoris	2	VAS	9.5±4.8 Nm	Healthy adults
Kremenic et al., 2004 [29]	Magstim Rapid with four booster units	110-mm double-circular	20, 30, 40	2	Main trunk of femoral nerve	3	None	Approximately 70% of MVC "estimated"	Healthy adults
Kremenic et al., 2009 [30]	Magstim Rapid with eight booster units	110-mm double-circular	25	2	Main trunk of femoral nerve	3	None	89.6%±9.6% of MVC	Healthy adults
Fukunaga et al., 2019 [31]	Magstim Rapid with eight booster units	110-mm double-circular	35	2	Main trunk of femoral nerve	3	None	168.0±79.8 Nm	Post-reconstruction of the anterior cruciate ligament

"Estimated" refers to the values determined from the figures in the papers.
KET, knee extensor torque; VAS, visual analogue scale; MVC, maximum voluntary contraction.

study results indicate that not only the stimulation intensity, but also the size and shape of the coil affect the larger KET induced by Stim B than that induced by Stim A. The coil size of Stim B (191 cm^2) was larger than that of Stim A (10.1 cm^2). Although the stimulation was applied at the center of the optimal point, a fairly wide area of VL could have been stimulated by Stim B because it has a larger coil. The optimal point for magnetic stimulation in this study was just above the superficial proximal sub-branch of the VL branch arising from the femoral nerve trunk [17]. The central and distal sub-branches of the VL branch may also have been stimulated by Stim B. In addition, a part of the large coil was also placed on the rectus femoris; therefore, it may have cause partial contraction of the rectus femoris.

The coil shape in Stim A was rectangular with rounded corners, while that in Stim B was round. The round coil reportedly provides deeper stimulation than the rectangular coil [18]. Various factors influence muscle contraction force, and the cross-sectional area and volume of the muscle are known predictors of KET [24]. A thicker muscle reportedly produces a stronger KET [25]. Furthermore, thick subcutaneous fat decreases rPMS-induced KET because of the increase in electrical resistance and increase in the distance from the skin to muscles and nerves [20]. The present study results suggest that the deep proximal sub-branch of the VL branch was stimulated by the rounded coil of the Stim B by penetration of the magnetic waves through the subcutaneous fat. We hypothesize that Stim B was able to induce a stronger KET than Stim A, owing to the several factors mentioned above.

The intensity of resistance exercise commonly used to strengthen the quadriceps femoris muscle in older adults is reportedly 40%–85% of the MVC when performed 1–3 times a week for 6–52 weeks [1]. The present study revealed that stimulating the VL at B70% could induce more than 30% of the MVC in the knee extensors. The cross-sectional area of the VL is approximately 36.3% of the entire quadriceps femoris and that of the rectus femoris was approximately 11.4%; therefore, the contractile force of the VL or rectus femoris alone is approximately 1/3 or 1/9 [26]. Thus, when stimulated at B70%, >40% of the MVC of the VL alone can be induced, even if both the VL and rectus femoris contract. This value corresponds to the intensity of resistance exercises generally used for muscle strengthening. However, it was assumed that less than 40% of the MVC of the VL alone was induced when stimulated with Stim A. This contraction force may not have reached the intensity of resistance exercises required for muscle strengthening. Therefore, differences in the size and shape of the coils were found to be clinically important.

In the present study, the VAS value for Stim A was less than that for Stim B, and the higher stimulation intensity of Stim B produced a stronger pain. The relationship between intensity and pain in our study was consistent with those of several previous reports, validating the results of previous studies [7,8,21,27]. The VAS score for Stim A, with a smaller area, was less than that for Stim B. A large coil area expands the area being stimulated; thus, we hypothesized that Stim B was more likely to stimulate the Aδ fibers that conduct pain sensation than Stim A [28]. Therefore, stimulations with VAS values of less than 70/100 are clinically acceptable.

In this study, we compared the contraction force of a single muscle, namely the VL, between two stimulators when induced with rPMS. However, if rPMS were to be used for the purpose of strengthening muscles in a clinical setting, it would be necessary to stimulate various muscles. Additionally, even if the contractile force of stimulated muscles increases, it is unclear whether this contributes to physical activity. In the near future, intervention studies should be conducted to confirm that rPMS can be used on several muscles of the lower extremities in older persons to strengthen the muscles and to improve motor function.

The comprehensive literature search revealed that KET was measured in only four studies. In the study in which rPMS was applied to the rectus femoris using a stimulator without booster units, a strong contractile force was not induced. In the three other studies, although it was determined that >70% of MVC can be induced by direct stimulation of the main trunk of the femoral nerve, pain assessment was not reported. Because the femoral nerve contains sensory fibers, the participants must have experienced severe pain. Additionally, the stimulator was equipped with booster units to increase the stimulation frequency. However, considering the weight of the booster units, the clinical utility would be reduced [29-31]. The mean KET in the present study exceeded that of a previous report that stimulated muscle branches when induced at B100% (66.1 Nm) and B70% (54.9 Nm). Additionally, pain assessment indicated that Stim B was suitable for clinical use.

Bustamante et al. [10,11] reported on the effect of rPMS in patients with chronic obstructive pulmonary disease. Although KET induced by rPMS to the femoral nerve with a stimulator used for TMS was as low as 10 Nm, the MVC and walking endurance increased after 8 weeks of intervention [11]. How-

ever, stimulators used for TMS generate excessive heat with prolonged use. Therefore, to conduct intervention studies confirming the effect of muscle strengthening by inducing a strong KET, it is necessary to use a stimulator that does not generate excessive heat. These dedicated stimulators are expected to strengthen the muscles and improve walking endurance in older adults, but is problematic to conclude that they are a compensatory method for resistance exercise. Future studies are needed to examine whether rPMS improves physical function, whether there is pain or fatigue after continuous application of rPMS, and whether there is an overall feeling of satisfaction with rPMS.

Another limitation of this study is that the relationship between the participant characteristics and the rPMS-induced KET was not evaluated in detail. Various variables such as body size, BMI, thigh circumference, femoral length, and gender should be considered as factors of the muscle contraction force induced by rPMS. In the future, it will be necessary to investigate how the patient characteristics affect rPMS-induced KET. Based on these findings, the effectiveness of rPMS for muscle strengthening should be verified.

CONFLICTS OF INTEREST

Our university has signed a joint research agreement with OG Wellness Technologies Co., Ltd. The funders did not have any role in the study design, collection and analysis of data, preparation of the manuscript or the decision to submit the manuscript for publication.

FUNDING INFORMATION

We have borrowed equipment and received research funds from OG Wellness Technologies Co., Ltd.

AUTHOR CONTRIBUTION

Conceptualization: Kamiue M, Tsubahara A, Ito T. Methodology: Kamiue M, Tsubahara A, Ito T. Formal analysis: Kamiue M, Tsubahara A, Ito T, Koike Y. Funding acquisition: Kamiue M, Tsubahara A, Ito T. Project administration: Kamiue M, Tsubahara A, Ito T. Visualization: Kamiue M, Tsubahara A, Ito T. Writing – original draft: Kamiue M, Tsubahara A, Ito T. Writing – review and editing: Kamiue M, Tsubahara A, Ito T. Approval of final manuscript: all authors.

ACKNOWLEDGMENTS

Our university has entered into a joint research agreement with OG Wellness Technologies Co., Ltd., from whom we have borrowed equipment and received research funds. We express our deepest gratitude to Dr. Hiroshi Ishida and Dr. Chiharu Kurozumi for their guidance and support.

ORCID

Masanori Kamiue, https://orcid.org/0009-0007-2989-2953
Akio Tsubahara, https://orcid.org/0009-0007-7159-6103
Tomotaka Ito, https://orcid.org/0000-0002-2833-3945
Yasuhiro Koike, https://orcid.org/0000-0002-2726-428X

REFERENCES

1. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev 2010;9:226-37.
2. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. Med Sci Sports Exerc 2011;43:249-58.
3. Manini TM, Hong SL, Clark BC. Aging and muscle: a neuron's perspective. Curr Opin Clin Nutr Metab Care 2013;16:21-6.
4. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889-96.
5. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr 2009;90:1579-85.
6. Krenn M, Haller M, Bijak M, Unger E, Hofer C, Kern H, et al. Safe neuromuscular electrical stimulator designed for the elderly. Artif Organs 2011;35:253-6.
7. Barker AT, Freeston IL, Jalinous R, Jarratt JA. Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. Neurosurgery 1987;20:100-9.
8. Barker AT. An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysiol 1991;8:26-37.
9. Ito T, Tsubahara A, Watanabe S. Use of electrical or magnetic stimulation for generating hip flexion torque. Am J Phys Med Rehabil 2013;92:755-61.
10. Bustamante V, Casanova J, López de Santamaría E, Mas S, Sellarés J, Gea J, et al. Redox balance following magnetic stimulation training

in the quadriceps of patients with severe COPD. Free Radic Res 2008;42:939-48.
11. Bustamante V, López de Santa María E, Gorostiza A, Jiménez U, Gáldiz JB. Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients. Respir Med 2010;104:237-45.
12. Yang SS, Jee S, Hwang SL, Sohn MK. Strengthening of quadriceps by neuromuscular magnetic stimulation in healthy subjects. PM R 2017;9:767-73.
13. Baek J, Park N, Lee B, Jee S, Yang S, Kang S. Effects of repetitive peripheral magnetic stimulation over vastus lateralis in patients after hip replacement surgery. Ann Rehabil Med 2018;42:67-75.
14. Kinoshita S, Ikeda K, Hama M, Suzuki S, Abo M. Repetitive peripheral magnetic stimulation combined with intensive physical therapy for gait disturbance after hemorrhagic stroke: an open-label case series. Int J Rehabil Res 2020;43:235-9.
15. Suzuki K, Ito T, Okada Y, Hiraoka T, Hanayama K, Tsubahara A. Preventive effects of repetitive peripheral magnetic stimulation on muscle atrophy in the paretic lower limb of acute stroke patients: a pilot study. Prog Rehabil Med 2020;5:20200008.
16. Kamiue M, Ito T, Tsubahara A, Kishimoto T. Development of high-frequency magnetic stimulator to induce stronger knee extension torque. Kawasaki J Med Welf 2022;28:29-38.
17. Tsubahara A, Kamiue M, Ito T, Kishimoto T, Kurozumi C. Measurement of maximal muscle contraction force induced by high-frequency magnetic stimulation: a preliminary study on the identification of the optimal stimulation site. Jpn J Compr Rehabil Sci 2021;12:27-31.
18. Madariaga VB, Manterola AG, Miró EL, Iturri JB. [Magnetic stimulation of the quadriceps: analysis of 2 stimulators used for diagnostic and therapeutic applications]. Arch Bronconeumol 2007;43:411-7. Spanish.
19. Tomazin K, Verges S, Decorte N, Oulerich A, Millet GY. Effects of coil characteristics for femoral nerve magnetic stimulation. Muscle Nerve 2010;41:406-9.
20. Tomazin K, Verges S, Decorte N, Oulerich A, Maffiuletti NA, Millet GY. Fat tissue alters quadriceps response to femoral nerve magnetic stimulation. Clin Neurophysiol 2011;122:842-7.
21. Amassian VE, Maccabee PJ, Cracco RQ. Focal stimulation of human peripheral nerve with the magnetic coil: a comparison with electrical stimulation. Exp Neurol 1989;103:282-9.
22. Gerdle B, Karlsson S, Crenshaw AG, Fridén J. The relationships between EMG and muscle morphology throughout sustained static knee extension at two submaximal force levels. Acta Physiol Scand 1997;160:341-51.
23. Caso G, McNurlan MA, Mileva I, Zemlyak A, Mynarcik DC, Gelato MC. Peripheral fat loss and decline in adipogenesis in older humans. Metabolism 2013;62:337-40.
24. Moreau NG, Simpson KN, Teefey SA, Damiano DL. Muscle architecture predicts maximum strength and is related to activity levels in cerebral palsy. Phys Ther 2010;90:1619-30.
25. Strasser EM, Draskovits T, Praschak M, Quittan M, Graf A. Association between ultrasound measurements of muscle thickness, pennation angle, echogenicity and skeletal muscle strength in the elderly. Age (Dordr) 2013;35:2377-88. Erratum in: Age (Dordr) 2013;35:2025-6.
26. Toumi H, Best TM, Mazor M, Coursier R, Pinti A, Lespessailles E. Association between individual quadriceps muscle volume/enthesis and patello femoral joint cartilage morphology. Arthritis Res Ther 2014;16:R1.
27. Han TR, Shin HI, Kim IS. Magnetic stimulation of the quadriceps femoris muscle: comparison of pain with electrical stimulation. Am J Phys Med Rehabil 2006;85:593-9.
28. Oh KJ, Kim SH, Lee YH, Kim JH, Jung HS, Park TJ, et al. Pain-related evoked potential in healthy adults. Ann Rehabil Med 2015;39:108-15.
29. Kremenic IJ, Ben-Avi SS, Leonhardt D, McHugh MP. Transcutaneous magnetic stimulation of the quadriceps via the femoral nerve. Muscle Nerve 2004;30:379-81.
30. Kremenic IJ, Glace BW, Ben-Avi SS, Nicholas SJ, McHugh MP. Central fatigue after cycling evaluated using peripheral magnetic stimulation. Med Sci Sports Exerc 2009;41:1461-6.
31. Fukunaga T, Johnson CD, Nicholas SJ, McHugh MP. Muscle hypotrophy, not inhibition, is responsible for quadriceps weakness during rehabilitation after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 2019;27:573-9.

Original Article

Ann Rehabil Med 2024;48(3):211-219
eISSN: 2234-0653
https://doi.org/10.5535/arm.240010

Annals of Rehabilitation Medicine

Changes in Health-Related Quality of Life by Patient Education and Rehabilitation Based on a Behavior Change Program in Knee Osteoarthritis

Takako Nagai, MD, PhD[1,2], Hiroshi Uei, MD, PhD[3], Kazuyoshi Nakanishi, MD, PhD[3]

[1]*Department of Rehabilitation Medicine, Nihon University Hospital, Tokyo, Japan*
[2]*Department of Rehabilitation Medicine, Tokyo Women's Medical University, Tokyo, Japan*
[3]*Department of Orthopedic Surgery, Nihon University School of Medicine, Tokyo, Japan*

Objective: The purpose of this study was to examine how rehabilitation and patient education for knee osteoarthritis improves health-related quality of life (HRQOL) and to identify factors influencing HRQOL.

Methods: Between May 2020 and March 2022, 30 patients with osteoarthritis of the knee were treated conservatively and rehabilitated with a patient education program. The patient education program was based on the health belief model by Sedlak et al., and patient education using pamphlets was provided during the rehabilitation intervention. The survey items were patient basic information, instrumental activities of daily living (ADL) (FAI), fear of falling (FES), degree of depression (GDS), HRQOL (SF-8), knee function assessment (JOA score), and X-ray classification (K-L classification), and the survey method was a self-administered questionnaire at the start of rehabilitation, 1 month after the intervention, and at the end of the rehabilitation intervention. We examined factors affecting the physical component summary (PCS) and mental component summary (MCS) of HRQOL scores.

Results: JOA score, FES, FAI, GDS, and SF-8 improved significantly ($p<0.01$). MCS was also negatively correlated with FES and age ($r=-0.486$, -0.368). Sex was extracted as a factor for PCS as a factor affecting HRQOL ($p<0.01$). MCS was extracted with FES as a factor ($p=0.046$).

Conclusion: A rehabilitation intervention incorporating patient education in osteoarthritis of the knee showed improvement in HRQOL and may be useful for improving depression, fear of falling, and instrumental ADL.

Keywords: Knee osteoarthritis, Patient education, Rehabilitation, Health-related quality of life

Received: January 23, 2024
Revised: April 10, 2024
Accepted: May 14, 2024

Correspondence:
Takako Nagai
Department of Rehabilitation Medicine, Tokyo Women's Medical University, 8-1 Kawadacho, Shinjuku, Tokyo 162-0054, Japan.
Tel: +81-3-3353-8111
Fax: +81-3-5269-7639
E-mail: ntnyf092@yahoo.co.jp

INTRODUCTION

Knee osteoarthritis is one of the representative motor disorders in the elderly [1]. The number of patients with knee osteoarthritis in Japan is estimated to be 25.3 million, and the need for medical intervention as a common disease is inevitably increasing [2]. It can also be a risk of locomotive syndrome, which limits daily activities and increases the risk of nursing care [3]. There is also a risk that pain from knee osteoarthritis reduces exercise opportunities, leading to decreased activity and quality

© 2024 by Korean Academy of Rehabilitation Medicine

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

of life. Park et al. [4] suggest that knee osteoarthritis is significantly associated with decreased mental health and health-related quality of life (HRQOL). We verified and informed the time-dependent change of HRQOL by the rehabilitation intervention on 62 cases of old osteoarthritis patients treated conservatively [5]. As a result, knee function, fear of falling, and instrumental activities of daily living (ADL) was significantly improved from the start of rehabilitation to 3 months after the intervention. However, there was no improvement in depression and HRQOL scores, physical component score and mental component score. It is necessary to establish treatment measures based on psychological factors such as depression caused by chronic pain in knee osteoarthritis. Meeus et al. [6] reported on the effects of patient education, which improved psychological factors related to pain. Snyder and Engström [7] reported on the effectiveness of oral and pamphlet teaching as a method of patient education and described its effectiveness.

Therefore, for patients with knee osteoarthritis, the introduction of patient education aimed at improving chronic pain and psychological factors as part of rehabilitation may be effective for the reduction of pain and psychological factors such as depression and anxiety, and may prevent the decrease of activity and the decrease of HRQOL. However, there have been no reports that have examined the effects and trends of rehabilitation incorporating patient education for knee osteoarthritis on psychological factors such as pain, depression, and fear of falling, as well as HRQOL. Furthermore, there have been no reports examining the time course of HRQOL in patients with knee osteoarthritis using patient education and rehabilitation intervention based on behavior change.

The purpose of this study was to examine the effect of combined patient education and conservative rehabilitation on pain, psychological factors, and change of HRQOL in patients with knee osteoarthritis.

METHODS

Subjects

The object patients were 30 patients over 65 years old who were diagnosed as osteoarthritis of the knee and underwent conservative treatment and rehabilitation from May 2020 to March 2022. Conservative treatment refers to the use of external preparations, oral medications, braces, or intra-articular injections according to symptoms. Surgical treatments were excluded. Patients were also included if they had other motor disorders and were diagnosed with knee pain and osteoarthritis on radiography.

This study was a pilot study with 30 subjects. We prospectively investigated the change over time in patient education effect in the osteoarthritis conservative treatment example.

In consideration of ethical issues, after sufficient informed consent to participate in the study, the subject's voluntary consent form was obtained. This study was approved by the Institutional Review Board of the Nihon University Hospital (IRB No. 20200403), and informed consent was obtained from each patient.

Methods

Method of patient education

The behavior change program using the pamphlet as educational tool was carried out.

The contents of patient guidance included questionnaires, individual guidance using educational tools, and goal setting. Present a questionnaire to help you discover what you want to ask. In addition, information on items related to health status and HRQOL was extracted. In the individual guidance using the education tool, the pamphlet which described the gist of the content in the patient education was used. The pamphlet in which the description on the gonarthrosis which Japanese Orthopaedic Association (JOA) announced was described was used for the method of the patient education [8]. The pamphlets describe the causes of knee osteoarthritis, the characteristics of the symptoms, the classification of the degree of progression on X-ray, and the treatment. The symptoms described include pain in the knees and difficulty walking up and down stairs, difficulty squatting or sitting upright, and stiff knees when standing up. Causes and characteristics: The causes of knee osteoarthritis can be either primary, for which the cause cannot be clearly determined, or secondary, for which an injury or disease around the knee joint affects.

Previous injuries, such as meniscus and ligament injuries, sprains and fractures, and diseases such as rheumatoid arthritis and pseudogout are classified as secondary, but most cases are primary knee osteoarthritis for which the cause cannot be determined. It is explained that the grade in the X-ray is classified from 1 to 4 according to the size of the gap of the joint. For treatment, conservative treatment such as injection and internal use, rehabilitation, and operative treatment are explained.

On the basis of this pamphlet, the knowledge on purpose, on the disease state, the guidance was carried out on prevention

method, range of motion training and muscle strengthening practice, walking practice, activity of daily living practice and home exercise program according to the individual condition. The home program included a stepwise walking program, range of motion training for bathing, and locomo training was performed at home three times a day. Locomo training consists of standing on each leg for 1 minute and squatting 5 to 6 times [9]. Patient education was provided at the start of rehabilitation, 1 month after the start of rehabilitation, and at the end of rehabilitation intervention.

Practice of behavior change programs

The behavior change program was based on the health belief model by Sedlak et al. [10]. It consists of the following; I. motivate, II. persuade verbally, and III. elicit physiologically and emotionally.

I. Motivate

The risk caused by osteoarthritis of the knee is explained. The risks of pain, restricted walking, and decreased ability to live were discussed in the pamphlet published by the JOA.

II. Persuade verbally

Goal level decisions were verbal persuasion based on achievement. Exercise therapy consisted of one-to-one gait correction, muscular strength and endurance training, and range of motion training, depending on the individual's level.

III. Elicit physiologically and emotionally

Attention should be paid to improvements in knee function and pain as a result of exercise therapy.

As a method to confirm whether the patient understood the contents of the instruction, the degree of understanding was confirmed by interviewing the patient to confirm whether the patient understood the contents of the instruction and having the patient explain it verbally at the time of patient follow-up. The period of instruction was 5 months.

Rehabilitation methods

The physical therapist intervened in the rehabilitation. The rehabilitation menu included range-of-motion exercises, muscle strengthening exercises mainly for the quadriceps femoris, gait training, and balance training [11]. For patients with knee pain, we administered drugs and intra - articular injection of hyaluronic acid to control pain and implemented an education program. The frequency of rehabilitation was once every 2 weeks for 40 minutes. For patients with knee pain, we administered drugs and intra-articular injection of hyaluronic acid to control pain and implemented an education program. The rehabilitation period was 5 months.

Evaluation of measurement index

Evaluations were performed at three time points: before exercise therapy intervention, 1 month into intervention, at the end of the intervention. The items investigated were as follows: (1) knee osteoarthritis severity, (2) knee osteoarthritis staging, (3) fear of falling, (4) instrumental ADL, (5) degree of depression, and (6) HRQOL. Fear of falling, instrumental ADL, degree of depression, and HRQOL were determined using a self-administered questionnaire directly to subjects, which they returned completed following their medical examination.

The degree of progression of knee osteoarthritis was classified using the Kellgren-Lawrence (K-L) grading system [12]. The K-L system consists of five grades from 0–4: 0 is no osteoarthritis; 1 is doubtful narrowing of the joint space and/or possible osteophytes; 2 is definite osteophytes and possible narrowing of the joint space; 3 is multiple osteophytes, definite narrowing of the joint space, and some sclerosis and deformity of the bone ends; and 4 is large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of bone ends. Also, knee osteoarthritis severity, Fear of falling, Instrumental ADL, Degree of depression, and HRQOL were assessed at the beginning and end of rehabilitation.

(1) Knee osteoarthritis severity

Knee osteoarthritis severity was measured using the patient's JOA score [13]. It is a measure to evaluate the degree of functional impairment. Rate pain, walking ability, stair climbing, flexion angle, and swelling on a scale of 1 to 100. The higher the score, the higher the knee joint function.

(2) Fear of falling

Fear of falling was evaluated using the Fall Efficacy Scale (FES) was advocated for Tinetti et al. [14]. The FES is a tool that measures the degree of confidence of a person to perform 10 different ADL without falling on a four-point scale. Scores are expressed from 10 to 40 points, and a lower score indicates less fear of falling.

(3) Instrumental ADL

Instrumental ADL was evaluated using the Frenchay Activities Index (FAI) developed by Holbrook and Skilbeck [15]. It was evaluated 15 applied ADL and social life items on a four-point

scale from 0–3 points. The maximum score is 45 points, and a higher score indicates greater instrumental ADL ability and independent applied ADL.

(4) Degree of depression

Degree of depression was evaluated using the Geriatric Depression Scale (GDS). The GDS was developed to measure depression, and a higher score means a higher degree of depression [16-18].

(5) HRQOL

The evaluation of HRQOL used Short Form-8 (SF-8) which was short version of Short-Form Health Survey (SF-36) [19]. SF-8 can be evaluated efficiently with a minimum number of items, and consists of the following eight items (subscales): general health (GH), physical functioning (PF), role physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). A higher score indicates higher QOL. Physical component summary (PCS) and mental component summary (MCS) scores are also calculated using regression equations based on the weighting of each item. Use of the SF-8 in this study was registered with the Institute for Health Outcomes & Process Evaluation Research to obtain a license. For fear of falling, instrumental ADL, depression, and HRQOL, questionnaires were given to the patients at the beginning and one month after the rehabilitation intervention and at the end of the intervention, and the questionnaires were collected after the patients answered the questionnaire contents. Correlations and associations were statistically verified for each score.

Statistical analysis

The controlled analysis included outcomes of PCS and MCS, HRQOL scores, and tested for influencing factors. For the validation method, the dependent variables were PCS and MCS, and the independent variables were age, sex, FES, FAI, and GDS, with a significance probability of 0.05%. In addition, factors correlated with PCS and MCS scores were verified by correlation coefficients. The statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp.). Normally distributed variables were expressed as the mean±standard deviation and variables with a skewed distribution as the median and interquartile range. The chi-square test, unpaired t-test, Mann–Whitney U-test, χ^2 test, and the Fisher exact test were used, as appropriate, to compare variables between the groups.

RESULTS

The baseline characteristics of the subjects are presented in Table 1.

Changes in JOA score are shown in Fig. 1. The JOA score was significantly improved 1 month after the patient education intervention compared to before the intervention ($p<0.01$). There was no significant difference in the presence or absence of painkillers or intra-articular injections in each period. Results of PCS and MCS scores for SF-8 items are shown (Fig. 2). MCS score ranged from 47.9 before the intervention to 48.6 at the end

Table 1. Clinical characteristics of the participants

Characteristic	Value (n=30)
Age (yr)	73.0±6.6
Sex, female	23 (76.7)
BMI (kg/m^2)	22.9±3.9
K-L classification	
1	13 (43.3)
2	12 (40.0)
3	3 (10.0)
4	2 (6.7)
CCI	
0	10 (33.3)
1	12 (40.0)
2	8 (26.7)
≥3	0 (0)
Follow up period (day)	90.4±43.7

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; K-L, Kellgren-Lawrence; CCI, Charlson Comorbidity Index.

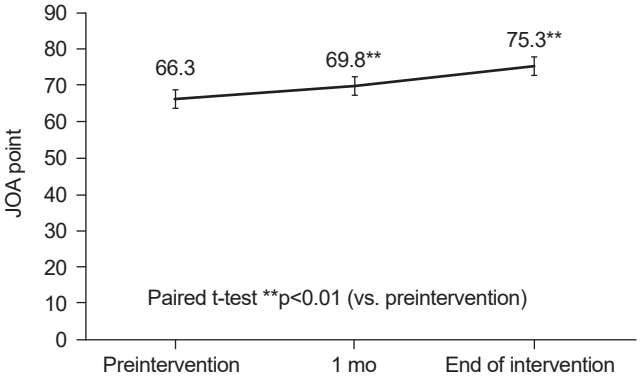

Fig. 1. Change in average Japanese Orthopaedic Association (JOA) score. JOA scores at 1 month after the intervention and at the end of the intervention were significantly improved from those at the beginning of the intervention (**p<0.01). Knee joint function was significantly improved.

of the intervention. The PCS score ranged from 40.8 before the intervention to 48.4 at the end of the intervention. PCS score was significantly improved 1 month after the patient education intervention compared to the start (p<0.01). There were no significant differences in MCS scores between the time periods.

Changes in FES and FAI are shown in Figs. 3, 4. At the end of the patient education intervention, it was significantly lower than at the start (p<0.01). GDS score is shown in Fig. 5. GDS score was significantly improved 1 month after the patient education intervention compared to the start (p<0.01). Table 2 shows the correlation between PCS score, MCS score, and measurement items at each time period. PCS score was negatively correlated with FES before and 1 month after the patient education intervention (p<0.01, p<0.05). MCS score was negatively correlated with Age and FES (p<0.05, p<0.01).

Results of multiple regression analysis with PCS and MCS scores at final follow-up as dependent variables and age, sex, FES, FAI and GDS as independent variables are shown in Table 3. Sex was extracted as an influencing factor for PCS scores (p<0.01). FES was also extracted as an influencing factor of MCS score (p=0.046).

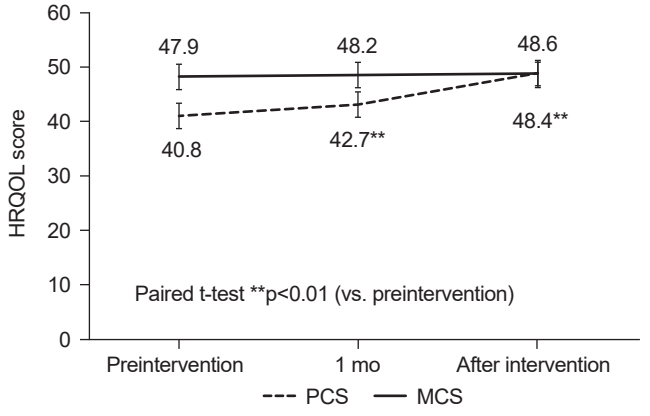

Fig. 2. Change in average health-related quality of life (HRQOL) score. The physical component summary improved significantly with rehabilitation and patient education (**p<0.01), but the mental component summary showed no apparent improvement. PCS, physical component summary; MCS, mental component summary.

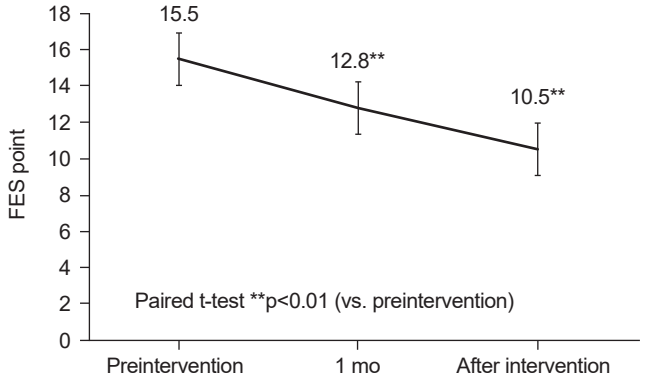

Fig. 3. Change in average Fall Efficacy Scale (FES). The FES was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).

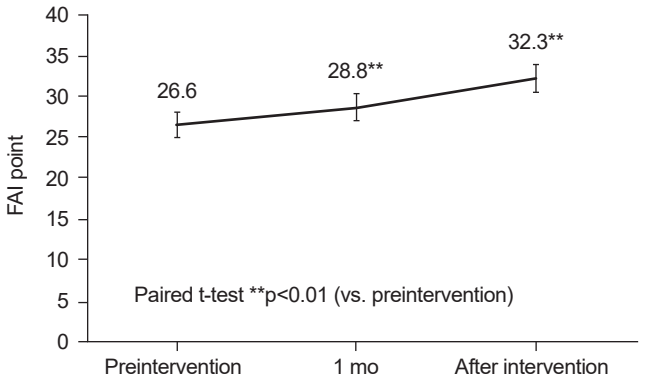

Fig. 4. Change in average Frenchay Activities Index (FAI). The FAI was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).

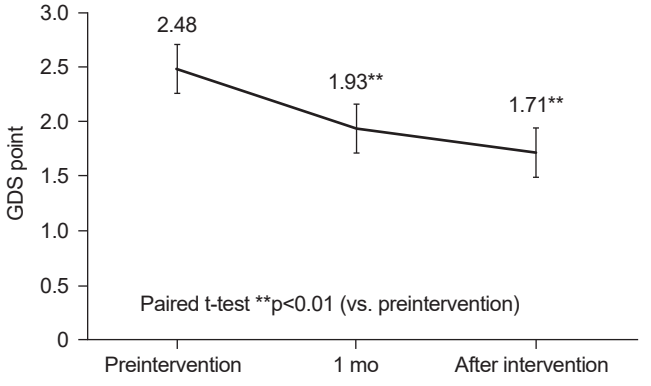

Fig. 5. Change in average Geriatric Depression Scale (GDS). The GDS was significantly improved 1 month after the intervention by the intervention of rehabilitation and patient education (**p<0.01).

Table 2. Health-related quality of life scale correlations

	Age	JOA	K-L	GDS	FAI	FES
PCS						
Preintervention	-0.140	-0.274	-0.077	-0.266	0.008	-0.472**
1 mo	-0.215	-0.147	0.047	-0.236	-0.053	-0.431*
End of intervention	-0.028	-0.148	0.234	-0.108	-0.242	-0.192
MCS						
Preintervention	-0.397*	-0.186	-0.132	-0.264	0.279	-0.469**
1 mo	-0.366*	-0.212	-0.083	-0.296	0.347	-0.474**
End of intervention	-0.368*	-0.179	-0.049	-0.273	0.314	-0.486**

JOA, Japanese Orthopaedic Association; K-L, Kellgren-Lawrence grading system; GDS, Geriatric Depression Scale; FAI, Frenchay Activities Index; FES, Fall Efficacy Scale; PCS, physical component summary; MCS: mental component summary.
Spearman rank correlation coefficient, *p<0.05 and **p<0.01.

Table 3. Multiple linear regression analysis of the time from PCS and MCS

Variable	Unstandardized		Standardized β	p-value	95% CI	
	B	SE			Lower	Upper
PCS						
Age	0.122	0.149	0.170	0.422	-0.187	0.431
Sex	-5.761	2.003	-0.531	0.009	-9.915	-1.608
FES	-0.882	0.873	-0.184	0.323	-2.692	0.928
FAI	-0.200	0.139	-0.259	0.165	-0.489	0.089
GDS	-0.182	0.345	-0.104	0.602	-0.897	0.532
MCS						
Age	-0.156	0.188	-0.175	0.418	-0.546	0.235
Sex	-2.226	2.529	-0.166	0.388	-7.471	3.019
FES	-2.303	1.095	-0.389	0.046	-4.563	-0.043
FAI	0.168	0.172	0.176	0.340	-0.188	0.524
GDS	-0.287	0.401	-0.132	0.482	-1.114	0.541

SE, standard error; 95% CI, 95% confidence interval; PCS, physical component summary; MCS: mental component summary; FES, Fall Efficacy Scale; FAI, Frenchay Activities Index; GDS, Geriatric Depression Scale.

DISCUSSION

A prospective cohort study of patient education interventions for osteoarthritis of the knee shows two major finds. First, the patient education intervention improved PCS score but not MCS score. Second, age was found to be an influencing factor for PCS score, and fair of falling was found to be an influencing factor for MCS score.

Muraki et al. [20] describes HRQOL in knee osteoarthritis, revealed that in severe cases, the PCS score decreases and correlated with pain. The PCS score also correlated with pain and grip strength. On the other hand, the MCS is not related to the severity of knee osteoarthritis, and a variety of factors were involved. In our previous studies have examined changes in HRQOL when knee osteoarthritis is treated with rehabilitation without patient education. As a result, JOA scores, fear of falling, and instrumental ADL improved significantly from the start of rehabilitation to three months after the intervention. However, depression and mental and PCS score did not significantly improve. In the current study with patient education, depression and PCS score were significantly better than before patient education, indicating that patient education may be effective for depression and physical HRQOL. To improve MCS, it is necessary to review the contents of the current education program and verify the education program for cases with severe psychosomatic elements.

The association between MCS and PCS scores tended to correlate with fear of falling, indicating that taking a fall prevention approach may improve HRQOL.

Second, age was found to be an influencing factor for PCS score, and fear of falling was extracted as a factor influencing MCS score at the end of patient education. FES showed a negative correlation with MCS score. The results suggest that fear of falling affects MCS more than PCS score. Therefore, educa-

tional guidance and functional training to reduce fear of falling were considered necessary to improve MCS score.

For fear of falling and HRQOL, Stanghelle et al. [21] examined whether balance training in vertebral fractures affects fear of falling and HRQOL. Balance training reduced the fear of falling and showed improvements in muscle strength and balance ability. However, they noted that balance training did not improve HRQOL. We have verified and reported the transition of HRQOL in osteoarthritis of the knee by rehabilitation intervention [5]. As with the results of Stanghelle et al. [21] there was no improvement in HRQOL with the exercise intervention, but there was a significant improvement in fear of falling.

In this study, we investigated the effects of a rehabilitation intervention incorporating patient education on HRQOL, psychological factors and motor function in patients with knee osteoarthritis. As a result, improvements in PCS score were observed in osteoarthritis of the knee by the patient education program. The patient program we implemented introduced the behavior change program proposed by Sedlak et al. [10]. As to reasons for the lack of improvement in MCS score, it is possible that the behavior change program proposed by Sedlak et al. [10] consisted of I. motivate, II. persuade verbally, and III. elicit physiologically and emotionally, which had an improving effect on the physical approach but not enough intervention on the psychological approach. It is necessary to strengthen the approach to mental health, role emotional and social functioning which are the items of MCS score.

Fear of falling was also identified as an influencing factor of HRQOL in the multivariate analysis. The reason for this was thought to be that when the fear of falling is high, the mental health may be affected by the decreased opportunity to go out and the decreased social function caused by the fear of falling. It is possible that rehabilitation approaches that reduce the fear of falling, such as strengthening gait stability, trunk balance, and lower limb muscle strength, may be effective in improving HRQOL. Regarding the relationship between fear of falling and HRQOL, Stanghelle et al. [21] examined the effects of a resistance and balance exercise program on physical fitness, HRQOL and fear of falling in osteoporotic vertebral compression fractures. The results showed that there was no significant improvement in HRQOL, although there were two weeks of a supervised multicomponent resistance and balance exercise program improved muscle strength and balance and reduced fear of falling. Our validation with the exercise therapy intervention also showed no improvement in HRQOL. Exercise therapy interventions for motor disorders, which are common among the elderly, did not improve HRQOL, and an approach to life anxiety associated with old age, such as senile depression and fear of falling, is necessary to improve HRQOL. Taglietti et al. [22] also reported on the association between knee osteoarthritis and fearing of falling, stating that sensory instability is related to fearing of falling in knee osteoarthritis. In order to improve the fearing of falling in knee osteoarthritis, it is necessary to enhance trunk stability. Simsek et al. [23] also reported that fear of falling is higher among older females over 80, especially if they live alone. In order to reduce the fear of falling in the elderly, not only an exercise therapy approach, but also the enhancement of social support and support for the elderly living alone would lead to a decrease in the fear of falling and further improve HRQOL.

In our study, we introduced risk guidance for knee pain and an approach to anxiety, self-directed training guidance, and a patient education program for osteoarthritis of the knee, and examined the effects of improving HRQOL. They found improvement in PCS score, but not in MCS score. No research has examined the transition of HRQOL due to the introduction of a patient education program in patients with knee osteoarthritis, and it is necessary to improve and verify the education program considering the MCS score items of mental health, role emotional and social functioning. In addition, considering the social background, it is expected that in elderly people living alone, not only the approach of an exercise therapy but also the support for the enhancement of social support will reduce the fair of falling and lead to the improvement of HRQOL.

Furthermore, multivariate analysis extracted sex as an influential factor in PCS score. This may be because osteoarthritis of the knee is reported to be more likely to be severe in postmenopausal females [24], and as a result, sex may have been extracted as an influential factor in PCS score.

One of the limitations of this study is that, first, because of the exploratory study, we were able to verify changes and transitions over time in the same subjects through the intervention of the patient education program, but the validation of the effectiveness of the validation patient education program was insufficient. Since this study is a single arm design study, it is considered to be a limitation that it cannot be compared with a control group. It is considered that the verification g compared with the control group is necessary in future. Second, there was insufficient verification of the relationship between the patients' backgrounds, such as the presence or absence of mental illness,

the presence or absence of a history of psychiatric visits, and the use of psychotropic drugs. It is necessary to examine the influence of psychiatric disorders on knee osteoarthritis in the future.

As a result of patient education that included motivate, persuade verbally, elicit physiologically and emotionally as a behavior change program, PCS score of HRQOL items improved, but MCS score did not. In the following, it is necessary to verify patient education programs focusing on mental health, role emotional and social functioning as a treatment approach to improve HRQOL of knee osteoarthritis. The results also indicate that an educational approach to fear of falling may improve anxiety and that functional training may be effective in improving HRQOL in knee osteoarthritis.

CONFLICTS OF INTEREST

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

FUNDING INFORMATION

None.

AUTHOR CONTRIBUTION

Conceptualization: Nagai T. Methodology: Nagai T, Uei H. Formal analysis: Nagai T, Uei H. Project administration: Nagai T, Nakanishi K. Visualization: Nagai T, Uei H. Writing – original draft: Nagai T, Uei H. Writing – review and editing: Nagai T, Nakanishi K. Approval of final manuscript: all authors.

ACKNOWLEDGMENTS

The authors sincerely thank their study subjects and also gratefully acknowledge the Nihon University Hospital. I would also like to thank H.Wakabayashi for his advice. Finally, we are grateful to the referees for useful comments.

ORCID

Takako Nagai, https://orcid.org/0000-0001-6048-7058
Hiroshi Uei, https://orcid.org/0000-0001-9631-4861
Kazuyoshi Nakanishi, https://orcid.org/0000-0001-7497-8667

REFERENCES

1. Curry ZA, Beling A, Borg-Stein J. Knee osteoarthritis in midlife women: unique considerations and comprehensive management. Menopause 2022;29:748-55.
2. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 2009;27:620-8.
3. Yoshimura N, Muraki S, Nakamura K, Tanaka S. Epidemiology of the locomotive syndrome: the research on osteoarthritis/osteoporosis against disability study 2005-2015. Mod Rheumatol 2017;27:1-7.
4. Park HM, Kim HS, Lee YJ. Knee osteoarthritis and its association with mental health and health-related quality of life: a nationwide cross-sectional study. Geriatr Gerontol Int 2020;20:379-83.
5. Nagai T, Tsurusaki M, Horaguchi T, Uei H, Nagaoka M. Verification of phycological factors related to health-related quality of life in elderly knee osteoarthritis: a prospective cohort study. J Orthop Sci 2020;25:868-73.
6. Meeus M, Nijs J, Hamers V, Ickmans K, Oosterwijck JV. The efficacy of patient education in whiplash associated disorders: a systematic review. Pain Physician 2012;15:351-61.
7. Snyder H, Engström J. The antecedents, forms and consequences of patient involvement: a narrative review of the literature. Int J Nurs Stud 2016;53:351-78.
8. The Japanese Orthopaedic Association. Exercise therapy for knee osteoarthritis [Internet]. The Japanese Orthopaedic Association; 2003 [cited 2020 May]. Available from: https://www.joa.or.jp/public/publication/pdf/knee_osteoarthritis.pdf.
9. Hashimoto M, Yasumura S, Nakano K, Kimura M, Nakamura K, Fujino K, et al. [Feasibility study of locomotion training in a home-visit preventive care program]. Nihon Ronen Igakkai Zasshi 2012;49:476-82. Japanese.
10. Sedlak CA, Doheny MO, Jones SL. Osteoporosis education programs: changing knowledge and behaviors. Public Health Nurs 2000;17:398-402.
11. Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, et al. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J 2019;25:127-33.
12. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
13. Koshino T. [Japanese Orthopaedic Association knee scoring system]. J Jpn Orthop Assoc 1988;62:900-2. Japanese.
14. Tinetti ME, Richman D, Powell L. Falls efficacy as a measure of fear

of falling. J Gerontol 1990;45:239-43.
15. Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing 1983;12:166-70.
16. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983;17:37-49.
17. Asokan GV, Awadhalla M, Albalushi A, Al-Tamji S, Juma Z, Alasfoor M, et al. The magnitude and correlates of geriatric depression using Geriatric Depression Scale (GDS-15) - a Bahrain perspective for the WHO 2017 campaign 'Depression - let's talk'. Perspect Public Health 2019;139:79-87.
18. Dias FLDC, Teixeira AL, Guimarães HC, Barbosa MT, Resende EPF, Beato RG, et al. Accuracy of the 15-item Geriatric Depression Scale (GDS-15) in a community-dwelling oldest-old sample: the Pietà Study. Trends Psychiatry Psychother 2017;39:276-9.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
20. Muraki S, Akune T, Nagata K, Ishimoto Y, Yoshida M, Tokimura F, et al. Does osteophytosis at the knee predict health-related quality of life decline? A 3-year follow-up of the ROAD study. Clin Rheumatol 2015;34:1589-97.
21. Stanghelle B, Bentzen H, Giangregorio L, Pripp AH, Skelton DA, Bergland A. Effects of a resistance and balance exercise programme on physical fitness, health-related quality of life and fear of falling in older women with osteoporosis and vertebral fracture: a randomized controlled trial. Osteoporos Int 2020;31:1069-78. Erratum in: Osteoporos Int 2020;31:1187.
22. Taglietti M, Dela Bela LF, Dias JM, Pelegrinelli ARM, Nogueira JF, Batista Júnior JP, et al. Postural sway, balance confidence, and fear of falling in women with knee osteoarthritis in comparison to matched controls. PM R 2017;9:774-80.
23. Simsek H, Erkoyun E, Akoz A, Ergor A, Ucku R. Falls, fear of falling and related factors in community-dwelling individuals aged 80 and over in Turkey. Australas J Ageing 2020;39:e16-23.
24. Sayre EC, Guermazi A, Nicolaou S, Esdaile JM, Kopec JA, Singer J, et al. A whole-joint, unidimensional, irreversible, and fine-grained MRI knee osteoarthritis severity score, based on cartilage, osteophytes and meniscus (OA-COM). PLoS One 2021;16:e0258451.

Original Article

Ann Rehabil Med 2024;48(3):220-227
eISSN: 2234-0653
https://doi.org/10.5535/arm.230011

arm
Annals of Rehabilitation Medicine

Predictors for Failed Removal of Nasogastric Tube in Patients With Brain Insult

Shih-Ting Huang, MD[1], Tyng-Guey Wang, MD[2], Mei-Chih Peng, NP[1], Wan-Ming Chen, PhD[3], An-Tzu Jao, MS[3], Fuk Tan Tang, MD[1], Yu-Ting Hsieh, MD[1], Chun Sheng Ho, MD, PhD[1], Shu-Ming Yeh, MD[1]

[1]*Department of Physical Medicine and Rehabilitation, Lotung Poh-Ai Hospital, Lo-Hsu Foundation, Yilan County, Taiwan (R.O.C.)*
[2]*Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, School of Medicine, National Taiwan University, Taipei City, Taiwan (R.O.C.)*
[3]*Big Data Center, Lotung Poh-Ai Hospital, Lo-Hsu Foundation, Yilan County, Taiwan (R.O.C.)*

Objective: To construct a prognostic model for unsuccessful removal of nasogastric tube (NGT) was the aim of our study.
Methods: This study examined patients with swallowing disorders receiving NGT feeding due to stroke or traumatic brain injury in a regional hospital. Clinical data was collected, such as age, sex, body mass index (BMI), level of activities of daily living (ADLs) dependence. Additionally, gather information regarding the enhancement in Functional Oral Intake Scale (FOIS) levels and the increase in food types according to the International Dysphagia Diet Standardization Initiative (IDDSI) after one month of swallowing training. A stepwise logistic regression analysis model was employed to predict NGT removal failure using these parameters.
Results: Out of 203 patients, 53 patients (26.1%) had experienced a failed removal of NGT after six months of follow-up. The strongest predictors for failed removal were age over 60 years, underweight BMI, total dependence in ADLs, and ischemic stroke. The admission prediction model categorized patients into high, moderate, and low-risk groups for removal failure. The failure rate of NGT removal was high not only in the high-risk group but also in the moderate-risk groups when there was no improvement in FOIS levels and IDDSI food types.
Conclusion: Our predictive model categorizes patients with brain insults into risk groups for swallowing disorders, enabling advanced interventions such as percutaneous endoscopic gastrostomy for high-risk patients struggling with NGT removal, while follow-up assessments using FOIS and IDDSI aid in guiding rehabilitation decisions for those at moderate risk.

Keywords: Deglutition disorders, Gastrointestinal intubation, Stroke, Traumatic brain injury

Received: November 1, 2023
Revised: March 25, 2024
Accepted: May 2, 2024

Correspondence:
Shu-Ming Yeh
Department of Physical Medicine and Rehabilitation, Lotung Poh-Ai Hospital, Lo-Hsu Foundation, 8F., No. 186, Xingfu 2nd Rd., Dongshan Township, Yilan County 269, Taiwan (R.O.C.).
Tel: +886-3954-3131#6390
Fax: +886 3-9543151
E-mail: zomur680314@gmail.com

INTRODUCTION

Dysphagia is a common complication following stroke and traumatic brain injury (TBI), with reported incidence rates ranging from 27% to 80% [1,2]. Patients with these conditions often require nasogastric tube (NGT) feeding to maintain nutritional supply in acute stage and are frequently encountered in rehabilitation settings. Dysphagia can lead to malnutrition, aspiration pneumonia, prolong hospitalization, and increase the risk of morbidity and mortality [3,4]. NGT feeding may suffice for patients requiring nutritional support for up to 4 weeks [5]. Extended utilization of an NGT can lead to various adverse events,

© 2024 by Korean Academy of Rehabilitation Medicine

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

such as nasal wing lesions, chronic sinusitis, gastroesophageal reflux, gastrointestinal bleeding, and aspiration pneumonia [6-8]. Therefore, for extended periods, the placement of a gastrostomy tube should be taken into consideration to avoid the side effects of long-term usage of NGT for nutrition supply [5].

Bedside swallowing assessments can quickly detect dysphagia, but predicting its recovery is challenging. Early identification of dysphagia recovery prognosis would enable prompt administration of appropriate therapies and consideration of suitable feeding methods such as NGT or gastrostomy tube. Preexisting studies have found that patients with high National Institutes of Health Stroke Scale (NIHSS) scores, aspiration during swallowing assessments, advanced age, dysarthria, and intubation are at a higher risk of experiencing prolonged dysphagia lasting for more than 6 weeks [9-11]. However, no work has mentioned the exact percentage of failure of complete oral feeding through the above mentioned parameters. As a result, our work attempts to develop a model capable of predicting the unsuccessful removal of NGT in dysphagia patients who have experienced a stroke or TBI. Additionally, the model may provide the information for the early intervention of gastrostomy tube.

METHODS

From January 2020 to December 2022, we retrospectively analyzed clinical data of patients admitted to the rehabilitation department in a regional hospital, who experienced stroke or TBI with dysphagia and requiring NGT feeding. A total of 203 patients, comprising 133 males and 70 females, were enrolled in the study, and their NGT removal failure rates were tracked over a six-month period. Baseline demographic characteristic of age, sex, admission diagnosis (ischemic stroke, hemorrhagic stroke, or TBI), initial Glasgow Coma Scale (GCS), body mass index (BMI), Functional Independence Measure (FIM) score, level of activities of daily living (ADLs) dependence were recorded. We define a patient as ADLs total dependent when they are completely unable to perform four aspects: personal hygiene, heavy hygiene (toilet and bathing), eating, and dressing. If the criteria mentioned above are not met, the patient is referred to as ADLs partial dependent. Clinical variables were correlated after one month of swallowing training, including the improvement in Functional Oral Intake Scale (FOIS) levels and variation in the numbers of food type according to International Dysphagia Diet Standardization Initiative (IDDSI). The swallowing training consists of direct method such as modifying food texture, utilizing chin tuck and head turn/tilt compensatory techniques, and indirect method such as applying thermal tactile stimulation, practicing pharyngeal wall contraction exercises (Masako maneuver) and practicing effortful swallowing, according to the evaluation of swallowing condition of the patients. We utilized both videofluoroscopic swallowing study, fiberoptic endoscopic evaluation of swallowing, or bedside clinical swallow assessment by physicians to evaluate patients' swallowing function. Simultaneously, we integrate the assessment conducted by the speech-language therapist to determine the optimal timing for NGT removal.

This study received approval from the Research Ethics Committee of Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approval number: IRB112-206-B). Due to its retrospective nature, the requirement for informed consent was waived.

SAS Software version 9.4 (SAS Institute) was used for statistical analysis. Exclude patients with missing data and conduct individual subgroup analyses on the available data, resulting in variations in the total number of patients for different variables. The categorical variables were demonstrated as counts and percentages. The continuous variables were presented. Comparisons of these clinical data between each group were made by using the chi-square test for categorical variables and the two sample t-test for continuous variables. A stepwise logistic regression analysis was used to develop a model for predicting failure of NGT removal. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 203 patients were included in the study, of which 150 (73.9%) had their NGT successfully removed, while 53 (26.1%) experienced removal failure after six months of follow-up. Table 1 provides an overview of the subjects' demographic and clinical variables. Univariate analysis demonstrates a significant correlation between age, admission diagnosis, BMI, FIM score, and ADLs dependence and the failure of NGT removal. The age stratification involves incorporating patients' age groups into the logistic regression analysis to obtain odds ratios (ORs), and both the age groups of 60–70 and over 70 were found to be significant variables. Using a stepwise regression analysis, we examined the effect of these significant variables. Age between 60–70 years (OR, 3.44; $p<0.05$), age over 70 years (OR, 6.16; $p<0.05$), underweight BMI (OR, 5.09; $p<0.05$), total depen-

dence in ADLs (OR, 9.90; p<0.05), and ischemic stroke (OR, 4.10; p<0.05) were found to be the strongest predictors for failed removal (Table 2). According to the OR values of significant variables, directly rounding to the nearest integer to convert to weight scores, for example: the OR for low BMI was 5.09, then its weight score would be 5. Using the weight scores derived from the predictive model for tube removal failure, the total weight score for tube removal failure in patients is calculated. Analysis of the OR distribution derived from spline regression reveals three distinct risk trends within the graphic representation (Fig. 1). Further categorization stratifies risk into groups scoring 0–6, 7–16, and 17 points or more. Following these groupings, logistic regression is utilized to estimate the ORs prior to the adjustment of other variables (Table 3). The failure rates of NGT removal were 5.1% in the low-risk group, 21.5% in the moderate-risk group, and 73.0% in the high-risk group (Table 3).

After swallowing training in high-risk and low-risk populations, the degree of improvement in FOIS and IDDSI does not impact the risk of failure in NGT removal as much as it does in the moderate-risk population. Therefore, we primarily focused on the moderate-risk population for further analysis. As shown in Table 4, for patients who did not show improvement in FOIS levels after training, the failure rate of NGT removal was 81.2% six months later. For those who improved by one FOIS level, the failure rate was 50.0%, while for those who improved by two FOIS levels, the failure rate was 37.5%. For patients whose IDDSI food types did not change after training, the failure rate

Table 1. Baseline clinical variables of the patients

Variable	Total		Nasogastric tube weaning				p-value
			Success		Failure		
	n	% or mean±SD	n	% or mean±SD	n	% or mean±SD	
Age	203	64.7±15.5	150	61.8±15.4	53	73.2±12.3	<0.0001*
Sex							0.5622
Female	70	34.5	50	33.3	20	37.7	
Male	133	65.5	100	66.7	33	62.3	
BMI	198	23.9±8.0	148	24.4±8.7	50	22.4±5.4	0.1344
BMI level							0.0124*
Normal (18.5≤BMI≤24.0 kg/m^2)	92	45.3	67	44.7	25	47.2	
Underweight (<18.5 kg/m^2)	25	12.3	13	8.7	12	22.6	
Overweight (>24.0 kg/m^2)	86	42.4	70	46.7	16	30.2	
Diagnosis							0.0016*
Hemorrhagic stroke	76	37.4	63	42.0	13	24.5	
TBI	43	21.2	36	24.0	7	13.2	
Ischemic stroke	84	41.4	51	34.0	33	62.3	
GCS	191	10.4±3.9	139	10.6±3.8	52	9.7±4.0	0.1665
ADLs							<0.0001*
Partial dependent	100	49.3	89	59.3	11	20.8	
Totally dependent	103	50.7	61	40.7	42	79.2	

BMI, body mass index; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ADLs, activities of daily living.
*Significant difference among groups (p<0.05).

Table 2. Stepwise logistic regression analysis for predicting nasogastric tube removal failure model

Variable	Odds ratio	95% Wald CI		p-value	Assigned weight points
		Lower	Upper		
60≤Age<70 yr	3.44	1.09	10.86	0.0352*	3
70 yr≤Age	6.16	2.10	18.08	0.0009*	6
Ischemic stroke	4.10	1.69	9.95	0.0018*	4
BMI underweighted (<18.5 kg/m^2)	5.09	1.57	16.46	0.0066*	5
ADLs totally dependent	9.90	4.04	24.27	<0.0001*	10

CI, confidence interval; BMI, body mass index; ADLs, activities of daily living.
*Significant difference among groups (p<0.05).

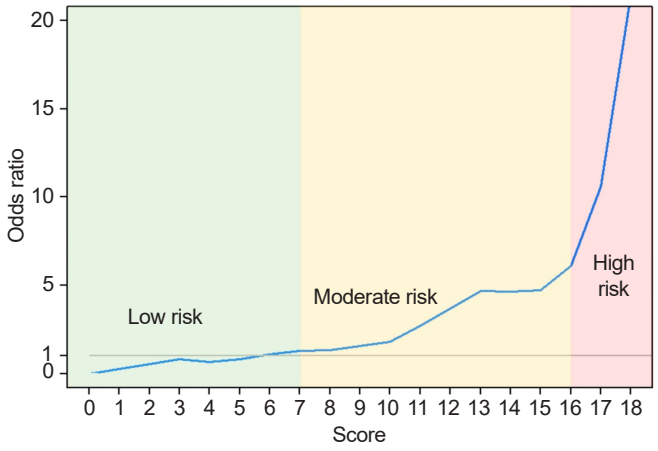

Fig. 1. Estimated graph of the odds ratio between weight scores and the likelihood of nasogastric tube removal.

Table 3. Predictive nasogastric tube removal failure model for risk stratification of tube removal failure

Group	Score	Weaned (n)	Non-weaned (n)	Non-weaned/ total (%)
Low risk	0–6	56	3	5.1
Moderate risk	7–16	84	23	21.5
High risk	≥17	10	27	73.0
Total		150	53	

of tube removal was 85.7%. However, for those who improved by one type of food, the failure rate was 10.0%, and for those who improved by two types of food, the failure rate was 21.4%. In the moderate-risk group, improvements in FOIS levels and an increase in IDDSI food types after one month of swallowing training may be used to predict the likelihood of NGT removal failure after six months of follow-up observation. We amplified our model sample using bootstrapping by 1,000 times for internal validation and obtained the area under the receiver operating characteristic (ROC) curve. The area under the ROC curve is 0.829. The sensitivity and specificity were 75.5% and 23.3%, respectively. In the Fig. 2, the blue line represents our model, while the dashed line represents the results obtained through bootstrapping. The Fig. 2 shows that the two lines almost overlap (DeLong test p-value=0.9831).

DISCUSSION

In this work, we identified several strong predictors for failed remove of NGT after six months of follow-up, including age between 60–70 years, age over 70 years, underweight BMI, total

Table 4. In the moderate-risk group, the improvement in FOIS level and the increase in the number of food types base on IDDSI correspond to the non-weaned rate of NGT removal

	Total (n)	Success (n)	Failure (n)	Non-weaned rate (%)
Improvement of FOIS levels	102	79	23	
0	16	3	13	81.2
1	14	7	7	50.0
2	8	5	3	37.5
3	64	64	0	0
Increase in the number of IDDSI food types (item)	99	76	23	
0	21	3	18	85.7
1	10	9	1	10.0
2	14	11	3	21.4
3	54	53	1	1.9

FOIS, Functional Oral Intake Scale; IDDSI, International Dysphagia Diet Standardization Initiative; NGT, nasogastric tube.

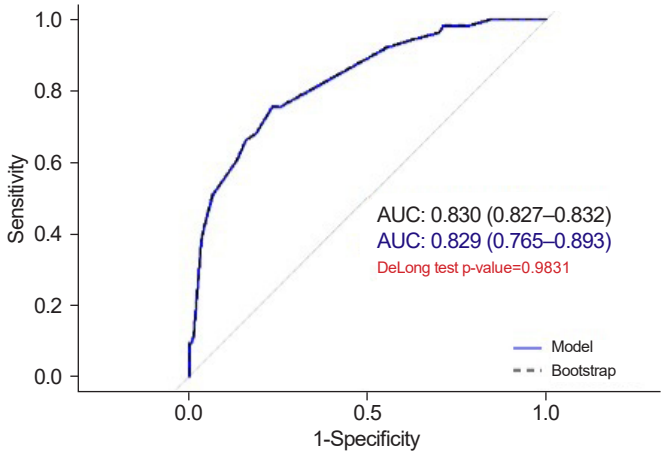

Fig. 2. The area under the receiver operating characteristic curve is 0.829. AUC, area under curve.

dependence in ADLs, and ischemic stroke. We also utilized the weighted scores of the ORs to create a formula to forecast the risk of NGT removal failure and found the risk score greater than 17 have 73.0% of failure of removing NGT.

For patients requiring nutritional support for up to 30 days, NGT feeding alone may be sufficient, but for longer durations, consideration should be given to percutaneous endoscopic gastrostomy (PEG) tube placement [5]. Compared to NGT, PEG offers several advantages, including a lower risk of intervention failure, fewer incidences of pneumonia among PEG recipients, improved quality of life, and higher levels of albumin [8]. Currently, PEG has become a recognized treatment option for temporary or permanent dysphagia resulting from neurological

disorders and oncological conditions [12]. Implementing continuous enteral nutrition at an earlier stage holds the potential to significantly enhance prognosis [12].

Additionally, with early gastrostomy placement, the prevalence of low albumin levels and higher comorbidity, both of which are risk factors for worse outcomes, would be reduced in patients chosen for this intervention [12]. Nevertheless, the benefits of PEG feeding remain uncertain in patient with advanced dementia, and elderly patients over 80 years old [5].

With this result, we propose the following recommendations for dysphagia patients with brain insult who require tube feeding for nutrition support: those identified as high risk based on the research results could early decide whether to undergo or not. Patients with moderate risk should evaluate improvements in FOIS and IDDSI scores after the first month of swallowing training. If there is no improvement observed, these patients may benefit from early decision of further management, considering the high failure rates of 81.2% and 85.7% for the FOIS and IDDSI non-improvement groups, respectively, as indicated in Table 4. Additionally, when suggesting PEG placement, it is advisable to take into account factors such as the presence of advanced dementia and whether the patient is over the age of 80, as per our model's recommendations.

In our study, we observed that 26.1% of the patients failure of removing the NGT after six months follow up. This finding aligns with previous research, which reported removal failure rates ranging from 26% to 69% [13-15]. In spite of antecedent studies investigating the correlation between various risk factors and NGT removal in stroke patients [16,17], our study provides processional data for predicting the risk of failure of removing. Moreover, preceding research has highlighted that swallowing difficulties resulting from TBI are comparable to those observed in stroke patients [1]. Therefore, we can do early decision of alternative management of NGT feeding for the patients with dysphagia such as insertion of gastrostomy, specifically focused on patients with stroke or TBI.

The parameters in our study consistent with preexisting research findings are age, sex, initial GCS and ADLs dependence. Former research has shown that older patients and those with lower FIM scores have a reduced likelihood of NGT removal [14,15]. A lower FIM score indicates that subject has a higher degree of dependency in their daily activities. In our investigation, we also noticed significant differences in age and ADLs dependence between the nonweaned group and the weaned group. The non-weaned group comprised individuals who are older and a larger number of individuals who are completely dependent on ADLs.

Previous studies demonstrated methodological variations and reported inconsistent associations between sex and oral intake recovery [3,16,18]. Certain studies [16,18] excluded sex as a variable in their multivariable analyses due to the absence of significant differences in bivariate analysis. One study indicated that female sex was associated with better outcomes [19]. In our study, there was no significant difference in sex between the NGT-weaned group and the NGT non-weaned group. Further research is needed to explore its impact on the recovery of swallowing disorders.

In individuals with TBI, a low initial GCS consistently indicated compromised oral intake [20]. Additionally, Morgan et al. [21] noted that low GCS scores were predictive of dysphagia in pediatric TBI patients. Another study found that among stroke patients, the deterioration in verbal response, assessed using the GCS, demonstrated a notably stronger association with swallowing recovery failure [22]. However, the statistical significance of the GCS variable in the present study may be influenced by the sample size. Numerous studies [9,10,11,23] in this domain have demonstrated a link between NIHSS scores and unfavorable recovery outcomes. One study found that higher NIHSS scores were associated with delayed removal times of NGT [14]. Nonetheless, while the NIHSS is mainly employed for prognostic assessment in post-stroke patients, the GCS has broader applications, encompassing prognostic evaluation in brain injury patients and even the assessment of recovery in swallowing disorders, in addition to its use with stroke patients.

A study proposed in 2021 that there is no correlation between body weight and NGT removal [17], which differs from our research findings. Our study highlighted the significant impact of being underweight on the failure of NGT removal. A BMI below 20 is widely acknowledged as an indicator of malnutrition, and a low BMI is correlated with a higher probability of probable sarcopenia [24,25]. Previous studies have also indicated a link between malnutrition and dysphagia [26], and there is evidence of a relationship between sarcopenia and decreased swallowing function, particularly among older adults in Japan [27]. This finding may inferred that malnutrition and sarcopenia may be risk factors for the poor recovery of swallowing function in individuals who have experienced a stroke or brain injury. The decline in overall muscle mass and strength that accompanies being underweight may contribute to the weakening of the muscles involved in the swallowing process [28]. This

weakened musculature could explain the increased likelihood of NGT removal failure observed in underweight individuals in our study. Furthermore, a separate study demonstrated that stroke survivors with lower BMI values, particularly those in the lowest quartiles, exhibited more severe stroke symptoms and experienced poorer functional recovery compared to individuals with higher BMI values [29]. These studies further support the association between underweight and greater severity of stroke, poorer functional recovery, and even swallowing function.

There are limited study mentioning the correlation between stroke types and the failure rate of NGT removal [17,30], and only one study identified intracerebral hemorrhage as a predictive factor for NGT removal [31]. Our study revealed a significant association between ischemic stroke and the failure rate of tube removal. Furthermore, another study published in Stroke provided additional insights by demonstrating that patients with cerebral infarction had poorer functional and neurological recovery compared to those with hemorrhagic stroke [32]. The relationship between stroke type and removal of NGT needs further study.

A retrospective study revealed that for each increase of one FOIS level, there was a 3.7-fold higher likelihood of tube removal [33]. Consistently, our study yielded similar results, indicating that the extent of FOIS level improvement after one month of swallowing training could predict the likelihood of NGT removal failure six months later. Patients who exhibited no change in FOIS levels following the initial month of swallowing training after experiencing a brain insult had the highest rate of tube removal failure, whereas those who demonstrated greater improvements had lower failure rates. Additionally, another study found that higher FOIS levels were correlated with a higher probability of returning to complete oral intake post-stroke [34]. Furthermore, our study identified that the greater improvement in the ability to consume various food items (according to IDDSI) after one month of swallowing training, the lower the likelihood of NGT removal failure six months after the brain insult. Although one study mentioned that FOIS at admission could predict the time to return to unrestricted oral intake [35], no previous study has evaluated the probability of NGT removal failure six months after brain insult using changes in FOIS and IDDSI following one month of swallowing training, which is a relatively unique feature of our predictive model.

Using our predictive model, patients with brain insults can be initially categorized into risk groups for swallowing disorders. Subsequently, advanced swallowing interventions can be implemented for high-risk patients who encounter difficulties in NGT removal. These interventions may include the combined use of repetitive transcranial magnetic stimulation or VitalStim, long-term education on NGT care, or alternative options for enteral feeding. For individuals at moderate risk, a progress assessment of NGT removal rate using FOIS and IDDSI can be conducted one month later. If there is no improvement, rehabilitation training similar to that for high-risk cases should be followed, while others can undergo regular swallowing rehabilitation training.

One study utilized FIM-motor, FIM-cognition, days after onset, and age to construct the equation [15]; the other utilized the Barthel index at admission, lip-closing status, ability to answer simple questions, and functional independence before stroke to construct the equation [17]. In contrast, ours utilizes patient age, stroke history, BMI, and total dependence in ADLs to form a risk prediction model, and provides early intervention recommendations. Our risk factors are relatively simple and applicable for predicting NGT removal in both stroke and TBI patients.

There are certain limitations in our study that need to be taken into account when interpreting these findings. Firstly, it is important to note that this study is retrospective in nature, which means we are unable to control for participant consistency. Secondly, due to the retrospective nature of this research, there may be instances of missing and incomplete clinical data. Thirdly, we faced the challenge of not being able to control the intervention methods applied to participants. Not all individuals in the study received the same swallowing training, leading to variations in the methods used. Fourthly, we did not actually have the patients undergo nutritional assessments or tests for sarcopenia. These constraints highlight the need for future research with more controlled settings and comprehensive data collection to further validate and refine our findings.

In conclusion, our study identified factors predicting NGT removal failure, including older age, underweight, complete ADLs dependence, and ischemic stroke. We also created a predictive model to assess this risk, aiding healthcare professionals in identifying high-risk patients and providing suitable interventions and training.

CONFLICTS OF INTEREST

Fuk Tan Tang is an Editorial Board member of Annals of Rehabilitation Medicine. The author did not engage in any part of the review and decision-making process for this manuscript.

Otherwise, no potential conflict of interest relevant to this article was reported.

FUNDING INFORMATION

The funding for this study was provided by Lotung Poh-Ai Hospital.

AUTHOR CONTRIBUTION

Conceptualization: Huang ST, Yeh SM, Wang TG, Tang FT, Hsieh YT, Ho CS. Methodology: Huang ST. Formal analysis: Huang ST, Yeh SM, Chen WM, Jao AT. Funding acquisition: Yeh SM. Project administration: Peng MC. Visualization: Huang ST, Yeh SM, Chen WM, Jao AT. Writing – original draft: Huang ST, Yeh SM. Writing – review and editing: Wang TG, Yeh SM. Approval of final manuscript: all authors.

ORCID

Shih-Ting Huang, https://orcid.org/0000-0003-3673-2345
Tyng-Guey Wang, https://orcid.org/0000-0003-3298-4916
Mei-Chih Peng, https://orcid.org/0009-0009-1438-2760
Wan-Ming Chen, https://orcid.org/0009-0009-6628-0635
An-Tzu Jao, https://orcid.org/0009-0005-0182-767X
Fuk Tan Tang, https://orcid.org/0000-0002-9189-6601
Yu-Ting Hsieh, https://orcid.org/0009-0006-4999-8600
Chun Sheng Ho, https://orcid.org/0000-0003-1568-1841
Shu-Ming Yeh, https://orcid.org/0000-0001-7213-2000

REFERENCES

1. Lee WK, Yeom J, Lee WH, Seo HG, Oh BM, Han TR. Characteristics of dysphagia in severe traumatic brain injury patients: a comparison with stroke patients. Ann Rehabil Med 2016;40:432-9.
2. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A systematic review of the prevalence of oropharyngeal dysphagia in stroke, Parkinson's disease, Alzheimer's disease, head injury, and pneumonia. Dysphagia 2016;31:434-41.
3. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke 2005;36:2756-63.
4. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. Chest 2003;124:328-36.
5. Rahnemai-Azar AA, Rahnemaiazar AA, Naghshizadian R, Kurtz A, Farkas DT. Percutaneous endoscopic gastrostomy: indications, technique, complications and management. World J Gastroenterol 2014;20:7739-51.
6. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. Curr Opin Gastroenterol 2007;23:178-82.
7. Hsu CY, Lai JN, Kung WM, Hung CH, Yip HT, Chang YC, et al. Nationwide prevalence and outcomes of long-term nasogastric tube placement in adults. Nutrients 2022;14:1748.
8. Gomes CA Jr, Andriolo RB, Bennett C, Lustosa SA, Matos D, Waisberg DR, et al. Percutaneous endoscopic gastrostomy versus nasogastric tube feeding for adults with swallowing disturbances. Cochrane Database Syst Rev 2015;2015:CD008096.
9. Ickenstein GW, Höhlig C, Prosiegel M, Koch H, Dziewas R, Bodechtel U, et al. Prediction of outcome in neurogenic oropharyngeal dysphagia within 72 hours of acute stroke. J Stroke Cerebrovasc Dis 2012;21:569-76.
10. Kumar S, Doughty C, Doros G, Selim M, Lahoti S, Gokhale S, et al. Recovery of swallowing after dysphagic stroke: an analysis of prognostic factors. J Stroke Cerebrovasc Dis 2014;23:56-62.
11. Mandaville A, Ray A, Robertson H, Foster C, Jesser C. A retrospective review of swallow dysfunction in patients with severe traumatic brain injury. Dysphagia 2014;29:310-8.
12. Dietrich CG, Schoppmeyer K. Percutaneous endoscopic gastrostomy- too often? Too late? Who are the right patients for gastrostomy? World J Gastroenterol 2020;26:2464-71.
13. Lin YN, Chen SY, Wang TG, Chang YC, Chie WC, Lien IN. Findings of videofluoroscopic swallowing studies are associated with tube feeding dependency at discharge in stroke patients with dysphagia. Dysphagia 2005;20:23-31. Erratum in: Dysphagia 2005;20:388.
14. Lee JH, Kim SB, Lee KW, Lee SJ, Park JG, Ri JW. Associating factors regarding nasogastric tube removal in patients with Dysphagia after stroke. Ann Rehabil Med 2014;38:6-12.
15. Oto T, Kandori Y, Ohta T, Domen K, Koyama T. Predicting the chance of weaning dysphagic stroke patients from enteral nutrition: a multivariate logistic modelling study. Eur J Phys Rehabil Med 2009;45:355-62.
16. Ikenaga Y, Nakayama S, Taniguchi H, Ohori I, Komatsu N, Nishimura H, et al. Factors predicting recovery of oral intake in stroke survivors with dysphagia in a convalescent rehabilitation ward. J Stroke Cerebrovasc Dis 2017;26:1013-9.
17. Lee KC, Liu CT, Tzeng IS, Chie WC. Predictors of nasogastric tube removal in patients with stroke and dysphagia. Int J Rehabil Res 2021;44:205-8.
18. Nakadate A, Otaka Y, Kondo K, Yamamoto R, Matsuura D, Honaga

K, et al. Age, body mass index, and white blood cell count predict the resumption of oral intake in subacute stroke patients. J Stroke Cerebrovasc Dis 2016;25:2801-8.
19. Inooka Y, Yamana H, Shinoda Y, Inokuchi H, Matsui H, Fushimi K, et al. Predictive factors for oral intake recovery after acute stroke: analysis of a Japanese nationwide inpatient database. Dysphagia 2022;37:1623-32.
20. Muscari A, Falcone R, Pirazzoli E, Faccioli L, Muscari S, Pastore Trossello M, et al. Predicting failure to recover swallowing in patients with severe post-stroke dysphagia: the DIsPHAGIc score. Dysphagia 2023;38:290-304.
21. Morgan A, Ward E, Murdoch B, Kennedy B, Murison R. Incidence, characteristics, and predictive factors for Dysphagia after pediatric traumatic brain injury. J Head Trauma Rehabil 2003;18:239-51.
22. Mackay LE, Morgan AS, Bernstein BA. Swallowing disorders in severe brain injury: risk factors affecting return to oral intake. Arch Phys Med Rehabil 1999;80:365-71.
23. Rhie SH, Choi JW, Jeon SJ, Kang SD, Joo MC, Kim MS. Characteristics of patients with aneurysmal subarachnoid hemorrhage and risk factors related to dysphagia. Ann Rehabil Med 2016;40:1024-32.
24. Campillo B, Paillaud E, Uzan I, Merlier I, Abdellaoui M, Perennec J, et al. Value of body mass index in the detection of severe malnutrition: influence of the pathology and changes in anthropometric parameters. Clin Nutr 2004;23:551-9.
25. Curtis M, Swan L, Fox R, Warters A, O'Sullivan M. Associations between body mass index and probable sarcopenia in community-dwelling older adults. Nutrients 2023;15:1505.
26. Veldee MS, Peth LD. Can protein-calorie malnutrition cause dysphagia? Dysphagia 1992;7:86-101.
27. Kuroda Y, Kuroda R. Relationship between thinness and swallowing function in Japanese older adults: implications for sarcopenic dysphagia. J Am Geriatr Soc 2012;60:1785-6. Erratum in: J Am Geriatr Soc 2012;60:2385.
28. Maeda K, Takaki M, Akagi J. Decreased skeletal muscle mass and risk factors of sarcopenic dysphagia: a prospective observational cohort study. J Gerontol A Biol Sci Med Sci 2017;72:1290-4.
29. Kim Y, Kim CK, Jung S, Yoon BW, Lee SH. Obesity-stroke paradox and initial neurological severity. J Neurol Neurosurg Psychiatry 2015;86:743-7.
30. Fernández-Pombo A, Seijo-Raposo IM, López-Osorio N, Cantón-Blanco A, González-Rodríguez M, Arias-Rivas S, et al. Lesion location and other predictive factors of dysphagia and its complications in acute stroke. Clin Nutr ESPEN 2019;33:178-82.
31. Ke Z, Liu W, Chen FY, Ge WY, Li XP, Fan XN, et al. Intracerebral hemorrhage and absence of pneumonia are independent predictors for nasogastric tube removal of post-stroke dysphagia. Ann Indian Acad Neurol 2023;26:90-3.
32. Paolucci S, Antonucci G, Grasso MG, Bragoni M, Coiro P, De Angelis D, et al. Functional outcome of ischemic and hemorrhagic stroke patients after inpatient rehabilitation: a matched comparison. Stroke 2003;34:2861-5.
33. Chuang ST, Yen YH, Hsu H, Lai MW, Hung YF, Tsai SW. Predictive factors for nasogastric tube removal in post-stroke patients. Medicina (Kaunas) 2023;59:368.
34. Ikenaga Y, Fudeya M, Kusunoki T, Yamaguchi H. Factors contributing to complete oral intake in dysphagic stroke patients with enteral feeding tubes in convalescent rehabilitation wards. Prog Rehabil Med 2023;8:20230011.
35. Hansen TS, Engberg AW, Larsen K. Functional oral intake and time to reach unrestricted dieting for patients with traumatic brain injury. Arch Phys Med Rehabil 2008;89:1556-62.

Instructions for authors

Annals of Rehabilitation Medicine

Enacted in May, 2011
Revised on January 31, 2013
Revised on August 1, 2018
Revised on March 11, 2019
Revised on March 16, 2020
Revised on June 9, 2023
Revised on January 19, 2024

1. AIMS & SCOPE

Annals of Rehabilitation Medicine (ARM) is the official journal of the Korean Academy of Rehabilitation Medicine. It is an international, peer-reviewed open access journal, which aims to be a global leader in sharing up-to-date knowledge dedicated to the advancement of care and enhancing the function and quality of life of persons with various disabilities and chronic illnesses. As the official journal of one of the largest societies of rehabilitation medicine in Asia and Oceania, nearly 8,000 physiatrists receive this journal every two months as a member benefit. This journal is endorsed by the International Society of Physical and Rehabilitation Medicine (ISPRM) and the Asia-Oceanian Society of Physical and Rehabilitation Medicine (AOSPRM). International members comprise approximately half the editorial board and conduct peer-review of submitted manuscripts.

The journal encompasses all aspects of physical medicine and rehabilitation, including clinical practice, experimental and applied research, and education. Research areas covered by this journal include rehabilitation of brain disorders and spinal cord injury; electrodiagnosis; musculoskeletal disorders and pain; pediatric, geriatric, cardiopulmonary, sports, cancer, cognitive, and robotic rehabilitation; neuromodulation; neuroimaging; orthotics and prosthetics; physical modalities; clinical trials; quality of life issues; and basic research, as well as other emerging fields in rehabilitation medicine.

2. COPYRIGHTS AND CREATIVE COMMONS ATTRIBUTION LICENSE

The Korean Academy of Rehabilitation Medicine is the owner of all copyright to papers published in *ARM*, and has the right to publish, reproduce, distribute, and print the contents in other types of media. Authors of accepted papers must complete the Copyright Transfer Form. A letter of permission is required for any and all material that has been published previously. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to text, illustrations, and tables. This is identical to the Creative Commons (Attribution-Noncommercial) license available at http://creativecommons.org/.

3. GENERAL GUIDELINES

The manuscript guidelines for *ARM* are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals" published by the International Committee of Medical Journal Editors (http://www.icmje.org), and instructions which are not mentioned in the present guidelines are referred to the guidelines stated in the Recommendations. There are no fees payable to submit in this journal.

1) ARTICLE TYPES

Manuscripts include original articles, review articles, brief reports, case reports, images in this issue, and letters to the editor.

(1) Original articles

This form of publication represents original research articles reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers.

(2) Review articles

The Editorial Board welcomes state-of-the-art review articles. The *ARM* strongly prefers systematic reviews of the literature. Invited review articles provide a comprehensive review of a subject of importance to clinicians and researchers and are commissioned by the editorial board to an invited expert in the field.

(3) Brief reports

These manuscripts are short but important reports to provide preliminary communications with less complete data sets than would be appropriate for original contributions that present novel and impactful clinical and basic research of a more preliminary nature.

(4) Case reports

Case reports are considered for publication when at least one of the following criteria is met: (a) a rare condition is reported, (b)

atypical symptoms and signs are observed, (c) new diagnostic or therapeutic methods are introduced, (d) atypical clinical and laboratory findings for populations residing in Asia and the Pacific Rim. Descriptions of clinical cases (individual or a series) should be unique, should deal with clinical cases of exceptional interest or innovation and should preferably be a first-time report.

(5) Images in this issue

This form of publication represents images (e.g.,radiographs, CT, MRI, electrodiagnostic tracings, pathology, physical examination findings, photos of a patient or medical device) that are interesting and unique.

(6) Letters to the editor

Critical comments are welcomed for providing alternative interpretations or views about articles published in *ARM*. Letters should be directly related to the published article on which it comments. Letters being considered for publication ordinarily will be sent to the authors, who will be given the opportunity to reply. Letters will be published at the discretion of the editors and are subject to abridgement and editing for style and content.

2) LANGUAGE OF MANUSCRIPT

All manuscripts must be written in clearly under-standable English. Authors whose first language is not English are requested to have their manuscripts checked for grammatical and linguistic correctness before submission. Correct medical terminology should be used, and jargon should be avoided. Use of abbreviations should be minimized and restricted to those that are generally recognized. When using an abbreviated word, it should be spelled out in full on first usage in the manuscript followed by the abbreviation in parentheses. Numbers should be written in Arabic numerals, but must be spelled out when placed in the beginning of a sentence. Measurements should be reported using the metric system, and hematologic and biochemical markers should be reported in International System (SI) of Units. All units must be preceded by one space except percentage (%), temperature (°C), and degree (°).

4. RESEARCH AND PUBLICATION ETHICS

All manuscripts should be written with strict adherence to the research and publication ethics guidelines recommended by Council of Science Editors (http://www.councilscienceeditors.org/), International Committee of Medical Journal Editors (ICMJE, http://www.icmje.org/), World Association of Medical Editors (WAME, http://www.wame.org/), and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). For all studies involving human subjects, the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) should be upheld, informed consent must be obtained from all participants, and must be approved by a recognized Institutional Review Board (IRB) or research ethics committee. The editor may request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents. Experiments involving animals should comply with the NIH guidelines for the use of laboratory animals (https://www.nlm.nih.gov/services/research_report_guide.html) and/or be reviewed by an appropriate committee (e.g., Institutional Animal Care and Use Committee, IACUC) to ensure the ethical treatment of animals in research. Also, studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (e.g., Institutional Biosafety Committee, IBC). *ARM* will follow the guidelines by the Committee on Publication Ethics (COPE, http://publicationethics.org/) for settlement of any misconduct.

1) REDUNDANT PUBLICATION AND PLAGIARISM

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. No part of the accepted manuscript should be duplicated in any other scientific journal without the permission of the editorial board. If plagiarism or duplicate publication related to the papers of this journal is detected, the manuscripts may be rejected, the authors will be announced in the journal, and their institutes will be informed. There will also be penalties for the authors.

2) AUTHORSHIP

ARM follows the recommendations by International Committee of Medical Journal Editors (ICMJE,http://www.icmje.org/) and and the Korean Association of Medical Journal Editors (KAMJE, https://www.kamje.or.kr/en/main_en). Authorship is credited to those who have direct involvement in the study and have made significant contributions to (a) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (b) drafting the work or revising it critically for important intellectual content; AND (c) final approval of the version to be published; AND (d) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved as recommended by ICMJE. The primary investigator is designated the first author of the study, unless contested by the other authors. The correspond-

ing author is directly responsible for communication and revision of the submitted manuscript. Authors are required to include a statement of responsibility in the manuscript that specifies the contribution of every author at the end of the manuscript, in a section entitled "Author contribution". All persons who have made substantial contribution, but who are not eligible as authors should be named in the acknowledgments. In the case of change of authorship, a written explanation must be submitted. Change in either the first author or the corresponding author requires approval by the editorial board, and any changes in the other authors require approval by the editor-in-chief.

3) CONFLICT OF INTEREST

The corresponding author of an article is asked to inform the editor of the authors' potential conflicts of interest possibly influencing their interpretation of data. A potential conflict of interest must be disclosed during the online submission process on the appropriate web page. Such conflicts may be financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems based on the "ICMJE Uniform Disclosure Form for Potential Conflicts of Interest" (http://www.icmje.org/coi_disclosure.pdf). The editor will decide whether the information on the conflict should be included in the published paper. Before publishing such information, the editor will consult with the corresponding author. In particular, all sources of funding for a study should be explicitly stated.

4) REGISTRATION OF CLINICAL TRIAL

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" is recommended to be registered to the primary registry to be prior publication. *ARM* recommend, as a condition of consideration for publication, registration in a public trials registry. *ARM* accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/), ISRCTN Resister (www.isrctn.org), ANZCTR (https://www.anzctr.org.au/), EudraCT Database (https://eudract.ema.europa.eu/), Clinical Trials Information System (https://euclinicaltrials.eu/), University Hospital Medical Information Network (www.umin.ac.jp/ctr/index/htm), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/) or The Clinical Research Information Service (http://cris.nih.go.kr/). The clinical trial registration number will be published at the end of the abstract.

5) PROCESS FOR MANAGING RESEARCH AND PUBLICATION MISCONDUCT

When the journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/guidance/Flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

6) PROCESS FOR HANDLING CASES REQUIRING CORRECTIONS, RETRACTIONS, AND EDITORIAL EXPRESSIONS OF CONCERN

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts available from: https://publicationethics.org/guidance/Flowcharts. If correction needs, it will follow the ICMJE Recommendation for Corrections, Retractions, Republications and Version Control available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html.

7) ETHICS AND AUTHORSHIP IN THE USE OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

Authorship assignment to AI is prohibited. *ARM* discourages the use of generative AI tools for the purpose of creating any types of content (including text, tables, and figures) for scientific manuscripts. If such tools are used, the authors must report their use transparently. In addition, authors who employ generative AI tools are solely responsible for all content produced and submitted. However, the use of AI tools to enhance the linguistic quality of a submission is considered acceptable and does not require specific disclosure.

5. MANUSCRIPT SUBMISSION

All submissions are made online at the journal's online manuscript submission site (http://www.e-arm.org/submission) by the corresponding author. Submitted manuscripts are initially examined for format, and then appointed a submission number. For nonbiased peer review, authors' names and institutional affiliations should not be mentioned in the text. The revised manuscript should be submitted through the same web system under the same identification numbers. The date of final review for the

manuscript will be the date of acceptance for publication. If you have any questions about the online submission process, contact the Editorial Office by e-mail at edit@e-arm.org.

1) ARTICLE PROCESSING CHARGES

Annals of Rehabilitation Medicine is an open access journal. To publish in *Annals of Rehabilitation Medicine*, authors are asked to pay an article processing charge (APC) on acceptance of their research paper. The APC for all published papers is as follows, plus VAT or local taxes where applicable. The currency KRW will be applied to the submissions from South Korea.

- Original article / Brief Reports / Unsolicited review article: 600 USD or 600,000 KRW
- Solicited article: Free
- Case report: 300 USD or 300,000 KRW
- Image in this issue: 170 USD or 170,000 KRW
- Correspondence / erratum: 100 USD or 100,000 KRW

†Note: As categorized by the World Bank, low-income countries will be eligible for a 20% discount on the updated APCs for original articles/brief reports/review articles/case reports. To find out if your country qualifies, please refer to the World Bank's classification available at https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.

(This updated article processing charge is applied to all submissions as of Oct 1, 2023.)

6. PEER REVIEW PROCESS

1) EDITORIAL REJECT POLICY

Conformity of the submitted manuscript to the submission instructions is examined upon submission. The Editorial Board may reject the manuscript or request the author to resubmit in the following cases: 1) Topic clearly out of scope / insufficient perceptual content 2) Work clearly does not meet sufficient standards of novelty or quality 3) Manuscript incomplete or incorrectly formatted 4) Suspected plagiarism in the manuscript.

2) PEER REVIEW PROCESS

Submitted manuscripts will be reviewed by two or more peer reviewers selected from the board's database of expert reviewers. In addition, if deemed necessary, a review of statistics may be requested. Following review, the editorial board will decide whether the manuscript will be 1) accepted for publication, 2) subject to minor revision, 3) subject to major revision, or 4) rejected for publication. For manuscripts which are either subject to minor revision or subject to major revision, the corresponding author must resubmit the revised manuscript online. The revised manuscript should have the changes highlighted by using the Track Changes tool in Microsoft Office Word. In addition, the corresponding author must reply to both reviewers' comments point by point, and explain in detail what changes were made in the manuscript. When considered necessary, the editorial board may make changes to the structure and phrases of the manuscript without compromising the integrity of the original paper. After completion of the peer review process, the editorial board will determine acceptance for publication and notify the corresponding author by e-mail. Manuscripts which do not comply with the present guidelines will be notified for correction or withheld from publication.

When a manuscript is not resubmitted within 2 months of notification, it will be considered that the authors have withdrawn the manuscript from submission. Manuscripts accepted for publication are generally published in order of submission, depending on the category of the manuscript and the date of acceptance for publication.

7. PREPARATION OF THE MANUSCRIPT

Use Microsoft Office Word (versions after 2003) and ensure correct spelling and grammar. Setup the MS Word document for 1-inch margins on letter or A4-sized paper. The manuscript must be written in 12-point font and the sentences must be double-spaced, including tables and figure legends. Each page should be numbered in the middle of the lower margin, and all sentences must be numbered sequentially throughout the entirety of the manuscript, starting with the title page. All papers must be accompanied by a title page. The title page should contain the title of the manuscript, a short running title, the authors' names, academic degrees, respective affiliations, and ORCID. The corresponding author must be identified, and his or her contact information (postal address, e-mail, telephone and fax numbers) should be listed. The title should clearly describe the objective of the study and contain less than 20 words. The first letter of each word of the title should be in capital letters except for prepositions, articles, and conjunctions. Provide a short running title containing less than 10 words. In cases in which the authors belong to multiple affiliations, the affiliations during the study being reported should be matched to the authors' names using a superscript of Arabic numerals. Conflicts of interest, funding information, author contribution and acknowledgements (when applicable) should also be located in the title page.

1) ORIGINAL ARTICLES

Original papers should be structured in the following order: Abstract, Introduction, Methods, Results, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. Maximum word count is limited to 5,000 words.

(1) Abstract

A structured abstract with the headings of Objective, Methods, Results, and Conclusion must succinctly describe the paper in 250 words or less. Use complete sentences and do not number the results. At the end of the abstract, list up to 5 relevant keywords which are in accordance to the Medical Subject Headings (MeSH) in the Index Medicus (http://www.nlm.nih.gov/mesh).

(2) Introduction

Clearly present the objective of the study and its relationship to earlier work in the field. A brief background to inform the readers of the relevance of the study may be necessary. However, avoid extensive review of the literature.

(3) Methods

Describe the participants or research materials of the study, and explain in detail the inclusion and exclusion criteria for both the experimental and control groups. Describe the experimental methods in a logical and systematic manner so that they can be reproducible by another investigator. Experimental drugs should be stated in the generic name. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name. When using experimental devices or other products, state the brand name then follow with the name of the manufacturer, in parentheses, e.g., Flow Cytometer (Coulter Electronic Inc.). To ensure anonymity during the peer review process, the authors' affiliations or institutional setting of the study should not be revealed. Statistical analysis and criteria for determining significance should be described in enough detail to allow the knowledgeable reader with access to the original data to verify the reported results. An ethics statement should be placed here when the studies are performed using clinical samples or data, and animals.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and 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.

(4) Results

Summarize and describe logically the significant findings and trends observed in the results using text, figures and tables. Avoid extensive repetition of contents of the tables and figures in the text.

In statistical expression, mean and standard deviation should be described as mean ± SD, and mean and standard error as mean ± SE. In general, p-values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; p-values smaller than 0.001 should be reported as $p < 0.001$.

(5) Discussion

Interpret the results in respect to the objective of the study, and describe differences with previous studies and significant findings which lead to the deduction of the conclusion. Refrain from excessive review of historic studies, textbook facts, or irrelevant references. Accentuate newly obtained observations from the study, and include significant limitations of the study.

(6) Conflicts of interest

Any potential conflicts of interest relevant to the manuscript should be described. If there are no conflicts of interest, authors should state that none exists.

(7) Funding information

All sources of funding applicable to the study should be stated here explicitly. All original articles, editorials, reviews, and new technology articles must state funding sources for the study.

(8) Author contribution

The individual contributions of the authors to the manuscript should be specified in this section.

(9) Acknowledgments

Persons who have made contributions to the study, but who are not eligible for authorship can be named in this section. Their contribution must be specified, such as data collection, financial support, statistical analysis, or experimentation. The corresponding author must inform the named contributor of the acknowledgment, and acquire consent before manuscript submission.

(10) References

- Cite only references which are quoted in the text. Limit the number of references 40.

- When quoting a reference in the text, refrain from stating the author's name, and identify references with Arabic numerals in brackets such as [1], [2-4], and [5,7,9].
- The references should be listed in order of citation in the text.
- List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."
- Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).
- For more on references, refer to the NLM Style Guide for Authors, Editors, and Publishers (http://www.nlm.nih.gov/citingmedicine).

Journals

1. Jeon JH, Jung YJ, Lee JY, Choi JS, Mun JH, Park WY, et al. The effect of extracorporeal shock wave therapy on myofascial pain syndrome. Ann Rehabil Med 2012;36:665-74.
2. Geraud G, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatripan. Headache 2002;42 Suppl:S93-9.

Book & Chapter of book

3. Frontera W, Silver JK, Rizzo TD. Essentials of physical medicine and rehabilitation. 2nd ed. Saunders; 2008. p. 579-82.
4. Esquenazi A. Upper limb amputee rehabilitation and prosthetic restoration. In: Braddon RL, editor. Physical medicine and rehabilitation. 2nd ed. Saunders; 2000. p. 263-78.

Proceedings of academic conference

5. Harnden P, Joffe JK, Jones WG. Germ cell tumours V. Proceedings of the 5th Germ Cell Tumour Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer; 2002.

Thesis (Dissertation)

6. Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant, MI: Central Michigan University; 2002.

(11) Tables

Tables should be submitted separately from the text, and each table should be created in MS Word on separate pages, using double space throughout. They should be simple, self-explanatory, and not redundant with the text or the figures. Limit 5 tables per manuscript. The title of the tables should be written in phrases, and capitalized the first letter of the first word. The title should be placed above the table, and abbreviations and footnotes should be placed under the table. Number the tables in order of appearance in the text (e.g., Table 1, Table 2). All abbreviations used in the table must be spelled-out in full under the table in the following order: abbreviation, comma, full word (e.g., RM, rehabilitation medicine;). Table footnotes should be indicated in superscripts in the following order: [a], [b], [c]… but p-values should be indicated by asterisk (e.g., *$p<0.05$, **$p<0.01$. ***$p<0.001$).

(12) Figure legends

Legends should be submitted separately from the text, and each legend should be typed on separate pages. They should be written in full sentences to describe the content of the figure, and only the first letter of the legend should be capitalized. For lengthy legends continuing beyond one line, the left margin of the following lines should start at the same point as the first line. Any symbols, marks or abbreviations made in the figure must be explained in the legend. Figures containing histologic slides should be accompanied by legends explaining tissue origin, stain method, and microscopic amplification.

(13) Figures

Figures should be uploaded online as separate files and numbered in order of appearance in the text (e.g., Fig. 1). When a single numbered figure contains 2 or more figures, the figure should be numbered with an alphabet letter following the number (e.g., Fig. 1A, Fig. 1B). Indicate focus points in the figures with markers such as arrows and arrowheads, etc. Image files must be of resolutions higher than 300 dpi, and less than 3 MB, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. A single numbered figure containing more 2 or more figures such as Fig. 1A and Fig. 1B should be uploaded as a single file.

2) REVIEW ARTICLES

The abstract should contain no more than 250 words and 5 keywords. The text is structured in the order of Introduction, Main text, Conclusion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures.

3) BRIEF REPORTS

General guidelines are the same as for the original article. The manuscript is structured in the order of Abstract, Main text, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. A structured abstract is required and limited to 150 words, with no more than 3 keywords attached. Manuscripts

should be limited to 1,500 words of text including references and figure legends (not including abstract, tables, and figures), and no more than 10 references. The total number of figures and/or tables is limited to 3.

4) CASE REPORTS

General guidelines and order of manuscript preparation are the same as for the original article. Case reports are considered for publication only if they report rare conditions, atypical symptoms and signs, novel diagnostic or therapeutic approaches, or describe atypical findings for populations residing in Asia and the Pacific Rim. The editorial board will determine whether the case report fulfills the above criteria for acceptance of publication. The manuscript is structured in the order of Abstract, Introduction, Case report, Discussion, Conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), References, Tables, Figure legends, and Figures. The abstract should be nonstructured and limited to 150 words, with no more than 3 keywords attached. The introduction should briefly state the background and significance of the case. The actual case report should describe the clinical presentation and the diagnostic and therapeutic measures taken. The discussion should focus on the uniqueness of the case and should not contain extensive review of the disease or disorder. The combined number of tables and figures is limited to 5, and the number of references is limited to 10. Maximum word count is limited to 1,500 words including references and figure legends.

5) IMAGES IN THIS ISSUE

All images should be accompanied by a short description of the image and a brief and concise clinical review of the specific patient or clinical issue of no more than 500 words (excluding references) with references limited to 5. Image files must be of resolutions higher than 300 dpi for photographs, and 900 dpi for line art, waveforms, and graphs, in JPEG, GIF, TIFF, or Microsoft PowerPoint format. Images should make up a single figure, although they may contain more than one frame. The manuscript does not have an abstract.

6) LETTERS TO THE EDITOR

Letters should not have an abstract, tables, figures, and data supplements. Letters must be limited to roughly 500 words of text and no more than 5 references, 1 of which should be to the recent *ARM* article. Letters may have no more than 3 authors.

7) REPORTING GUIDELINES FOR SPECIFIC STUDY DESIGNS

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

8. SUBMISSION APPLICATION & COPYRIGHT TRANSFER

All submitted manuscripts must be accompanied by the official Submission Application & Copyright Transfer Form of the Korean Academy of Rehabilitation Medicine. The Submission Application & Copyright Transfer Form must contain the title of the manuscript, date of submission, names of all authors, authors' affiliations, and written signatures. Note the corresponding author and provide his/her affiliation, e-mail, telephone and fax numbers, and mailing address.

For the copyrights of the contributions published in *ARM*, see Creative Commons (Attribution-Noncommercial) at http://creativecommons.org.

9. MANUSCRIPTS AFTER ACCEPTANCE

ARM is published in English bi-monthly on the last days of February, April, June, August, October, and December.

1) FINAL VERSION UPLOAD

When accepted for publication, the authors' institutional affiliations should be inserted into the text of the final revised manuscript and uploaded to the online submission system. Files containing figures should be of the highest resolution (at least 300 dpi for color figures, and 900 dpi for line art and graphs) should be also be uploaded in JPEG, GIF, or TIFF format, and must be named according to the figure number (e.g., Fig. 1.jpg).

2) GALLEY PROOF

Galley proofs will be sent to the corresponding author for final corrections. Corrections should be kept to a minimum, must be returned within 2 days, otherwise publication may be delayed. Any fault found after the publication is the responsibility of the authors. We urge our contributors to proofread their accepted manuscripts very carefully. After the publication, if there are critical errors, they should be corrected as Corrigendum or Erratum.

3) PUBLICATION

The editorial board retains the right to request minor stylistic and major alterations that might influence the scientific content of the paper. The final manuscript will be published following final approval by the editor-in-chief.

Checklist for Authors

Annals of Rehabilitation Medicine

General

☐ All elements of the manuscript are printed in English and double-spaced with 1-inch margins at top, bottom, and sides. Right margins are unjustified.

☐ All pages are numbered in the following order: title page, structured or standard abstract, body of the text, conflict of interests, Funding information, Author contribution, Acknowledgments (when applicable), references, legends, and tables.

☐ The text is consecutively line numbered.

☐ The Submission Application & Copyright Transfer Form is signed by the guarantor at original submission.

Abstract (applied to original articles, review articles, brief reports, and case reports)

☐ A structured abstract with the headings of Objective, Methods, Results, and Conclusion (A nonstructured abstract for case reports) must succinctly describe the paper.

☐ At the end of the abstract, relevant keywords are listed.

References

☐ All references have been checked for accuracy and completeness.

☐ Cite only references which are quoted in the text. Limit the number of references 40 for original articles, 10 for brief reports and case reports, and 5 for images in this issue and letters to the editor.

☐ Are numbered consecutively in the order they are cited in the text; all listed references have been cited in the text.

☐ Do NOT parenthesize the superscript numerals, and hyphenate (-) when citing 3 or more references in consecutive order.

☐ The format prescribed by the "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" has been followed. Examples provided under Instructions for Authors have been uploaded.

☐ List all authors when there are 6 or fewer; when there are 7 or more, list the first 6, followed by "et al."

☐ Journal names should be abbreviated according to the format listed in the Index Medicus. If the journal is not listed in the Index Medicus, refer to the list of title word abbreviations by the ISSN network (http://www.issn.org/2-22660-LTWA.php).

Figure Legends

☐ Figure legends are provided for each figure.

☐ Figure legends are numbered and presented together in numeric order following reference page(s).

Tables

☐ Each table is headed by a title and numbered in Arabic numerals on a separate page.

☐ The title of the tables should be written in phrases, and capitalized the first letter of the first word.

☐ There are less than 5 tables in the text of original articles.

☐ Tables are cited in numeric sequence in the text.

Figures

☐ Each is numbered with an Arabic numeral and cited in numeric sequence in the text.

☐ Photographs of recognizable persons should be accompanied by a signed release from the patient or legal guardian authorizing publication. Masking eyes to hide identity is not sufficient.

Credits & Permissions

☐ In addition to the notice of informed consent and releases to publish photographs of recognizable persons, submit with the manuscript written permission to use non-original material (quotations exceeding 100 words, any table or illustration) from copyright holder of the original. No article will be accepted as a submission to Archives without all required permissions. Credit the source in a text or table footnote or in a legend.

A more complete description of each item that must be checked is provided under the appropriate heading in the Instructions for Authors.

I have reviewed this Checklist and have complied with its requirements.

Every author took a certain role and made contribution to the study and the manuscript. In case of publication, I agree to transfer all copyright ownership of the manuscript to the Korean Academy of Rehabilitation Medicine to use, reproduce, or distribute the article.

☐ Agree ☐ Disagree

Submission Application & Copyright Transfer Form

arm
Annals of Rehabilitation Medicine

Date _____

Title of Manuscript _____

In signing this form:

1. The authors warrant that the article is original work which has not been published before, and is not being considered for publication elsewhere in its final form.
2. The authors concede that the article will be reviewed and may be edited by the Korean Academy of Rehabilitation Medicine (KARM).
3. The authors agree to transfer copyright of the article to the KARM upon publication in the Annals of Rehabilitation Medicine.

CORRESPONDING AUTHOR

Name _____ Affiliation _____

E-mail _____ TEL _____ FAX _____

Address _____

	Author's name	Signature	Degree(s)	Affiliation
01				
02				
03				
04				
05				
06				
07				
08				
09				