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Original Article

Intrathecal Baclofen Injection Efficacy for Spasticity Management in Patients With Stroke: A Meta-Analysis

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HIGHLIGHTS

- Intrathecal baclofen injection could help the management of spasticity after stroke.
- Intrathecal baclofen injection could improve of thegait speed for spastic stroke.
- Intrathecal baclofen injection may be considered for severe spasticity.

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Intrathecal Baclofen Injection Efficacy for Spasticity Management in Patients With Stroke: A Meta-Analysis

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Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Although intrathecal baclofen injections have been used for spasticity management regarding stroke, spinal cord injury, and central nervous system diseases, their relative efficacy is controversial. This systematic review scoured 3 multinational electronic databases (Cochrane Library, MEDLINE, and Embase) to isolate relevant studies. We analyzed non-randomized studies and randomized control trials (RCTs) with direct comparisons against other spasticity management interventions for adult stroke patients. Risk of Bias (RoB) and the Risk of Bias Assessment tool for Non-randomized Studies evaluations were implemented with Cochrane's RoB tool. Meta-analysis was performed with Revman 5.4, and evidence validity was assessed with the Grading of Recommendations, Assessment, Development, and Evaluations method. Lastly, the intrathecal baclofen injection meta-analysis included 2 RCTs and 7 non-RCTs for assessing spasticity and 4 non-RCTs to measure gait velocity. Based on this data, intrathecal baclofen injection significantly impacted spasticity and gait speed. Thus, intrathecal baclofen injection can potentially treat severe spasticity unresponsive to conventional spasticity therapy. Furthermore, clinicians must consider individual patient characteristics and conditions when contemplating intrathecal baclofen injection for spasticity intervention.

Keywords: Stroke; Muscle Spasticity; Intrathecal Injection; Baclofen

INTRODUCTION

Spasticity is a velocity-dependent muscle tone increase in tonic stretch reflexes with hypertonic movements [1] caused by a central nervous system injury within the brain or spinal cord. Spasticity influences activity of daily living dependently in patients with stroke, and current treatments comprise oral medications and interventional procedures [2]. Oral medications can reduce spasticity by employing agents that affect central and peripheral systems, including baclofen, clonidine, tizanidine, benzodiazepines, and dantrolene. Interventional procedures inject focal botulinum toxin, phenol, or alcohol agents. Also, intrathecal baclofen pump can be a treatment option to control spasticity. Surgical treatments may also implement selective dorsal rhizotomy and neurectomy in the proper conditions [3].

Intrathecal baclofen injections have been utilized since 1984 to treat uncontrolled spasticity following stroke through continuous baclofen infusions from a subcutaneously implanted pump [4]. According to the 2016 Korean Standard Treatment Guidelines for Stroke Rehabilitation [5], appropriate posture, joint exercise, and stretching are recommended for preventing and treating spasticity. Serial casting, oral tizanidine or baclofen administrations, botulinum toxin injections, and repeated transcranial magnetic stimulations are advised for spasticity control in selective patients [6].

The 2016 Korean Standard Practice Guidelines for Spasticity Treatment do not address intrathecal baclofen injections. However, guidelines overseas recommend intrathecal baclofen injection for spasticity management when other treatments are ineffective [6,7]. Therefore, this study aimed to verify whether intrathecal baclofen injection improves spasticity.

MATERIALS AND METHODS

Study protocol registration

This study was designed during prior systematic steering meetings to develop Clinical Practice Guidelines for Stroke Rehabilitation in Korea. Part 1: Rehabilitation for Motor Function (2022).

Review criteria (patient, intervention, comparison, outcome [PICO])

1. Patient (P): Stroke patients 18 or older with cerebral infarction and hemorrhage.
2. Intervention (I): Intrathecal baclofen injection.
3. Comparison (C): Compared to other spasticity management interventions.
4. Outcomes (O): Spasticity (assessing Ashworth Scale and gait velocity).

Search and selection

The literature search utilized 3 multinational electronic databases: Cochrane Library, MEDLINE, and Embase. The search's scope did not specify a start date, but the end date was February 28, 2022, to ensure a comprehensive literature search. Searches were conducted using MeSH terms for MEDLINE, Cochrane Library and Emtree terms for Embase, and natural language to increase sensitivity (**Supplementary Table 1**). The 2 authors independently assessed and selected the relevant studies. Then, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was followed, including randomized control trials (RCTs) and non-RCTs with direct comparisons against other spasticity management strategies. Studies that did not meet PICO criteria or were written in a language other than English or Korean were excluded.

Risk of Bias (RoB) and Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) assessment

Two clinical specialists individually evaluated the final selected literature using a screening evaluation tool for each key question. Cochrane's Risk of Bias (RoB 1.0) was applied for RCT, while the Risk of Bias Assessment tool for Non-randomized Study 2.0 (RoBANS 2.0) was implemented for non-RCT studies. Evaluations were reviewed and discussed until a consensus was reached.

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Statistical analysis of evidence

Meta-analysis was conducted with Reviewer Manager Software 5.4 (Cochrane Collaboration, Oxford, UK) for data evaluation, and statistical analyses for continuous variables were performed. I^2 indicated the total variation percentage across trials to estimate heterogeneity; an I^2 value greater than 50.0% was considered substantial heterogeneity. For meta-analysis, studies were split into intrathecal baclofen injection intervention and conventional spasticity treatment groups. The meta-analysis model implemented an inverse variance method for continuous outcome variables. The 95% confidence intervals (CIs) of the standardized mean difference (SMD) and mean difference (MD) regarding intrathecal baclofen injection efficacy were determined in all analyses. To be included, zeroes within the SMD indicated no significant difference between interventions.

Assessment of evidence certainty

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method verifies evidence certainty as high, moderate, low, or very low. Depending on the study's design, evidence certainty is first determined as 'high.' Whether the evidence level can be lowered is determined by the guidelines. The 2 authors independently conducted these processes and discussed the evidence until a consensus was reached.

RESULTS

Study selection

This meta-analysis only assessed studies directly comparing intrathecal baclofen injections and conventional spasticity treatments for stroke patients. After a comprehensive literature search, 1,631 studies were selected. Two authors independently screened the literature following the PRISMA method (**Fig. 1**); 3 RCTs and 8 non-randomized studies were assessed. Two of the 3 RCTs presented results from a sub-analysis based on one study, whereas only one considered the spasticity improvement degree. Lastly, 2 RCTs were analyzed.

Study characteristics

Only 2 RCTs were selected because 2 research papers published by Creamer were from one RCT [8,9]. A study published by Meythale reported that intrathecal baclofen injection in patients with stroke maintained spasticity reduction [10]. Similarly, Creamer et al.'s study [9] determined that intrathecal baclofen injection in patients with stroke exhibited improved therapeutic effects compared to oral medications. Furthermore, spasticity was reduced in both upper and lower extremities when combined with physical therapy [9].

The non-randomized study implemented a meta-analysis on spasticity treatment effects and gait speed based on 8 studies [11-18]. However, the study by Reis et al. [15] was excluded as the comparative data were not clearly presented. Thus, spasticity fluctuations before and after intrathecal baclofen injection were analyzed in 7 studies, and gait speed changes were analyzed in 4. The selected studies' characteristics are presented in **Table 1**, and the analyzed RoB and RoBANS assessments are presented in **Fig. 2**.

Meta-analysis on intrathecal baclofen injection effects

Evidence summaries and GRADEs are displayed in **Table 2**, and the meta-analysis forest plots are presented in **Figs. 3** and **4**. The meta-analysis confirmed that intrathecal baclofen injection significantly impacted spasticity and gait speed.

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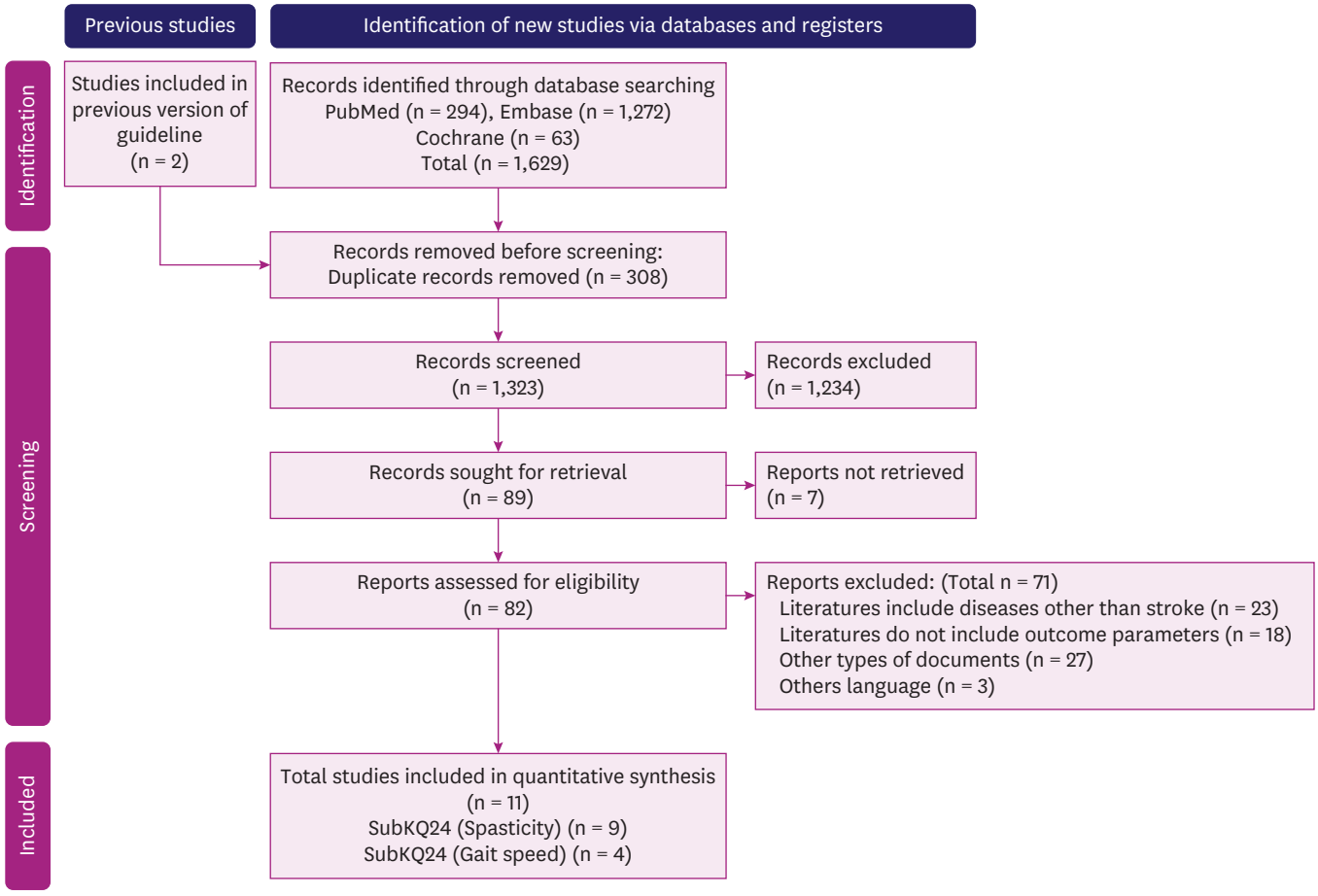

Fig. 1. Preferred reporting items for systematic reviews and the meta-analysis flow diagram for article selection.

Spasticity

The 2 analyzed RCTs indicated that intrathecal baclofen infusion could make the Ashworth Scale Score reduced and maintain spasticity reduction in both upper and lower limbs. The 7 non-RCTs analyzed the Ashworth Scale outcome measures, and the effect size was calculated using SMD. The result was 1.86 (95% CI, 1.39, 2.32) (**Fig. 3**). One study indicated that additional baclofen intrathecal injection doses may reduce spasticity further [16]. Thus, one grade was elevated as it indicated a positive dose-response gradient. The final evidence quality was of moderate grade.

Gait speed

Velocity predicated the outcome measures in 4 non-RCT analyses, and the effect size was calculated using SMD. The result was −0.41 (95% CI, −0.75, −0.08) (**Fig. 4**), and the evidence was low grade.

DISCUSSION

Canadian Stroke Best Practice Recommendations have recently suggested intrathecal baclofen for severe intractable, disabling, or painful spasticity treatments [7]. Based on our analysis, intrathecal baclofen injection significantly impacted spasticity and gait speed.

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Table 1. Study characteristics

1st author	Title	Journal	Year	Design	Intervention group	Intervention	Control group	Follow up	Outcome tool	Outcomes
Creamer et al. [8]	Effect of intrathecal baclofen on pain and quality of life in poststroke spasticity: A Randomized Trial (SISTERS)	*Stroke*	2018	RCT	ITB (n = 31)	Lioresal intrathecal	CMM (n = 29)	Week 6 (ITB arm only), month 3, month 6	1. Numeric Pain Rating Scale 2. EuroQol–5 dimensional 3 level utility score 3. Health status VAS score 4. SSQL 5. Patient satisfaction	Numeric Pain Rating Scale scores for actual pain (ITB vs. CMM: mean, −1.17 [SD, 3.17] vs. 0.00 [3.29]; median, −1.00 vs. 0.00; p = 0.0380) and least pain (mean, −1.61 [2.29] vs. 0.24 [3.07]; median, −1.00 vs. 0.00; p = 0.0136). EuroQol–5 dimensional 3 level utility scores (mean, +0.09 [0.26] vs. +0.01 [0.16]; median, +0.07 vs. 0.00; p = 0.0197). Increase from baseline to month 6 was observed in both treatment arms, with a slightly greater increase observed in ITB patients (mean change, +9.68 [20.42] for ITB and +4.40 [21.75] for CMM; p = 0.3807). The SS-QOL summary score, an increase from baseline to month 6 was observed in the ITB arm, whereas little change was observed in the CMM arm (mean changes, +0.26 [0.58] for ITB and +0.05 [0.58] for CMM; p = 0.2105).
Meythaler et al. [10]	Intrathecal baclofen for spastic hypertonia from stroke	*Stroke*	2001	RCT	Injection of 50 mg baclofen intrathecally (n = 11)	Intrathecal 50 μg baclofen	Injection of 1 mL normal saline intrathecally (n = 10)	Bolus 1, 2, 4, and 6 hr after injection for the limbs (extremities) Continuous 1-mon, 3-mon, 6-mon, 9-mon, and 12-mon intervals	1. The Ashworth (rigidity) score 2. Penn Spasm Frequency Scale 3. Reflex Scale	Bolus injection Lower extremity (affected) 1. Ashworth score from 3.3 ± 1.2 to 1.4 ± 0.7 (p = 0.0001) 2. Penn spasm frequency scale from 1.2 ± 1.2 to 0.1 ± 0.3 (p = 0.0224) 3. Reflex score from 2.1 ± 1.2 to 0.1 ± 0.5 (p < 0.0004) Upper extremity (affected) 1. Ashworth score from 2.8 ± 1.1 to 1.9 ± 0.8 (p < 0.0001) 2. Penn spasm frequency scale from 0.7 ± 1.0 to 0.2 ± 0.4 (p = 0.1544) 3. Reflex score from 2.1 ± 0.9 to 1.2 ± 0.9 (p = 0.0004) Continuous infusion of ITB Lower extremity (affected) 1. Ashworth score from 3.7 ± 1.0 to 1.8 ± 1.1 (p < 0.0001) 2. Penn spasm frequency scale from 1.2 ± 1.3 to 0.6 ± 1.0 (p = 0.4282) 3. Reflex score from 2.4 ± 1.3 to 1.0 ± 1.3 (p < 0.0001) Upper extremity (affected) 1. Ashworth score from 3.2 ± 1.1 to 1.8 ± 0.9 (p < 0.0001) 2. Penn spasm frequency scale from 0.7 ± 1.0 to 0.3 ± 0.8 (p = 0.8685) 3. Reflex score from 2.4 ± 0.8 to 1.5 ± 1.2 (p = 0.3337)
Creamer et al. [9]	Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS)	*J Neurol Neurosurg Psychiatry*	2018	RCT	ITB (n = 31)	Lioresal intrathecal	CMM (n = 29)	Week 6 (ITB arm only), month 3, month 6	1. Mean AS score (Lower extremity) 2. Mean AS score (Upper extremity) 3. FIM 4. Adverse events	ITB 1. Average AS score in the lower extremity of the affected side intention-to-treat −0.99 ± 0.75 (p = 0.0140); −0.667 (95.1% CI, −1.0000 to −0.1667) Per protocol −1.09 ± 0.63 (p = 0.0592); −0.667 (95.1% CI, −1.1667 to 0.0000) Modified intention-to-treat −1.11 ± 0.68 (p = 0.0019); −0.667 (95.1% CI, −1.1667 to −0.3333) intention-to-treat completers −1.01 ± 0.75 (p = 0.0240); −0.667 (95.1% CI, −1.0000 to −0.1667) 2. Average AS score in the upper extremity of the affected side intention-to-treat −0.66 ± 0.59 (p = 0.0042); −0.600 (95% CI, −1.0000 to −0.2000) Per protocol −0.64 ± 0.58 (p = 0.0494); −0.600 (95% CI, −1.0000 to 0.0000) 3. Baseline FIM 89.23 ± 28.76, 6 mon FIM 2.68 ± 10.31 (p = 0.0540) Baseline FIM motor 59.77 ± 24.96, 6 mon FIM motor 2.20 ± 8.90 (p = 0.0964) Baseline FIM cognition 24.45 ± 7.66, 6 mon FIM cognition 0.48 ± 3.92 (p = 0.2569)

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Table 1. (Continued) Study characteristics

1st author	Title	Journal	Year	Design	Intervention group	Intervention	Control group	Follow up	Outcome tool	Outcomes
										CMM 1. Average AS score in the lower extremity of the affected side intention-to-treat -0.43 ± 0.72 (p = 0.0140); −0.667 (95.1% CI, −1.0000 to −0.1667) Per protocol −0.48 ± 0.82 (p = 0.0592); −0.667 (95.1% CI, −1.1667 to 0.0000) Modified intention-to-treat −0.39 ± 0.71 (p = 0.0019); −0.667 (95.1% CI. −1.1667 to −0.3333) intention-to-treat completers −0.47 ± 0.73 (p = 0.0240); −0.667 (95.1% CI, −1.0000 to −0.1667) 2. Average AS score in the upper extremity of the affected side intention-to-treat −0.17 ± 0.70 (p = 0.0042); −0.600 (95% CI, −1.0000 to −0.2000) Per protocol −0.22 ± 0.78 (p = 0.0494); −0.600 (95% CI, −1.0000 to 0.0000) 3. Baseline FIM 96.10 ± 19.45, 6 mon FIM −2.58 ± 11.00 (p = 0.0540) Baseline FIM motor 66.45 ± 14.96, 6 mon FIM motor −0.96 ± 8.14 (p = 0.0964) Baseline FIM cognition 29.66 ± 7.41, 6 mon FIM cognition −1.62 ± 4.92 (p = 0.2569) Treatment-emergent adverse events occurred more frequently in the ITB-I group (24/25 [96%] patients, 149 events) than in the CMM+non implanted group (22/35 [63%] patients, 77 events). Fifty-eight treatment-emergent serious adverse events occurred: 34 events for 12/25 (48%) patients in the ITB-I group and 24 for 10/35 (29%) patients in the CMM+non-implanted group
Stokic et al. [18]	Comparison of clinical and neurophysio-logic responses to intrathecal baclofen bolus administration in moderate-to-severe spasticity after acquired brain injury	*Arch Phys Med Rehabil*	2005	Non-RCT	ITB (n = 30)	Single 50 μg ITB bolus	None	Before and at 2, 4, and 6 hr	1. Lower extremity AS score 2. H/M ratio 3. Abductor hallucise F wave 4. F/M ratio	1. Ashworth score on the more involved side decreased from 2.4 ± 0.7 at baselline to 1.5 ± 0.6 and 1.4 ± 0.6 at 4 and 6 hr ($p < 0.001$). 2. H/M ratio decreased bilaterally (more involved side 62.% ± 28% to 14% ± 19%; less involved side 59% ± 26% to 11% ± 20%, $p < 0.001$). 3. Fwave persistence decreased on the more involved side (86% ± 17% to 75% ± 13%, $p < 0.05$). 4. No changes in F/M ratio. 5. No correlation among the outcome measures before or after the ITB bolus injection.
Horn et al. [12]	Effect of intrathecal baclofen bolus injection on temporo-spatial gait characteristics in patients with acquired brain injury	*Arch Phys Med Rehabil*	2005	Non-RCT	ITB (n = 28)	A 50-μg ITB bolus injection	None	Before and at 2, 4, and 6 hr	1. AS scores 2. Selfselected gait velocity 3. Stride length 4. Cadence 5. Step length symmetry 6. Step width 7. Percentage of single support on the more involved side	1. Mean velocity increased significantly from 41 ± 26 cm/s at baseline to 47 ± 31 cm/s at the time of peak response ($p < 0.001$). 2. There was a significant correlation between baseline velocity and peak change in velocity after ITB bolus injection ($r = 0.39$, $p < 0.05$). 3. There was a significant increase in stride length from 69 ± 24 to 74 ± 27 cm ($p < 0.05$) Cadence also increased, from 63 ± 30 to 68 ± 34 strides/min; however, this change was not statistically significant. 4. Step width decreased from 21.5 ± 4.2 to 18.8 ± 4.8 cm at the time of peak response ($p < 0.001$). 5. The 16 subjects increased velocity after ITB, percentage in single support increased in 9 and was unchanged in 7. Five patients decreased valocity, percentage in single support decreased in 4 and was unchanged in 1. Seven patients with unchanged walking speed, percentage in single support was also unchanged in 6, and decreased in 1.

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Table 1. (Continued) Study characteristics

1st author	Title	Journal	Year	Design	Intervention group	Intervention	Control group	Follow up	Outcome tool	Outcomes
										6. Average lower-extremity AS score on the more involved side ranged from 1.0 to 2.8 (2.0 ± 0.5). After ITB bolus, the Ashworth score decreased to 1.6 ± 0.4 at 2 hr, to 1.4 ± 0.4 at 4 hr, and to 1.3 ± 0.3 at 6 hr ($p < 0.001$). 7. Significant inverse correlations at baseline between average lower-extremity AS and velocity ($r = 0.50$, $p < 0.01$), stride length ($r = 0.46$, $p < 0.05$), cadence ($r = 0.54$, $p < 0.005$), and percentage in single support ($r = 0.57$, $p < 0.005$). Baseline velocity correlated significantly with Ashworth score only in the hip extensors ($r = 0.51$, $p < 0.05$) and knee extensors ($r = 0.44$, $p < 0.05$).
Francisco et al. [11]	Improvement in Walking Speed in Poststroke Spastic Hemiplegia After Intrathecal Baclofen Therapy: A Preliminary Study	*Arch Phys Med Rehabil*	2003	Non-RCT	Implantation of ITB pump (n = 10)	The procedure involved bolus injection of 50 μg of baclofen via a lumbar puncture at the L2-3 interspace.	None	Follow-up interval that averaged 8.9 mon	1. Walking speed 2. Functional walking category 3. MAS scores 4. Functional mobility score	1. Mean walking speed over 50 ft was 15.4 ± 14.4 cm/s (range, 0.6–50.1 cm/s). The increase in walking speed was statistically significant ($z = 2.80$, $p = 0051$). 2. The functional mobility score improved in 6 of 10 participants, with the mean increase being 2.7 ± 2.9 points (range, 7–10). This improvement was statistically significant ($z = 2.20$, $p = 0277$). 3. Nine realized a spasticity reduction of at least 1 point in the mean lower-extremity MAS score, with the mean reduction being 1.6 ± 0.5 points (range, 0.9–2.3) and statistically significant ($z = 2.80$, $p = 0051$). 4. Three participants improved their functional walking category at the follow-up assessment.
Rémy-Néris et al. [16]	Intrathecal baclofen in subjects with spastic hemiplegia: assessment of the antispastic effect during gait	*Arch Phys Med Rehabil*	2003	Non-RCT	Implantation of ITB pump (n = 7)	Bolus of 50 μg to 100 μg baclofen by lumbar puncture	None	48-hr washout period using the appropriate dose of baclofen	1. Triceps and Quadriceps Ashworth scores 2. Gait analysis at preferred and maximal speed	1. Ashworth score at triceps and quadriceps data for the hemiplegic side was significantly reduced (mean quadriceps, 3.3 ± 0.8 vs. 1.3 ± 0.5; mean triceps, 3.4 ± 1.6 vs. 2.1 ± 0.9). 2. The preferred gait velocity increased significantly after ITB (pre-ITB, 0.53 ± 0.29 m/s; post-ITB, 0.60 ± 0.34). The maximum gait speed increased (pre-ITB, 0.82 ± 0.4 m/s; post-ITB, 0.93 ± 0.45 m/s) but was not statistically significant. The mean increase in maximum gait speed was 0.15 ± 0.08 m/s. The increase in walking speed correlated with a significant increase in stride length at both preferred (0.05 ± 0.03 m) and maximal walking speeds (0.11 ± 0.09 m). The stride frequency did not change significantly. The minimal knee flexion at maximal walking speed increased significantly after ITB (pre-ITB, 1.1° ± 5.9°; post-ITB, 3.1° ± 7.7°). 3. In Preferred walking speed, the slope of the moment-angle curve during triceps stretching was significantly reduced (0.4 ± 0.5 vs. 0.2 ± 0.3). In Maximal walking speed, maximal ankle dorsiflexion and maximal ankle flexion velocity was significantly increased (10.3° ± 11.4° vs. 13.0° ± 11.1°; -1.1° ±5.9° vs 3.1° ± 7.7°).
Reis et al. [15]	Intrathecal baclofen Infusion Pumps in the Treatment of Spasticity: A Retrospective Cohort Study in a Portuguese Centre	*Acta Med Port*	2019	Non-RCT	ITB infusion pumps in 155 patients (n = 155)	ITB infusion pumps	None	Follow-up period (1997–2015)	1. AS 2. Penn's scales 3. Katz index 4. Patients' global satisfaction	1. There was a significant improvement comparing the pre [Ash and Penn 4 (3 – 4)] to the postoperative [Ash 1 (1 – 2) and Penn 1 (0 – 1)], $p < 0.001$ for all subgroups of diagnoses. 2. Pre-operative Katz Index in 107 patients, and 43% (n = 46) were totally dependent, 39% (n = 42) partially dependent and 18% (n = 19) independent. 3. All patients were satisfied with the treatment (all answers ≥ 5).

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Table 1. (Continued) Study characteristics

1st author	Title	Journal	Year	Design	Intervention group	Intervention	Control group	Follow up	Outcome tool	Outcomes
Ivanhoe et al. [13]	Intrathecal baclofen management of poststroke spastic hypertonia: implications for function and quality of life	*Arch Phys Med Rehabil*	2006	Non-RCT	Stroke patient with ITB pump implantation (n = 72)	50 μg bolus of baclofen via lumbar puncture into the intrathecal space	None	Screening trial follow-up at 3 and 12 mon	1. AS scores 2. FIM 3. SIP 4. MMT	1. FIM scores improved significantly and increased 3.00 ± 7.69 (p = 0.001) from baseline to 3 mon and 2.86 ± 10.13 (p = 0.017) from baseline to 12 mon. FIM total score improved significantly from a baseline of 85.62 and increased 3.74 ± 8.15 (p = 0.002) from baseline to 3 mon and 3.47 ± 11.26 (p = 0.029) from baseline to 12 mon. 2. Mean SIP scores significantly improved 3.24 ± 9.10 (p = 0.003) at 3 mon and 4.32 ± 8.73 at 12 mon (p = 0.001). As compared with baseline, at 3 mon, the physical and psychosocial domains improved 2.24 ± 9.89 (p = 0.055) and 4.51 ± 12.30 (p = 0.002), whereas at 12 mon improvements were seen of 4.55 ± 10.65 (p = 0.001) and 4.91 ± 11.62 (p = 0.001). 3. Combined average AS score of the upper and lower limbs decreased significantly by 1.27 ± 0.76 (p = 0.001) at 3 mon and 1.39 ± 0.73 (p = 0.001) at 12 mon from baseline. A significant decrease in AS score on the affected side of 0.97 ± 0.87 (p = 0.001) at 3 mon and 1.11 ± 0.90 (p = 0.001) at 12 mon for upper extremities. A significant decrease in AS score for the lower extremities on the affected side of 1.44 ± 0.91 (p = 0.001) at 3 mon and 1.52 ± 0.96 (p = 0.001) at 12 mon. 4. MMT were not significant.
Kofler et al. [14]	Limitations of intrathecal baclofen for spastic hemiparesis following stroke	*Neurorehabil Neural Repair*	2009	Non-RCT	ITB bolus application (n = 5) continuous infusion via a temporary catheter system (n = 3)	ITB Bolus injection/ continuous injection	None	Baseline and following the highest dosage of ITB	1. MAS 2. MRC scale 3. Reflex scale 4. Modified EU Walking Scale 5. Revermead-visual Gait Assessment score	1. MAS scores across all 6 joints tested from 3.69 ± 0.62 to 2.50 ± 0.68 (p < 0.001). 2. MAS scores in the lower extremities (from 3.71 ± 0.62 to 2.38 ± 0.71; p < 0.001). 3. MAS scores in the upper extremities (from 3.67 ± 0.64 to 2.63 ± 0.65, p < 0.001). 4. Reflex scores from 3.6 ± 0.6 at baseline to 2.1 ± 0.6 during ITB application (p < 0.001). 5. No significant difference was observed between patients receiving bolus-ITB vs. continuous-ITB with regard to reduction of MAS, Reflex, or MRC scores (p > 0.1). 6. Modified EU Walking Score was significantly reduced by ITB from 3.5 ± 1.7 at baseline to 2.3 ± 1.4 during ITB application (p = 0.023). 7. Rivermead Visual Gait Assessment score was no significant change before 31.8 ± 8.5 and during ITB application 35.4 ± 6.9 (p = 0.73).
Schiess et al. [17]	Prospective 12-month study of intrathecal baclofen therapy for poststroke spastic upper and lower extremity motor control and functional improvement	*Neuromodulation*	2011	Non-RCT	Hemiplegic stroke patient with ITB pump implantation (n = 26)	ITB trials using 50 μg of baclofen	None	12 mon post ITB	1. MAS 2. MMT 3. Gait distance/ velocity 4. FIM 5. SSQL 6. Upper extremity manual activity log 7. VAS	1. Spastic tone in the lower extremity measured at pre-implant MAS = 2.21 ± 0.76 was reduced significantly when compared at 12 mon post ITB therapy with MAS = 1.51 ± 0.66; p < 0.001. Spastic tone in the upper extremity measured at pre-implant MAS = 2.4 ± 0.6 was reduced significantly when compared at 12 mon post ITB therapy with MAS = 1.8 ± 0.05; p < 0.01. 2. Strength in the lower extremity measured at pre-implant MMT = 1.78 ± 0.92 was increased significantly when compared at 12 mon post ITB MMT = 2.95 ± 1.15; p < 0.0001. Strength in the upper extremity measured at pre-implant MMT = 1.7 ± 1.1 was increased significantly when compared at 12 mon post ITB MMT = 2.6 ± 1.2; p < 0.05. 3. All FIM activities improved significantly after 12 mon post ITB therapy except bed mobility and dressing of the lower body. 4. Velocity at pre-implant 0.55 ± 0.26 m/sec compared with 0.77 ± 0.36 m/sec at 12 mon post ITB (p < 0.05) and 6-min walk distance preimplant of 558 ± 254 ft compared with 746 ± 368 ft at 12 mon post ITB (p < 0.05).

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Table 1. (Continued) Study characteristics

1st author	Title	Journal	Year	Design	Intervention group	Intervention	Control group	Follow up	Outcome tool	Outcomes
										5. There was no significant change in the domains of language, energy, mood, and vision. Pain as measured on the VAS ranged from 0 to 8 with a mean of 2.01 ± 2.34 at pre-implant and included 11 patients who rated themselves with 0 pains. At 12 mon post ITB therapy, the VAS pain range was reported as 0–7 with amean of 1.29 ± 2.03 and included 14 patients who rated themselves with 0 pains. 6. The function of the affected upper extremity was significantly improved in both gross motor and fine motor activities. 7. There was a weak negative correlation between MAS and MMT, r = −0.38. amount of use was positively correlated with thequality of movement, r = 0.98.

Gray shading indicates papers excluded from the meta-analysis.
RCT, randomized controlled trial; ITB, intrathecal baclofen; QoL, quality of life; CMM, conventional medical management; AS, Ashworth scale; FIM, functional independence measure; CI, confidence interval; H/M ratio, Hoffmann reflex/M-wave amplitude ratio; F/M ratio, F-wave/M-wave amplitude ratio; MAS, Modified Ashworth Scale; SIP, sickness impact profile; MRC, Medical Research Council; SSQL, Stroke-Specific Quality of Life Scale; MMT, Manual Muscle Test; VAS, Visual Analog Scale.

Table 2. Evidence summaries and GRADEs

Outcomes	No. of participants (No. of studies)	GRADE certainty of evidence	Statistical method	Effect estimated	Design
Spasticity	51 (2)	High	Narrative analysis	1. Meythaler et al. [8]. Intrathecal infusion of baclofen is capable of maintaining a reduction in the spastic hypertonia. 2. Creamer et al. [9]. Intrathecal delivery of baclofen provides an improved therapeutic effect versus conventional oral medications, with a reduction of the Ashworth scale score in both upper and lower limbs when used in conjunction with physiotherapy.	RCT
Spasticity	174 (8)	Moderate	Std. mean difference (IV, Random, 95% CI)	1.16 (1.03, 1.30)	Non-RCT
Gait velocity	71 (4)	Low	Std. mean difference (IV, Random, 95% CI)	−13.15 (−23.40, −2.91)	Non-RCT

GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; RCT, randomized controlled trial; Std, standard; IV, inverse variance; CI, confidence interval.

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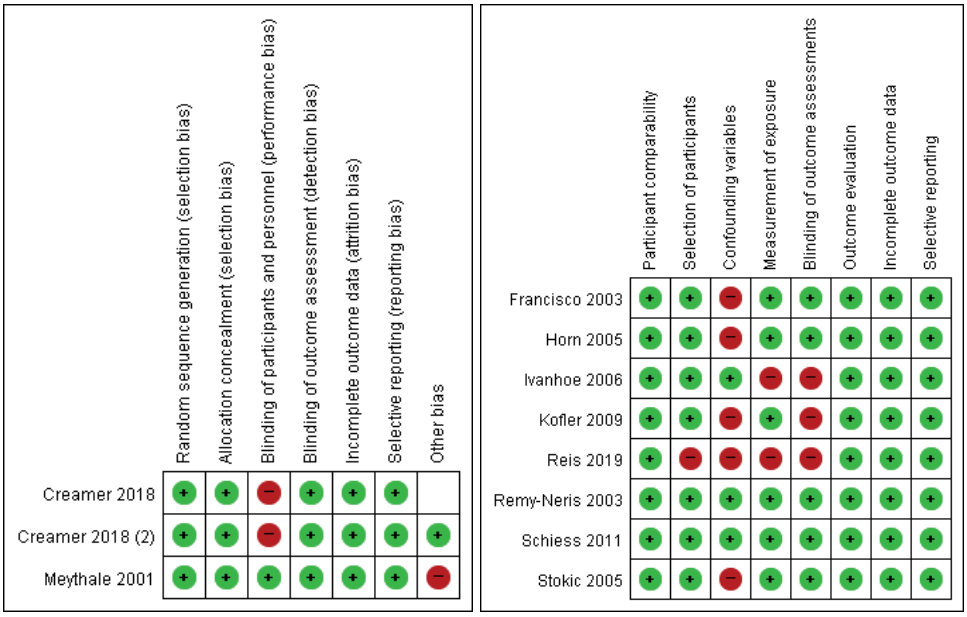

Fig. 2. RoB and RoBANS for the included studies. The included studies were independently assessed and agreed upon by the 2 authors using Cochrane's RoB 1.0 and RoBANS 2.0.
RoB, Risk of Bias; RoBANS, Risk of Bias Assessment tool for Non-randomized Studies.

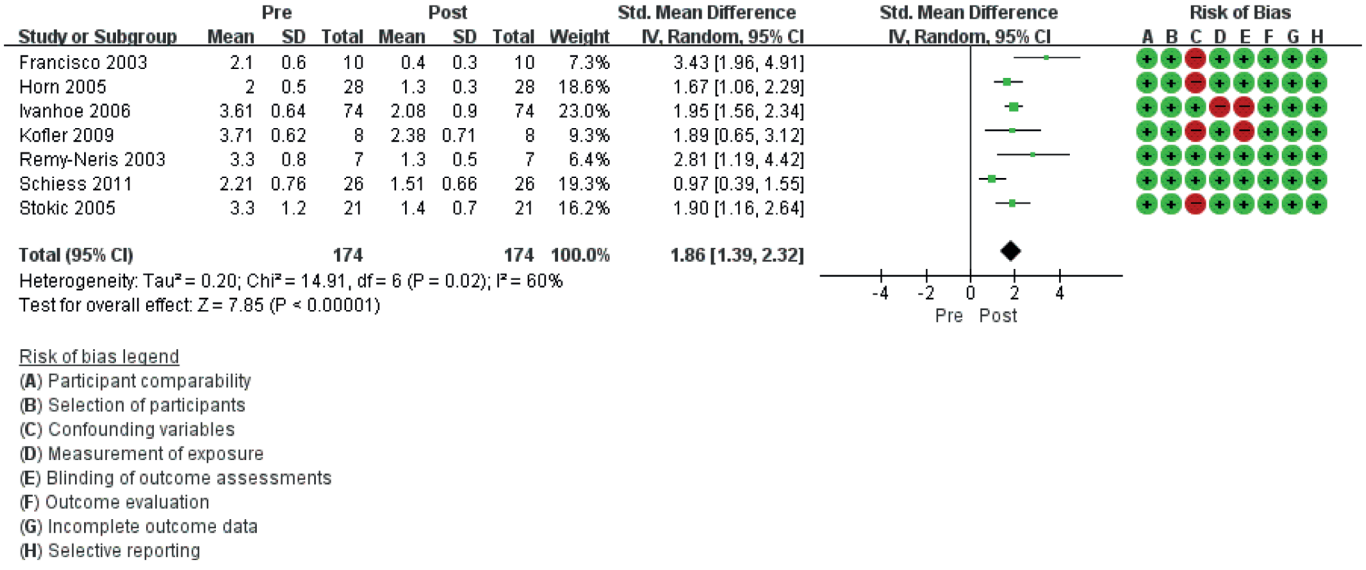

Fig. 3. Spasticity forest plots for non-randomized control trials.
Std., standard; SD, standard deviation; IV, inverse variance; CI, confidence interval.

This meta-analysis revealed that intrathecal baclofen injection reduced spasticity and gait disturbance in patients with spasticity after stroke, as lowering spasticity improved gait function, particularly gait velocity. These results support using intrathecal baclofen injection for patients with uncontrolled spasticity after stroke as an effective spasticity management strategy. However, the following clinical considerations should be contemplated:

1. Benefits and harm: There are complication risks and inconveniences when periodically replenishing drugs after inserting the device into the human body. However, this treatment manages spasticity in stroke patients unresponsive to other spasticity management options or severe spasticity.

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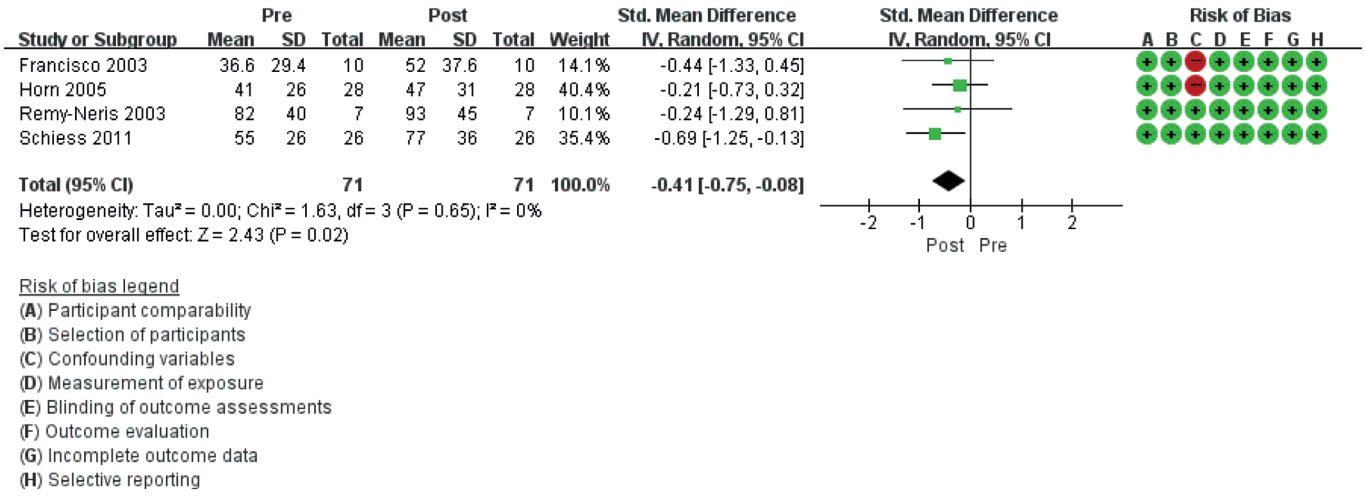

Fig. 4. Gait speed forest plots for non-randomized control trials.
Std., standard; SD, standard deviation; IV, inverse variance; CI, confidence interval.

2. Values and preferences: Intrathecal baclofen injection has yet to become a well-known treatment. However, clinicians should consider its medical benefits rather than patient choice, as patients with severe spasticity unresponsive to conventional spasticity management may benefit from this therapeutic method.
3. Obstacles, facilitating factors, and overcoming them: Patients must consider the costs of inserting the device into the body, completing the procedure, and injecting the necessary drugs. Patients with stroke who are candidates for intrathecal baclofen injection may require medical insurance support.
4. Resource (cost): Procedure and equipment costs for device insertion are expensive, and the prerequisites necessary for medical insurance coverage may be challenging to acquire. The Health Insurance Review and Assessment Service's standards for medical insurance benefits are: (1) when appropriate pain treatments (i.e., medication, nerve blocks) over 6 months are determined as ineffective, severe pain (a Visual Analog Scale [VAS] pain score of 7 or higher) persists, and incurable pain is apparent; (2) uncontrolled cancer pain (a VAS pain score of 7 or higher) despite oral administration of high morphine doses (200 mg per day) or other narcotic analgesics of equivalent potency and when life expectancy is expected to exceed one year; (3) cancer pain (a VAS pain score of 7 or higher) that cannot be treated due morphine or other narcotic analgesic side effects and a life expectancy of more than one year; and (4) when, despite appropriate spasticity management (i.e., medication), patients who continue to suffer with spasticity scale (Modified Ashworth Scale [MAS]) measurements higher than grade 3 for lower extremities or grade 2 for upper extremities but can improve by more than one MAS grade following intrathecal baclofen injection (Notice No. 2014-107).

In addition, costs covered by medical insurance are as follows: (1) pump implantation (relative value score of 4,598.47), (2) pump drug refill (relative value score of 541.77), (3) pump reprogramming (relative value score of 305.38), (4) catheter exchange (relative value score of 3,558.10), (5) pump exchange (relative value score of 3,186.40), and (6) catheter and pump removal (relative value score of 2,438.69).

This study does acknowledge limitations due to insufficient research results regarding complication incidence; therefore, caution is necessary when interpreting and analyzing these

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results. When evaluating evidence certainty using the GRADE method for prominent outcome indicators, there was no significant RoB, and inconsistency, indirectness, and publication bias were not observed in any outcome indicators. Evidence certainty was high for RCTs and moderate for non-RCT studies. The final evidence certainty was determined as moderate.

Moderate-level evidence indicates that intrathecal baclofen injection is effective for spasticity management and may be considered for treating severe spasticity unresponsive to conventional therapies. Furthermore, clinicians must consider individual patient characteristics and conditions when contemplating intrathecal baclofen injection for spasticity intervention.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Search terms and strategies

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