



## Original Research

# Comparative Effectiveness of Botulinum Toxin Injections and Extracorporeal Shockwave Therapy for Post-Stroke Spasticity: A Systematic Review and Network Meta-Analysis

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## ABSTRACT

**Background:** The anti-spasticity efficacy of botulinum toxin (BoNT) injection has been well established for patients with chronic stroke; however, extracorporeal shock wave therapy (ESWT), i.e. focused shockwave (FSW) and radial shockwave (RSW), has recently been applied. We aimed to investigate the comparative effectiveness of BoNT vs. ESWT in the reduction of spasticity among stroke survivors.

**Methods:** PubMed, EMBASE, MEDLINE and Cochrane CENTRAL were searched from the earliest record to September 2021 for randomized controlled trials. Weighted mean differences (WMDs) on the reduction of the Modified Ashworth Scale before or at the 6th post-treatment week (short-term) and between the 7th and 12th weeks (mid-term) after the intervention were calculated. Ranking probabilities of the WMD were simulated to determine which treatment had the potential to possess the best effectiveness. inplasy.com registration: INPLASY202170018.

**Findings:** A total of 33 studies comprising 1,930 patients were enrolled. The network meta-analysis revealed that BoNT injections, FSW and RSW were better in spasticity reduction than the control treatment(s) at the short term, with WMDs of -0.69 (95% CI, -0.87 to -0.50), -0.36 (95% CI, -0.69 to -0.03) and -0.62 (95% CI, -0.84 to -0.40), respectively. Likewise, mid-term effects of BoNT injections, FSW and RSW also revealed superiority, with WMDs of -0.44 (95% CI, -0.62 to -0.26), -0.74 (95% CI, -1.26 to -0.23) and -0.79 (95% CI, -1.07 to -0.51), respectively. Ranking probability analysis revealed that RSW had the highest probability of being the best treatment for spasticity reduction at the short-term (62.2%) and mid-term (72.3%) periods during the follow up.

**Interpretation:** BoNT injections and ESWT are effective in alleviating post-stroke spasticity at the mid-term. The effectiveness of ESWT was comparable to BoNT injections, and RSW had the potential to be the best treatment for spasticity reduction among the three treatment options. More prospective trials incorporating head-to-head comparisons of BoNT injections vs. ESWT are needed to validate the role of ESWT in reducing post-stroke spasticity.

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**Abbreviation:** BoNT, botulinum toxin; RSW, radial shockwave; FSW, focused shockwave; WMD, weighted mean difference; CI, confidence interval; ESWT, extracorporeal shock wave therapy; MAS, modified Ashworth scale

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## 1. Introduction

Hypertonia is a common muscle tone abnormality following stroke, while spasticity is one of the components that manifests as a velocity-dependent increase in muscle tone along with enhanced tendon jerks [1]. An imbalance in supraspinal inhibitory and

## Research in Context

### *Evidence before this study*

The anti-spasticity efficacy of botulinum toxin (BoNT) injection has been well established for patients with chronic stroke; however, extracorporeal shock wave therapy (ESWT), i.e. focused shockwave (FSW) and radial shockwave (RSW), has recently been applied. No systematic reviews and meta-analyses have been conducted to compare the clinical effectiveness between BoNT injections and ESWT for the treatment of post-stroke spasticity.

### *Added value of this study*

Based on 33 randomized controlled trials with 1,930 participants, BoNT injections, FSW and RSW were effective in alleviating post-stroke spasticity at least for 12 weeks. Ranking probability analysis revealed that RSW had the highest probability of being the best treatment for spasticity reduction at both the short-term and mid-term periods during the follow up.

### *Implications of all the available evidence*

BoNT injections and ESWT are effective in management of post-stroke spasticity at least for 12 weeks, and can be integrated into the multimodal approach for treating spasticity. The effectiveness of ESWT is comparable to BoNT injections, while RSW may be the best among the three treatment options. However, more prospective trials incorporating head-to-head comparisons of BoNT injections vs. ESWT are needed to validate the role of ESWT in reducing post-stroke spasticity.

generated pneumatically with a slow-growing pressure, and dissipates energy through the contacted skin to the deeper tissues [11]. The relevant mechanisms underlying ESWT have been attributed to its rheological effects, namely the alterations in muscle elasticity and extensibility [12,13], and induced nitric oxide production to act on neuromuscular junctions and to modulate secretion of interleukin [14–16].

A recent meta-analysis reviewed 16 randomized controlled trials (RCTs) of stroke patients, and reported that ESWT was effective in reducing upper-limb spasticity for more than 12 weeks [17]. Another meta-analysis demonstrated that the beneficial effects of ESWT in alleviating lower-limb spasticity could last for more than four weeks [18]. Compared with BoNT injections, ESWT is a non-drug therapy and does not elicit neuromuscular denervation. However, the anti-spasticity effectiveness of ESWT may vary according to the different applied modes that have not been probed by any prior meta-analysis. Therefore, the aim of this network meta-analysis was to synthesize and compare the effectiveness of BoNT injections, RSW, and FSW in reducing spasticity in patients with chronic stroke.

## 2. Methods

The present network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension guidelines for network meta-analysis (PRISMA-NMA) [19], and was prospectively registered on [inplasy.com](http://inplasy.com) (INPLASY202170018). The data used to support the findings of this research are available within the main article and its online supplementary files.

### 2.1. Search strategy

We searched four electronic databases (PubMed, EMBASE, MEDLINE and Cochrane CENTRAL) for relevant articles published from the earliest records up to September 2021. Other data sources such as the Cochrane Database of Systematic Reviews and [ClinicalTrials.gov](http://ClinicalTrials.gov) were also searched for eligible articles. Moreover, we manually screened the reference lists of the included articles for pertinent trials. The following PICO (i.e., Population/Patient, Intervention, Comparison, and Outcome) question guided the search strategy: “In patients with post-stroke spasticity, which kind of intervention among BoNT injections, RSW, and FSW, has a better effect in spasticity reduction when compared with others?” The following keywords were used: “stroke”, “cerebrovascular disease”, “cerebral infarction”, “intracerebral hemorrhage”, “hemiplegia”, “hemiparesis”, “spasticity”, “hypertonia”, “shock wave”, “shockwave therapy”, and “botulinum toxin” during the literature search without language limitations. The databases were investigated based on the following algorithm: [(stroke OR cerebrovascular disease OR cerebral infarction OR intracerebral hemorrhage OR hemiplegia OR hemiparesis) and (spasticity OR hypertonia) and (shock wave OR shockwave therapy)] OR [(stroke OR cerebrovascular disease OR cerebral infarction OR intracerebral hemorrhage OR hemiplegia OR hemiparesis) and (spasticity OR hypertonia) and botulinum toxin]. The complete search strategy is presented in the Supplementary Method.

### 2.2. Study selection

The detailed inclusion criteria for the network meta-analysis were as follows: (1) patients with post-stroke spasticity; (2) RCTs including at least two therapeutic arms comprising BoNT, RSW, FSW, or a control group; and (3) the use of the Modified Ashworth Scale (MAS) for spasticity measurements. Studies were excluded if they (1) enrolled patients with etiologies other than stroke (e.g., traumatic brain injury, multiple sclerosis, or spinal cord injury), (2) used combinational therapy (such as BoNT plus ESWT) instead of single treatments, (3) used

excitatory inputs at the spinal cord leads to spasticity, a hyper-excitable state of the stretch reflexes [2]. Spasticity can occur at any time after stroke, with a prevalence ranging from 17% to 46% [3]. While it also has positive effects during post-stroke recovery (e.g., by providing weight-bearing support during standing and ambulation), spasticity is a major cause of disability, and thus its management is crucial in post-stroke care [4].

Various approaches, including physical therapy, splinting, oral medications, chemical neurolysis, and surgical interventions, have been used in the management of spasticity [5,6]. Oral anti-spasticity medications (e.g., baclofen, tizanidine or diazepam) reduce muscle tone by acting on the central nervous system, but they may cause systemic side effects such as lethargy or drowsiness [7]. Chemodenervation (e.g., phenol block) carries the risk of sensory loss and dysesthesia over the injected limb [8]. Injection of botulinum toxin (BoNT), a protein neurotoxin derived from *Clostridium botulinum*, has emerged as one of the most effective anti-spasticity therapies, owing to its selective inhibition of acetylcholine release at the neuromuscular junction [9]. However, BoNT injections possess possible side effects of post-injection weakness if the dose is non-optimal, and can lead to the formation of neutralizing antibodies after repeated injections. Surgical interventions (e.g., selective peripheral neurotomy or intrathecal baclofen pump implantation) are usually reserved for those with severe spasticity after non-invasive treatment [10].

Extracorporeal shockwave therapy (ESWT), which includes focused shockwave (FSW) or radial shockwave (RSW) application, has recently been applied in the management of spasticity. FSW and RSW differ in their physical properties, depth of penetration, and mode of generation. FSW is driven by piezoelectric, electromagnetic, or electrohydraulic effects, generating a pressure surge within several nanoseconds with the energy concentrated at a focal point. RSW is

scales other than MAS for spasticity evaluation, or (4) were animal studies.

### 2.3. Data extraction and quality assessment

Two authors, who had similar expertise and experience in rehabilitation medicine (i.e. for more than 10 years), independently evaluated the eligible articles after removal of duplications. If the designated outcome variables were unavailable or incomplete in the published articles, we tried to contact the corresponding authors for the original data. The following information was extracted by both reviewers concurrently using the same form: the author(s), year, case number, patient demographics (average age, sex, and duration from onset), stroke type, details of applications of ESWT and BoNT, treatment sites, time frame of follow-up, and relevant outcomes. All the aforementioned information is summarized in [Tables 1 and 2](#).

The methodological quality of the enrolled studies was assessed using the Cochrane Risk of Bias Tool for RCTs [20]. The risk of bias was classified as high, low, or unclear. The quality assessment was based on the following aspects: selection bias (sequence generation and allocation concealment), performance (blinding of patients and personnel), detection (blinding of outcome assessment), attrition (incomplete outcome data), and reporting (selective outcome). Any discordance in reporting regarding article evaluation, data extraction, and risk of bias between the two assessors was resolved through discussion or by the judgment of a third author.

### 2.4. Data synthesis and analysis

The outcome was the weight mean difference (WMD) on MAS reduction in the short- and mid-term. The short- and mid-terms were defined as the periods before or at the 6<sup>th</sup> week post-treatment and between the 7<sup>th</sup> and 12<sup>th</sup> post-treatment weeks, respectively. Similar therapeutic arms in the same study (e.g., those comparing BoNT injections of different doses or ESWT of various sessions) were merged into a single group for analysis. The control treatments consisted of normal saline injection, sham ESWT, physical therapy, and oral anti-spastic medications. If there were several measurements within the same time frame (short- or mid-term), the outcome recorded at the last follow-up was chosen. In both time frames, we used a consistent strategy to extract our outcome variables. As a minimum of three weeks is needed for BoNT to take action [21], it would be better to extract data from the last follow-up point for better comparability with other active treatments. If the retrieved articles only reported the medians and interquartile range, the quantile estimation approach proposed by McGrath et al [22], was applied to estimate the mean and standard deviation.

For the pairwise meta-analysis, the random-effects model was used for data pooling. The Cochrane Q tests and  $I^2$  statistic were employed to determine the heterogeneity of direct comparisons, and significant heterogeneity was assumed in the case of an  $I^2$  value >50%. A mixed treatment comparison with a generalized linear mixed model was used for the network meta-analysis, enabling the indirect estimation of the differences between treatments A and B through their comparisons with treatment C. The existence of inconsistencies between the direct and indirect comparisons was examined using the loop inconsistency model. Probability ranking metrics were used to reflect clinically important relative differences in the outcomes which were shown on the ranking probability curves and the surface under the cumulative ranking area (SUCRA). The SUCRA value ranged between 0 and 1, and the treatments with a higher SUCRA value suggested better effectiveness and superior ranking [23]. It was presented as the percentage of the mean rank of each treatment in relation to the presumed best intervention [24].

Publication bias was examined using Egger's regression test and by inspection of the distribution pattern of the effect size on the

funnel plot. All analyses were performed using the statistical software package Stata (StataCorp. 2015, Stata Statistical Software: Release 14, StataCorp LP, College Station, TX, USA). Statistical significance was set at  $p < 0.05$ .

### 2.5. Role of the funding source

The funders had no direct role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The corresponding author had full access to the data in the study, and had final responsibility for the decision to submit for publication.

## 3. Results

### 3.1. Study selection and subject characteristics

A primary search of the databases yielded 3,785 related studies. After excluding 1,679 duplicate and 2,037 non-relevant studies, 69 articles were deemed eligible. A total of 36 studies were further discarded because 11 of them lacked retrievable MAS data, six studies enrolled non-stroke participants, three studies were secondary analysis of published trials, 13 studies used scales other than the MAS for spasticity measurements, and three studies compared therapeutic arms other than the inclusion criteria (Supplementary Table 1). The remaining 33 studies were included in the final meta-analysis ([Fig. 1](#)) [16,25–56].

Of the 33 included studies, 10 compared RSW with a control treatment [26–30,32,33,35,37,39], four compared FSW with a control treatment [25,31,34,38], one study compared FSW and RSW [36], one study compared RSW and BoNT [16], and 17 studies compared BoNT-A with a control treatment [40–56]. A total of 1,930 participants (1,277 men and 653 women) were enrolled in the meta-analysis. The mean age across the trials ranged from 44.1 to 69.7 years. The mean duration since stroke onset ranged from 1.4 to 84.9 months. The details regarding demographics, ESWT protocol, BoNT dosage, intervention sites, and duration of follow-up are presented in [Tables 1 and 2](#).

### 3.2. Quality assessment of the included studies

Supplementary Fig. 1 summarizes the risk of bias assessment for the included studies, and Supplementary Fig. 2 presents the risk of bias graph. Since our meta-analysis only enrolled RCTs, most studies had a detailed description of their randomization procedure. The domains with the most failures were blinding of the participants/personnel or outcome assessment because some of the studies used a single-blind design.

### 3.3. Comparison of WMDs (MAS scores before or at the 6<sup>th</sup> week after intervention)

In the pairwise meta-analysis ([Fig. 2A](#)), RSW, BoNT injections and FSW were significantly more effective than control treatments, with WMDs of -0.67 (95% CI, -0.80 to -0.55), -0.54 (95% CI, -0.57 to -0.50), and -0.34 (95% CI, -0.54 to -0.14) and, respectively. There were no significant differences when RSW was compared with FSW or BoNT injections.

The network graph is shown on [Fig. 3A](#), disclosing the geometry of the treatment network. In the network meta-analysis ([Fig. 4A](#)), BoNT injections, FSW, and RSW were superior to the control treatment in reducing spasticity, with WMDs of -0.69 (95% CI, -0.87 to -0.50), -0.36 (-0.69 to -0.03), and -0.62 (95% CI, -0.84 to -0.40), respectively. No significant differences were observed when other treatment pairs were compared. The league tables for the pairwise and network

**Table 1**  
Summary of the retrieved trials for treatment of post-stroke spasticity

Author, year	Blinding	Allocation concealment	Inclusion criteria	Intervention arm	Case number (Male/Female)	Age (year)	Stroke type (ischemic/hemorrhagic/embolic)	Post-stroke follow-up (months)
Bae et al. 2010	Not mentioned	Not mentioned	Aged 18-80 years; Onset of stroke > 12 months; MAS $\geq$ 2	FSW Control	23 (15/8) 9 (5/4)	56.7 $\pm$ 12.4 53.4 $\pm$ 16.8	13/10/0 3/6/0	22.0 $\pm$ 8.2 25.1 $\pm$ 14.6
Fouda et al. 2015	Not mentioned	Not mentioned	Onset of stroke > 3 months; MAS $\geq$ 2	RSW Control	15 (15/0) 15 (15/0)	52.7 $\pm$ 5.9 51.8 $\pm$ 6.8	6/9/0 5/10/0	14.6 $\pm$ 9.2 12.2 $\pm$ 8.1
Tirbisch et al. 2015	Single-blinded (assessors)	Yes	Onset of stroke between 3 weeks and 6 months; MAS > 2	RSW Control	4 (1/3) 4 (2/2)	49.5 $\pm$ 8.7 61.3 $\pm$ 11.1	3/1/0 3/1/0	4.0 $\pm$ 0.8 3.4 $\pm$ 1.6
Dymarek et al. 2016	Single-blinded (patients)	Not mentioned	Onset of stroke between 9 months and 10 years; MAS $\geq$ 1	RSW Control	30 (19/11) 30 (15/15)	61.4 $\pm$ 12.7 60.9 $\pm$ 9.5	30/0/0 30/0/0	51.3 $\pm$ 25.5 51.5 $\pm$ 26.1
Kim et al. 2016	Double-blinded (patients and assessors)	Not mentioned	Onset of stroke > 3 months; Hemiplegic and limited ROM of shoulder	RSW Control	17 (7/10) 17 (10/7)	65.9 $\pm$ 8.3 66.1 $\pm$ 15.8	8/9/0 5/12/0	28.8 $\pm$ 33.3 22.2 $\pm$ 18.3
Li et al. 2016	Single-blinded (assessors)	Not mentioned	Onset of stroke > 9 months; MAS $\geq$ 2	RSW – 1 session RSW– 3 sessions Control	20 (15/5) 20 (12/8) 20 (14/6)	56.8 $\pm$ 13.4 55.4 $\pm$ 13.6 56.0 $\pm$ 11.8	10/10/0 10/10/0 12/8/0	66.7 $\pm$ 42.8 61.7 $\pm$ 43.5 67.0 $\pm$ 62.8
Duan et al. 2017	Single-blinded (assessors)	Not mentioned	Aged 18-80 years; onset of stroke < 3 months; MAS between 1-3	RSW Control	24 (13/11) 24 (12/12)	50.6 $\pm$ 8.6 51.9 $\pm$ 9.4	7/17/0 9/15/0	1.6 $\pm$ 0.4 1.7 $\pm$ 0.5
Taheri et al. 2017	Not mentioned	Yes	Aged 17-70 years; onset of stroke > 1 month; ability to walk for 10 meters; MAS $\geq$ 2	FSW Control	13 (9/4) 12 (8/4)	56.5 $\pm$ 11.6 54.9 $\pm$ 9.4	11/2/0 11/1/0	33 $\pm$ 21.4 25.8 $\pm$ 9.9
Yoon et al. 2017	Not mentioned	Not mentioned	Onset of stroke > 6 months; MAS $\geq$ 2	FSW-Elbow belly FSW-Elbow junction Control-Elbow FSW-Knee belly FSW-Knee junction Control-Knee	26 (26/0) 28 (27/1) 26 (23/3) 13 (13/0) 13 (13/0) 18 (16/2)	58.7 $\pm$ 15.7 63.1 $\pm$ 11.8 64.4 $\pm$ 13.8 61.0 $\pm$ 2.2 66.9 $\pm$ 4.9 59.5 $\pm$ 16.9	NR NR NR NR NR NR	100.3 $\pm$ 98.3 66.8 $\pm$ 51.9 63.5 $\pm$ 94.1 99.1 $\pm$ 85.1 51.1 $\pm$ 36.0 38.7 $\pm$ 30.2
Xu et al. 2018	Not mentioned	Not mentioned	Onset of stroke between 2 weeks and 3 months; MAS between 1-3; simplified FMA < 50; MBI < 60	RSW Control	28 (17/11) 28 (18/10)	52.8 $\pm$ 12.0 54.2 $\pm$ 12.4	14/14/0 15/13/0	52.9 $\pm$ 13.2 53.6 $\pm$ 12.5
Wu et al. 2018 (EJPRM)	Double-blinded (patients and assessors)	Yes	Aged $\geq$ 18 years; onset of stroke > 6 months; MAS > 1; able to walk +/- orthosis	FSW RSW	15 (9/6) 16 (9/7)	60.3 $\pm$ 9.9 59.6 $\pm$ 11.3	10/5/0 10/6/0	53.2 $\pm$ 26.7 55.7 $\pm$ 26.1
Guo et al. 2019*	Single- blinded (assessors)	Not mentioned	Onset of stroke > 6 months; 1 < MAS < 4	RSW Control	30 (16/14) 30 (16/14)	66.8 $\pm$ 11.0 69.7 $\pm$ 11.1	12/18/0 13/17/0	3.2 $\pm$ 4.5 3.5 $\pm$ 5.1
Lee et al. 2019	Double-blinded (patients and assessors)	Not mentioned	Aged 30 -70 years; onset of stroke > 6 months; MAS > 1	FSW Control	9 (7/2) 9 (9/0)	50.9 $\pm$ 8.8 44.1 $\pm$ 4.1	4/5/0 2/7/0	12.9 $\pm$ 9.0 10.4 $\pm$ 9.1
Tabra et al. 2021	Double-blinded (assessors, lack of details regarding patients)	Yes	Onset of stroke > 1 year; MAS > 1	RSW Control	20 (18/2) 20 (17/3)	55.7 $\pm$ 9.3 53.9 $\pm$ 10.2	13/7/0 11/9/0	33.5 $\pm$ 5.6 31.7 $\pm$ 9.2
Aslan et al. 2021	Double-blinded (patients and assessors)	Yes	Aged 20-80 years; MAS > 1	RSW Control	17 (9/8) 16 (9/7)	57.5 $\pm$ 14.3 58.8 $\pm$ 10.8	NR NR	35.5 $\pm$ 70.2 28.9 $\pm$ 76.5
Wu et al. 2018 (APMR)	Single-blinded (assessors)	Yes	Aged > 20 years; onset of stroke > 6 months; MAS > 1	RSW BoNT	21 (13/8) 21 (15/6)	60.0 $\pm$ 11.1 62.0 $\pm$ 10.2	11/9/0 10/10/0	38.8 $\pm$ 5.9 39.5 $\pm$ 6.2
Hesse et al. 1998 *	Double-blinded (patients and assessors)	Not-mentioned	Onset of stroke between 6-12 months; upper limb flexor spasticity MAS $\geq$ 3 and nonfunctional	BoNT / Control	24 (12/12)	52.3 (32-73) <sup>1</sup>	18/6	7.45 (6-11) <sup>1</sup>
Bakheit et al. 2000	Double-blinded (patients and assessors)	Not-mentioned	Onset of stroke > 3 months; MAS $\geq$ 2 in wrist, elbow, and finger flexors	BoNT Control	63 (39/24) 19 (12/7)	62.2 $\pm$ 13.0 63.6 $\pm$ 14.1	36/12/10 (5 unknown) 8/3/4 (4 unknown)	NR NR
Bhakta et al. 2000	Double-blinded (patients and assessors)	Yes	MAS > 2 of finger flexor or elbow flexor; at least moderate difficulty with 2 out of 8 items defining patient disability	BoNT Control	20 (13/7) 20 (10/10)	60.2 (22.6–77.6) <sup>2</sup> 53.8 (11.2–72.8) <sup>2</sup>	15/5 15/5	37.2 (9.6-398.4) <sup>2</sup> 32.4 (6-180) <sup>2</sup>
Bakheit et al. 2001	Double-blinded (patients and assessors)	Not-mentioned	Onset of stroke > 3 months; MAS $\geq$ 2 in at least 2 out of the elbow, wrist and finger	BoNT Control	27 (11/16) 32 (15/17)	67.0 $\pm$ 11.1 64.1 $\pm$ 13.2	14/8/2 (3 unknown) 15/3/11 (3 unknown)	NR NR

(continued on next page)

Table 1 (Continued)

Author, year	Blinding	Allocation concealment	Inclusion criteria	Intervention arm	Case number (Male/Female)	Age (year)	Stroke type (ischemic/hemorrhagic/embolic)	Post-stroke follow-up (months)
Childers et al. 2004	Double-blinded (patients and assessors)	Yes	flexors and > 1 in the remaining area Aged 21–80 years; body weight > 60 Kg; onset of stroke > 6 weeks; wrist flexor MAS $\geq 3$ and elbow flexor MAS $\geq 2$	BoNT- low dose BoNT- middle dose BoNT- highest dose Control	21 (16/5) 23 (15/8) 21 (17/4) 26 (13/13)	59.3(30.4–76.1) <sup>1</sup> 61.1(39.6–79.4) <sup>1</sup> 59.0(35.4–77.7) <sup>1</sup> 60.6(33.8–76.0) <sup>1</sup>	51/19/16 (5 unknown)	28.7 (0.9–108.5) <sup>1</sup> 31.2 (1.2–226.9) <sup>1</sup> 16.5 (2.6–99.2) <sup>1</sup> 26.6 (2.1–211.7) <sup>1</sup>
Jahangir et al. 2007	Double-blinded (Lack of detail)	Not-mentioned	Aged $\geq 21$ years; stroke onset > 1 year; spasticity > 3 months and wrist and fingers MAS $\geq 2$	BoNT Control	27 (18/9) 25 (15/10)	60.48 $\pm$ 11.6 61.08 $\pm$ 10.9	27/0/0 22/3/0	49.70 $\pm$ 35.5 40.36 $\pm$ 44.5
Marco et al. 2007	Double-blinded (patients and assessors)	Yes	Aged $\geq 18$ years; onset of stroke > 3 months; MAS $\geq 3$ ; moderate-severe spastic shoulder pain	BoNT Control	14 (10/4) 15 (11/4)	63.9 $\pm$ 10.6 67.2 $\pm$ 7.4	14/0/0 15/0/0	5.8 (2.9–8.8) <sup>3</sup> 4.4 (3.7–7) <sup>3</sup>
McCrorry et al. 2009	Double-blinded (patients and assessors)	Yes	Aged $\geq 18$ years; onset of stroke > 6 months; MAS $\geq 2$ in at least 2 out of 3 of wrist, elbow and finger, and $\geq 1+$ for the third area	BoNT Control	54 (32/22) 42 (26/16)	59.7 $\pm$ 12.2 58.4 $\pm$ 14.6	NR NR	63.6 $\pm$ 104.4 79.2 $\pm$ 151.2
Kaji et al. 2010 (J Neurol)	Double-blinded (patients and assessors)	Yes	Aged 20–80 ears; body weight $\geq 50$ Kg; onset of stroke $\geq 6$ months; ankle flexor MAS $\geq 3$	BoNT Control	58 (50/8) 62 (46/16)	62.4 $\pm$ 8.7 62.5 $\pm$ 9.3	NR NR	80.8 $\pm$ 72.8 72.0 $\pm$ 30.3
Kaji et al. 2010 (CMRO)	Double-blinded (patients and assessors)	Yes	Aged 20–80 years; body weight $\geq 40$ Kg; onset of stroke $\geq 6$ months; wrist flexor MAS 3 or 4 and finger flexor MAS $\geq 2$ ; 2 or 3 on the DAS for at least one of 4 areas of functional disability	BoNT- low dose BoNT- high dose Control	51 (36/15) 21 (19/2) 37 (19/18)	63.5 $\pm$ 9.3 62.7 $\pm$ 9.7 63.2 $\pm$ 10.6	NR NR NR	82.2 $\pm$ 83.5 91.3 $\pm$ 63.4 79.2 $\pm$ 61.8
Shaw et al. 2011	Single-blinded (assessor)	Yes	Aged > 18 years; onset of stroke $\geq 1$ month; elbow MAS $\geq 2$ ; reduced upper limb function (ARAT 0–56)	BoNT Control	170 (110/60) 162 (115/47)	67 (58.8 to 74) <sup>3</sup> 66 (59.8 to 72.3) <sup>3</sup>	140/27/3 131/24/7	9.3 (4.9 to 38.2) <sup>3</sup> 10.8 (4.3 to 46.3) <sup>3</sup>
Hesse et al. 2011	Single-blinded (assessor)	Not-mentioned	Aged < 80 years; onset of stroke > 4–6 weeks; 0 < MAS < 2 of finger and/or wrist flexors; Barthel index > 25 and FMA motor score < 20	BoNT Control	9 (3/6) 9 (3/6)	57 $\pm$ 11 66 $\pm$ 11	6/3/0 7/2/0	1.5 $\pm$ 0.3 1.4 $\pm$ 0.3
Marciniak et al. 2012	Double-blinded (patients and assessors)	Yes	Aged $\geq 18$ years; body weight $\geq 88$ lbs, pain VAS $\geq 4$ ; upper limb MAS $\geq 3$	BoNT Control	10 (6/4) 11 (7/4)	60.2 $\pm$ 7.8 59.8 $\pm$ 10.3	NR NR	NR NR
Wolf et al. 2012	Double-blinded (patients and assessors)	Not-mentioned	Onset of stroke 3–24 months; volitional activation of wrist and finger muscles	BoNT Control	12 (5/7) 13 (5/8)	48.8 $\pm$ 15.6 49.8 $\pm$ 13.7	NR NR	NR NR
Prazeres et al. 2018	Double-blinded (patients and assessors)	Yes	Aged 50–70 years; onset of stroke between 1–5 years; presented with post-stroke spasticity	BoNT Control	20 (12/8) 20 (12/8)	52.5 $\pm$ 11.0 52.1 $\pm$ 12.5	16/4/0 19/1/0	34.2 $\pm$ 21.4 32.1 $\pm$ 14.9
Rosales et al. 2018	Double-blinded (Lack of detail)	Not-mentioned	Aged 18–80 years; onset of stroke 2–12 weeks; MAS $\geq 2$ in primary targeted muscle group of upper limb	BoNT Control	28 (23/5) 14 (10/4)	61.5 $\pm$ 13.2 56.5 $\pm$ 9.7	20/8/0 10/4/0	1.5 $\pm$ 0.7 1.6 $\pm$ 0.6
Kerzoncuf et al. 2020	Double-blinded (patients and assessors)	Yes	Stroke onset > 1 year; MAS $\geq 2$	BoNT Control	23 (12/11) 26 (12/14)	53.4 $\pm$ 14.8 50.7 $\pm$ 12.9	10/13/0 14/12/0	50.0 $\pm$ 28.7 71.0 $\pm$ 67.1

Data format: Presented as mean  $\pm$  standard deviation, except <sup>1</sup> indicates mean (minimum value to maximum value)

<sup>2</sup> indicates median (minimum value to maximum value) and <sup>3</sup> indicates median (25 percentile value to 75 percentile value).

Abbreviations: ARAT, Action Research Arm Test; APMR, *Archives of Physical Medicine and Rehabilitation*; BoNT, botulinum toxin; CMRO, *Current Medical Research and Opinion*; EJPRM, *European Journal of Physical and Rehabilitation Medicine*; FMA: Fugl-Meyer Assessment; FSW, focused shockwave; MAS, modified Ashworth scale; MBI, modified Barthel index; NR, not recorded; ROM, range of motion; RSW, radial shockwave; VAS, visual analog scale

\* The study contains four study arms, and two of them were selected into meta-analysis after exclusion of the arms combining treatment other than ESWT and BoNT.

**Table 2**  
Summary of intervention details in the retrieved trials

Author, year	Intervention arm	Intervention detail	Guidance	Evaluating joint/muscle	Outcome measurement	Follow-up
Bae et al. 2010	FSW	ESWT (1200 shots, 0.12mj/mm <sup>2</sup> , 4 Hz to biceps brachii; once per week for 3 weeks) + physiotherapy	Ultrasound	Upper limb (biceps brachii)	MAS, modified Tardieu scale and modified Barthel index	Immediate after 1 <sup>st</sup> session and before 2 <sup>nd</sup> session, 1 week after last session
	Control	Physiotherapy	N/A			Immediate
Fouda et al. 2015	RSW	ESWT (1500 shots, 2.5 bar for forearm flexor muscles; 3200 shots, 2.5 bar for palmar interosseous muscles; once per week for 5 weeks) + physiotherapy	Landmark	Upper limb (wrist, finger)	MAS, pROM, VAS	Immediate
	Control	sham RSW + physiotherapy	Landmark			
Tirbisch et al. 2015	RSW	ESWT (2000shots, 0.03mj/mm <sup>2</sup> , 10 Hz; 3 times per week for 3 weeks) + physiotherapy	Landmark	Lower limb (soleus and gastrocnemius)	MAS, modified Tardieu scale, ROM	Immediate
	Control	Physiotherapy	N/A			
Dymarek et al. 2016	RSW	ESWT (1500 shots, 0.030mj/mm <sup>2</sup> , 1.5 bar, 5Hz to FCR and FCU; single session)	Landmark	Upper limb (elbow, wrist, finger)	MAS*, bioelectrical activity, temperature distribution	Immediate, 1 and 24 hours
	Control	Sham ESWT	Landmark			
Kim et al. 2016	RSW	ESWT (3000 shots, 0.39-1.95mj/mm <sup>2</sup> , 1.0-5.0 bar, 12Hz to greater and lesser tuberosities of the humeral head; 4 times per week for 2 weeks)	Ultrasound	Upper limb (supraspinatus and subscapularis)	VAS*, CMS, MAS, ROM, FMA	1, 2 and 4 weeks
	Control	Sham RSW	Ultrasound			
Li et al. 2016	RSW	ESWT (1500 shots, 3.5 bar, 5Hz for FCU, FCR; 4000 shots, 3.5bar, 5 Hz for intrinsic muscles and flexor digitorum tendon; once per week for 3 weeks (n =20), Single session (n=20))	Ultrasound	Upper limb (Wrist and hand)	MAS*, FMA	Immediate, 1, 4, 8, 12 and 16 weeks
	Control	Sham RSW	Ultrasound			
Duan et al. 2017	RSW	ESWT (1500 shots, 3.0bar, 8Hz to biceps brachii; 3 times per week for 2 weeks) + physiotherapy	Landmark	Upper limb (biceps brachii)	MAS, FMA	Immediate
	Control	Physiotherapy	N/A			
Taheri et al. 2017	FSW	ESWT (1500 shots, 0.1 mj/mm <sup>2</sup> , 4Hz to gastrocnemius muscle; once per week for 3 weeks) + Stretching exercise + oral anti-spastic medications	Landmark	Lower limb (ankle plantar flexor)	MAS, VAS, ROM, Clonus score, 3-m walk duration, and lower extremity functional score	1, 3 and 12 weeks
	Control	Stretching exercise + oral anti-spastic medications	N/A			
Yoon et al. 2017	FSW	ESWT (1500 shots, 0.068–0.093 mj/mm <sup>2</sup> , 15Hz to muscle belly or myotendinous junction of biceps brachii /semite ndinosus; once per week for 3 weeks) + physiotherapy	Ultrasound	Upper limb (elbow flexor) and lower limb (knee flexor)	MAS, modified Tardieu scale	Immediate after each treatment session
	Control	Physiotherapy	N/A			
Xu et al. 2018	RSW	ESWT (2000 shots, 2.0-3.0 bar, 8Hz to biceps brachii; once per week for 4 weeks) + physiotherapy	Landmark	Upper limb (biceps brachii)	MAS, FMA, modified Barthel index	2 and 4 weeks
	Control	Sham ESWT + physiotherapy	Landmark			
Wu et al. 2018 (EJPRM)	FSW	ESWT (3000 shots, 0.10 mj/mm <sup>2</sup> , 5 Hz to gastrocnemius and soleus muscles; once per week for 3 weeks) + physiotherapy	Landmark	Lower limb (gastrocnemius)	MAS*, Tardieu angles, ankle pROM, dynamic foot plantar contact area, gait speed	1, 4 and 8 weeks
	RSW	ESWT (3000 shots, 2.0 bar, 5Hz, once per week for 3 weeks to gastrocnemius and soleus muscles) + physiotherapy	Landmark			
Guo et al 2019	RSW	ESWT (2000 shots, 2.0-3.0 bar, 8 Hz to the intrinsic muscles and flexor digitorum tendon of the hand; 5 times per week for 4 weeks) + physiotherapy	Ultrasound	Upper limb (lack of detailed information)	MAS, FMA	1, 3 and 6 months
	Control	Physiotherapy	N/A			
Lee et al. 2019	FSW	ESWT (2000 shots, 0.1mj/mm <sup>2</sup> , 4Hz to gastrocnemius; single session) + physiotherapy	Ultrasound	Lower limb (ankle plantar flexor)	MAS, FMA, ROM	30 minutes, 1 and 4 weeks
	Control	Sham ESWT + physiotherapy	Ultrasound			
Tabra et al. 2021	RSW	ESWT (2000-3000 shots, 0.25-0.84 mj/mm <sup>2</sup> with pressure 2.8 bar, 15 Hz. to FCU, FCR, flexor digitorum and intrinsic hand muscles; once per week for 3 weeks) + physiotherapy	Landmark	Upper limb (wrist and hand)	MAS, FMA, Motricity Index, H/M ratio of FCR	2 weeks and 3 months
	Control	Physiotherapy	N/A			

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**Table 2 (Continued)**

Author, year	Intervention arm	Intervention detail	Guidance	Evaluating joint/muscle	Outcome measurement	Follow-up
Aslan et al. 2021	RSW	ESWT (1500 shots, 2 bar, 10 Hz to gastrocnemius muscle; twice per week for 2 weeks) + physiotherapy	Landmark	Lower limb (ankle plantar flexor muscles)	MAS, Tardieu Scale, ankle ROM, 6-meter times walk test, modified Barthel index, strain index	2 and 6 weeks
	Control		Landmark			
Wu et al. 2018 (APMR)	RSW	ESWT (3000 shots, 3.5 bar, 5Hz to FCU, FCR and biceps brachii; once per week for 3 weeks) + physiotherapy	Landmark	Upper limb (elbow flexor and wrist flexor)	MAS, Tardieu angle, pROM, FMA, treatment response rate	1, 4 and 8 weeks
	BoNT		EMG			
Hesse et al. 1998	BoNT	BoNT (Dysport®) 1000 U: biceps brachii 250U, BR 250U, FCU 125U, FCR 125U, FDP 125U, FDS 125U + physiotherapy	EMG	Upper limb (elbow, wrist, finger)	MAS*, limb position at rest, ORS	2, 6 and 12 weeks
Bakheit et al. 2000	BoNT	BoNT-A (Dysport®): - 500 U: biceps brachii 200U, FDP 75, FDS 75, FCU 75, FCR 75 - 1000 U: biceps brachii 400U, FDP 150, FDS 150, FCU 150, FCR 150 - 1500 U: biceps brachii 600U, FDP 225, FDS 225, FCU 225, FCR 225	EMG	Upper limb (elbow, wrist, finger)	MAS*, aROM, pROM, pain, Rivermead motor assessment, Barthel index, ORS	2, 4, 8, 12 and 16 weeks
	Control		Landmark			
Bhakta et al. 2000	BoNT	Placebo BoNT-A (Dysport®) 1000U: biceps brachii, brachioradialis, FDS, FDP, FCU	Landmark	Upper limb (elbow, finger)	Disability Scale *, CBS*, MRC, MVG, MAS, pROM, aROM, total pain score of paretic limb	1, 2, 6 and 12 weeks
	Control		Landmark			
Bakheit et al. 2001	BoNT	BoNT-A (Dysport®) 1000U: biceps brachii, brachioradialis, FDS, FDP, FCU	Landmark	Upper limb (elbow, wrist, finger)	MAS*, aROM, pROM, pain, Barthel index, goal attainment scale, ORS	4, 8, 12 and 16 weeks
Childers et al. 2004	BoNT	BoNT-A (Botox®): -Low dose (90U): biceps brachii 50U, FCR 15U, FCU 10U, FDP 7.5U, FDS 7.5U -Middle dose (180U): biceps brachii 100U, FCR 30U, FCU 20U, FDP 15U, FDS 15U -High dose (360U): biceps brachii 200U, FCR 60U, FCU 40U, FDP 30U, FDS 30U	EMG	Upper limb (elbow, finger)	MAS*, Disability Scale, pain, FIM, SF-36, Global assessment of response to treatment	1, 2, 3, 4, 5, 6, 9, 12, 18 and 24 weeks
	Control		Landmark			
Jahangir et al. 2007	BoNT	BoNT-A (Botox®) 80U: FCR 20U, FCU 20U, FDS 20U, FDP 20U + physiotherapy	EMG NR	Upper limb (wrist and finger)	MAS, Barthel index, EQ-5D	1 and 3 months
Marco et al. 2007	BoNT	Placebo + physiotherapy BoNT-A (Dysport®) 500U to pectoralis major + TENS + physiotherapy	NR EMG	Upper limb (shoulder)	Pain*, MAS, pROM	1 week, 1, 3 and 6 months
McCrary et al. 2009	Control	Placebo + TENS + physiotherapy BoNT-A (Dysport®) 750-1000U to distal upper limb	EMG	Upper limb (elbow, wrist and finger joints)	AQoL*, Pain, Hospital Anxiety and Depression Rating Scale, Goal Attainment Scaling, MAS Modified Motor Assessment Scale, Carer Burden scale, Patient disability scale, Global Assessment of Benefit	8,12,20, and 24 weeks
	BoNT		EMG			
Kaji et al. 2010 (J Neurol)	BoNT	BoNT-A (Botox®) 300U: medial head of gastrocnemius 75U, lateral head of gastrocnemius 75U, soleus 75U, tibialis posterior 75U	EMG	Lower limb (ankle)	MAS*, Gait pattern scale, gait speed, clinical global impression	1, 4, 6, 8 and 12 weeks
	Control		EMG			

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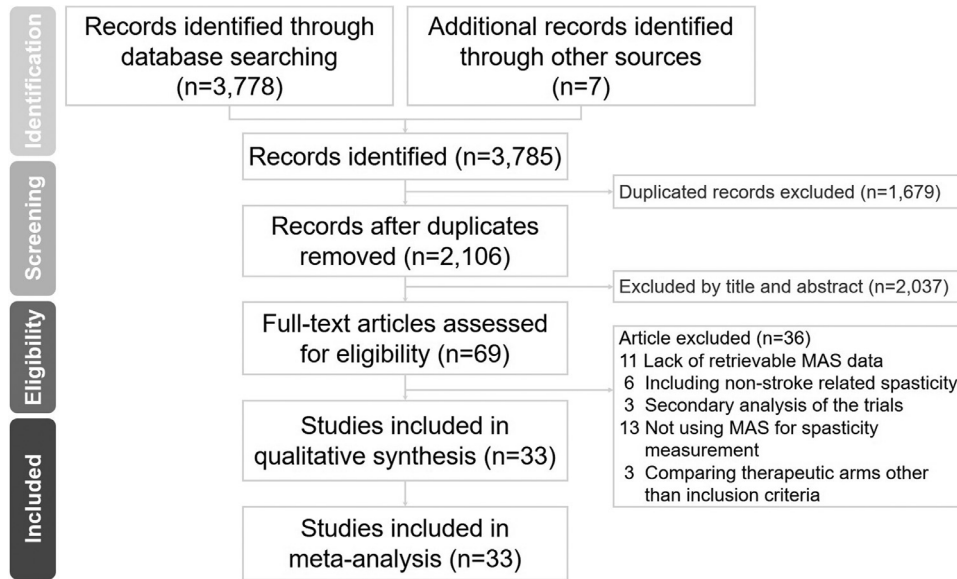
Table 2 (Continued)

Author, year	Intervention arm	Intervention detail	Guidance	Evaluating joint/muscle	Outcome measurement	Follow-up
Kaji et al. 2010 (CMRO)	BoNT	BoNT-A (Botox®) - High dose (200U): 50U FCR, 50U FCU, 50U FDP, 50U FDS +/- 20U FPL, 20U adductor pollicis (if thumb spasticity MAS $\geq 2$ ) - Low dose (120U): 30U FCR, 30U FCU, 30U FDP, 30U FDS +/- 15U FPL, 15U adductor pollicis (if thumb spasticity MAS $\geq 2$ )	EMG	Upper limb (wrist, finger, thumb)	MAS*, disability assessment scale, clinical global impression	1, 4, 6, 8 and 12 weeks
Shaw et al. 2011	Control	Placebo	EMG	Upper limb (elbow)	Action Research Arm Test*, MAS, Motricity Index, MVG, Nine Hole Peg Test, ORS, Barthel index, pain	1, 3 and 12 months
	BoNT	BoNT-A (Dysport®) median dose 200 units (range 100–300 U) + physiotherapy	NR			
Hesse et al. 2011	Control	Physiotherapy	N/A	Fingers flexors II–V	MAS*, REPAS, FMA motor score, Disability Scale	1 and 6 months
	BoNT	BoNT-A (Xeomin®) 150 MU to the deep, superficial finger and wrist flexors + physiotherapy	Ultrasound			
Marciniak et al. 2012	BoNT	BoNT-A (Botox®) mean 188 U (range 140–200 U): 100–150 U pectoralis major +/- 40–60 U teres major	N/A	Upper limb (shoulder)	VAS*, MAS, disability assessment scale, FMA, ROM, McGill Pain Questionnaire short Form, FIM (hygiene)	2, 4 and 12 weeks
	Control	Placebo	EMG			
Wolf et al. 2012	BoNT	BoNT-A (Botox®) max dose 300 U over wrist and finger muscles + physiotherapy	NR	Upper limb (wrist)	Wolf Motor Function Test*, Stroke Impact Scale, MAS, aROM	1,2 and 3 months
Prazeres et al. 2018	Control	Placebo + physiotherapy	NR	Upper limb (wrist, elbow)	Time up and go test*, 6 minute walking test*, FMA*, MAS	3, 6 and 9 months
	BoNT	BoNT-A (Dysport®): lack of detail information	NR			
Rosales et al. 2018	Control	Placebo	NR	Upper limb	Time to re-injection, MAS, motor recovery score, Global assessment	4,6,8,10 and 12 weeks
	BoNT	BoNT-A (Dysport®): 500U in targeted muscle of upper limb	NR			
Kerzoncuf et al. 2020	BoNT	BoNT-A (Botox®) max dose 300 U, and the muscles were selected following assessment: 50–160 U soleus, 50–100 U gastrocnemius, tibialis posterior and FDL, 25–50U FHL and 25 U EHL	EMG	Lower limb (soleus, gastrocnemius, tibialis posterior)	Quantified balance assessment*, MAS, occurrence of a clonus, ROM, proprioceptive and discriminative sensitivity, occurrence of falls, walking speed, functional ambulation classification, FIM	4 to 6 weeks
	Control	Placebo	EMG			

Abbreviations: APMR, *Archives of Physical Medicine and Rehabilitation*; aROM, active range of motion; AQoL, Assessment of Quality of Life instrument; CBS, Caregiver Burden Scale; CMRO, *Current Medical Research and Opinion*; CMS, Constant-Murley score; BoNT, botulinum toxin; EHL, extensor hallucis longus; EJPRM, *European Journal of Physical and Rehabilitation Medicine*; EMG, electromyography; EQ-5D, EuroQoL five-dimensional; ESWT, extracorporeal shockwave therapy; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDL, flexor digitorum longus; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FHL, flexor hallucis longus; FIM, Functional Independence Measure; FMA, Fugl-Meyer Assessment; FMS, Fugl-Meyer scale; FPL, flexor pollicis longus; FSW, focused shockwave; H/M ratio, ratio of maximum H reflex to maximum M response; Kg, kilogram; MAS, modified Ashworth scale; MVG, maximum voluntary grip strength; N/A, not applicable; NR, not recorded; ORS, ordinal rating score the difficulties encountered in performing functional activities; pROM, passive range of motion; ROM, range of motion; RSW, radial shockwave; TENS: transcutaneous electrical nerve stimulation; VAS, visual analog scale

\* Indicates primary outcome.





**Figure 1.** Flow diagram for the study selection process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

meta-analyses are summarized in Supplemental Table 2. The loop inconsistency model (Supplementary Fig. 3A) did not reveal significant inconsistencies between direct and indirect comparisons.

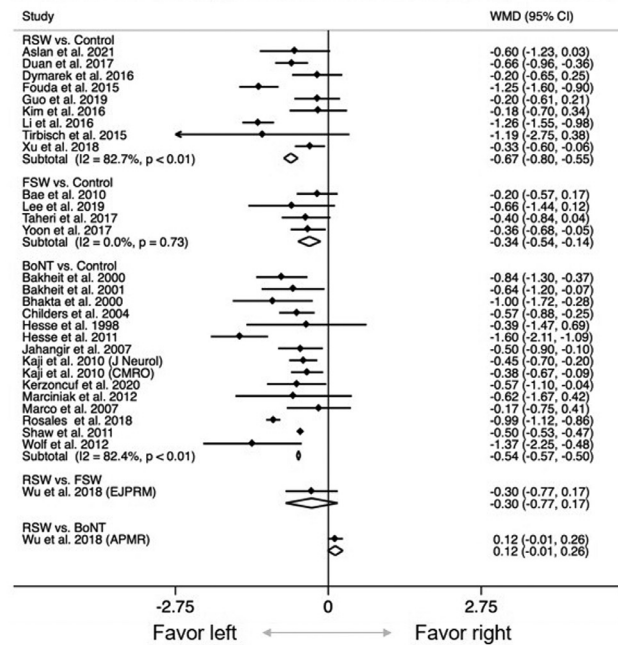
In terms of treatment outcome before or at the 6<sup>th</sup> week post-intervention, the rank probability results and the value of SUCRA are presented in Fig. 5A and Table 3, respectively. RSW had the highest probability (62.2%) for being the best treatment, whereas BoNT injections had the highest probability (61.6%) to rank second-best. Furthermore, FSW and the control treatment were likely to be the third-best (98.1%) and the worst (99.9%) treatments, respectively.

### 3.4. Comparison of WMDs (MAS scores between the 7<sup>th</sup> and 12<sup>th</sup> weeks)

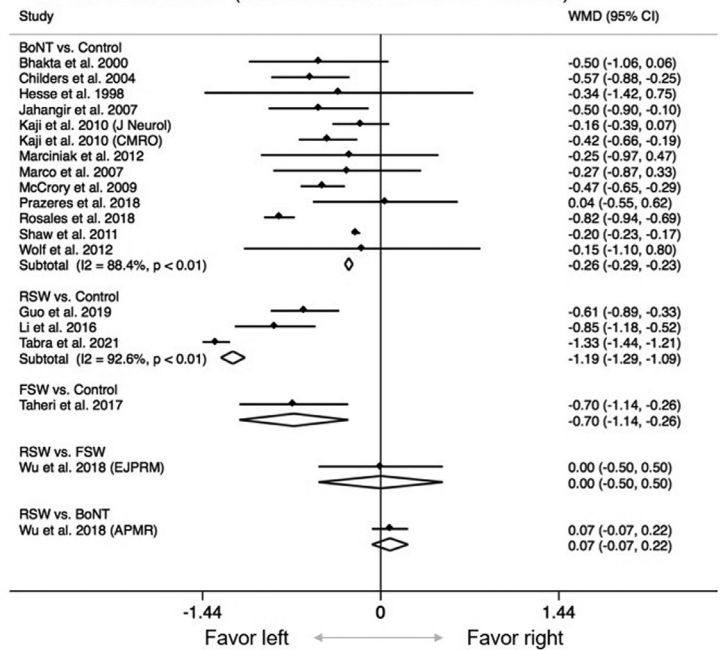
In the pairwise meta-analysis (Fig. 2B), RSW, BoNT injections, and FSW were significantly superior to control treatments, with WMDs of -1.19 (95% CI, -1.29 to -1.09), -0.26 (95% CI, -0.29 to -0.23), and -0.70 (95% CI, -1.14 to -0.26), respectively. No significant differences were found in the comparisons of RSW vs. FSW and RSW vs. BoNT injections.

The network graph is shown on Fig. 3B, disclosing the geometry of the treatment network. In the network meta-analysis (Fig. 4B), BoNT

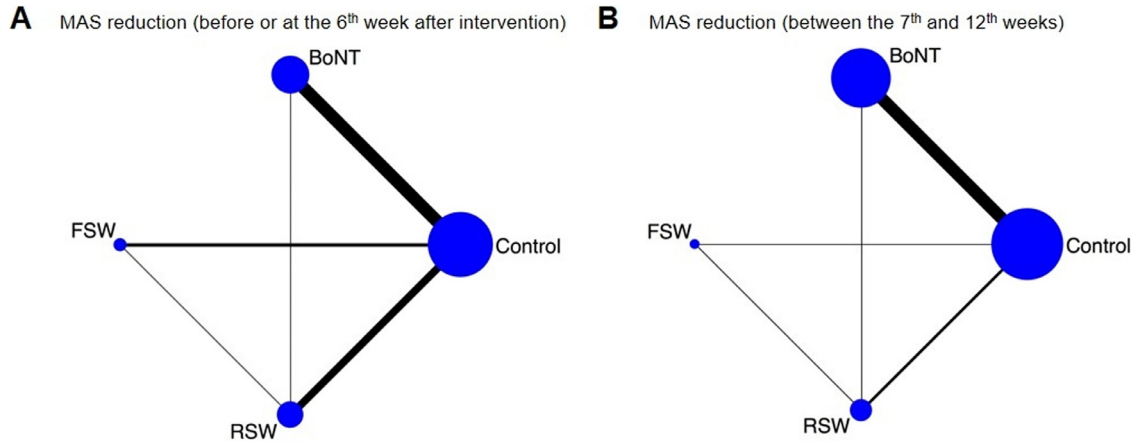
### A MAS reduction (before or at the 6<sup>th</sup> week after intervention)



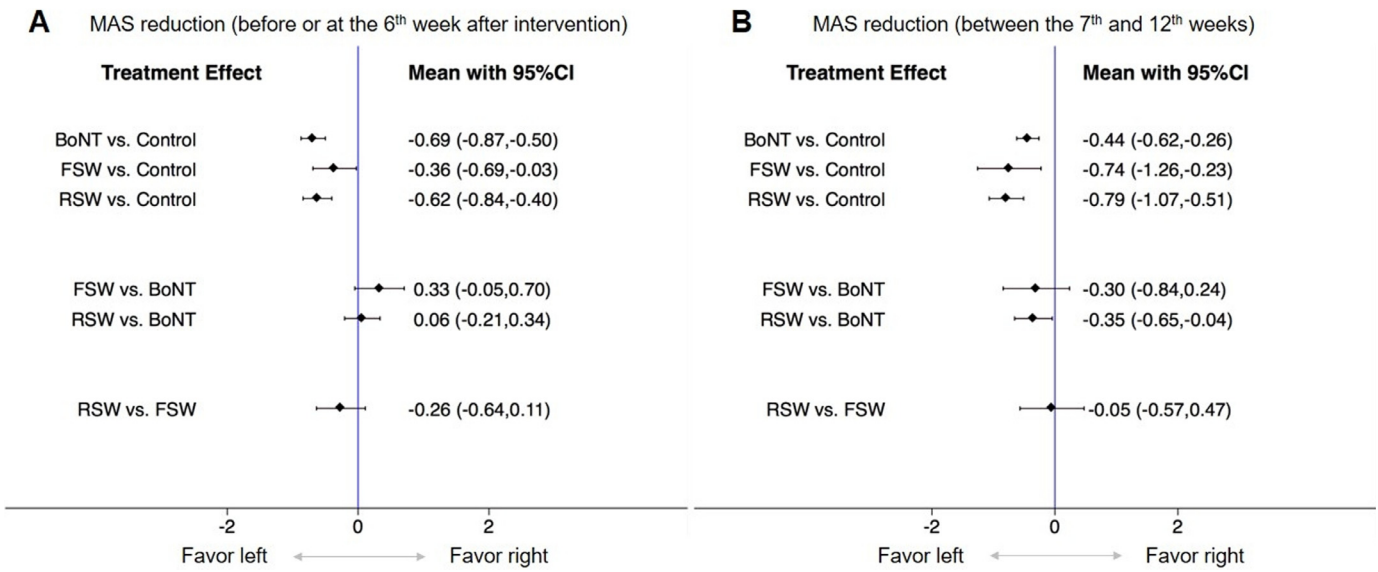
### B MAS reduction (between the 7<sup>th</sup> and 12<sup>th</sup> weeks)



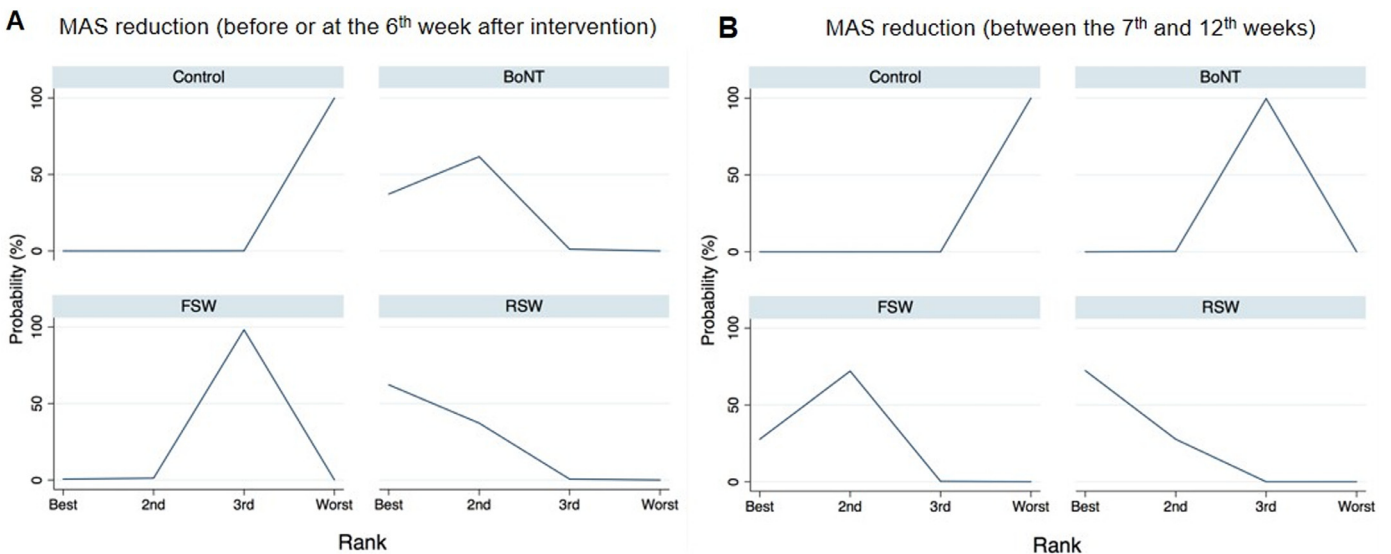
**Figure 2.** Forest plots of pairwise comparison in terms of MAS reduction (A) before or at the 6<sup>th</sup> week after intervention and (B) between the 7<sup>th</sup> and 12<sup>th</sup> weeks after interventions. WMD, weighted mean difference. CI, confidence interval represents the mean treatment effect. FSW, focused shockwave; RSW, radial shockwave; MAS, modified Ashworth scale. APMR, Archives of Physical Medicine and Rehabilitation; BoNT, botulinum toxin; CMRO, current medical research and opinion; EJPRM, European Journal of Physical and Rehabilitation Medicine.



**Figure 3.** Network plots of enrolled treatments in terms of the MAS reduction (A) before or at the 6<sup>th</sup> week after intervention and (B) between the 7<sup>th</sup> and 12<sup>th</sup> weeks after interventions. BoNT, botulinum toxin; FSW, focused shockwave; RSW, radial shockwave; MAS, modified Ashworth scale.



**Figure 4.** Forest plots of network comparisons in terms of MAS reduction (A) before or at the 6<sup>th</sup> week after intervention and (B) between the 7<sup>th</sup> and 12<sup>th</sup> weeks after interventions. CI, confidence interval represents the mean treatment effect. BoNT, botulinum toxin; FSW, focused shockwave; RSW, radial shockwave; MAS, modified Ashworth scale.



**Figure 5.** Ranking probabilities for different treatment options in terms of MAS reduction (A) before or at the 6<sup>th</sup> week after intervention and (B) between the 7<sup>th</sup> and 12<sup>th</sup> weeks after interventions. BoNT, botulinum toxin; FSW, focused shockwave; RSW, radial shockwave; MAS, modified Ashworth scale.

**Table 3**

Surface Under the Cumulative Ranking (SUCRA) of the reduction of the MAS reduction before or at the 6<sup>th</sup> week after intervention and between the 7<sup>th</sup> and 12<sup>th</sup> weeks after interventions.

Rank	MAS Reduction before or at the 6 <sup>th</sup> week after intervention		MAS Reduction between the 7 <sup>th</sup> and 12 <sup>th</sup> weeks after interventions	
	Treatment	SUCRA	Treatment	SUCRA
1	RSW	87.2	RSW	90.8
2	BoNT	78.7	FSW	75.8
3	FSW	34.1	BoNT	33.4
4	Placebo	0.0	Placebo	0.0

Abbreviation: BoNT, botulinum toxin; FSW, focused shockwave; RSW, radial shockwave; MAS, modified Ashworth scale.

injections, FSW, and RSW appeared to be significantly better than the control treatment, with WMDs of -0.44 (95% CI, -0.62 to -0.26), -0.74 (95% CI, -1.26 to -0.23), and -0.79 (-1.07 to -0.51), respectively. The effectiveness of RSW was superior to that of BoNT injections (WMD, -0.35; 95% CI, -0.65 to -0.04). No significant differences were observed when the other treatment pairs were compared. The league tables for the pairwise and network meta-analyses are summarized in Supplemental Table 3. The loop inconsistency models (Supplementary Fig. 3B) showed no significant inconsistencies between the direct and indirect comparisons.

Regarding the reduction in the MAS between the 7<sup>th</sup> and 12<sup>th</sup> weeks, the rank probability results and the value of SUCRA are presented in Figure 5B and Table 3, respectively. The simulation of rank probabilities demonstrated that RSW had the highest probability (72.3%) to be the best treatment, followed by FSW as the second-best (72.0%). BoNT injections and the control treatment were likely to be the third-best (99.7%) and worst treatments (100.0%), respectively.

### 3.5. Publication bias

The funnel plots did not show obvious asymmetry in the inter-group comparisons of WMDs before or at the 6<sup>th</sup> week and between the 7<sup>th</sup> and 12<sup>th</sup> weeks (Supplementary Fig. 4). The *p* values of Egger's test for the effect sizes before or at the 6<sup>th</sup> week and those between the 7<sup>th</sup> and 12<sup>th</sup> weeks were 0.048 and 0.183, respectively.

## 4. Discussion

The present meta-analysis explored the comparative effectiveness of BoNT injections vs. ESWT in the management of post-stroke spasticity using evidence from RCTs. The results indicated that BoNT injections, FSW, and RSW were all effective in alleviating spasticity for at least 12 weeks in comparison to control treatments. RSW was likely to have the best anti-spasticity effect among the three treatments included in this analysis.

Our results revealed attenuation of the anti-spasticity efficacy of BoNT injections in contrast to ESWT during mid-term follow-up. The effectiveness of BoNT injections has been well studied, showing a decline at six to eight weeks after administration [57,58]. Among the reviewed articles, abobotulinumtoxinA was the most commonly used formulation, followed by onabotulinumtoxinA and incobotulinumtoxinA. However, the doses of BoNT administered to each muscle group varied significantly. Two antecedent studies confirmed a dose-response relationship, revealing a better anti-spasticity outcome with the use of higher BoNT doses per target muscle [43,46]. We found that a study employed minimal doses (e.g., onabotulinumtoxinA 15 U and 7.5 U for flexor carpi ulnaris and flexor digitorum superficialis muscles, respectively) [43] which were much lower than recent recommendations [41,43,59]. Moreover, the injection protocols varied across the enrolled studies, comprising differences in the types of BoNT, targeted muscles groups, dosage of BoNT and the timing of injections after the onset of stroke (Table 2). The spastic muscles were injected with a standard dose per muscle in most of the trials, while five trials allowed the physicians to decide about the

injection dose per muscle within a given range [16,48,49,52,54], and one trial allowed physicians to choose the targeted muscles for BoNT injections [55]. Care should be taken since heterogeneity in the doses and regimens could lead to the lack of superiority of BoNT injections over ESWT as far as the reduction in mid-term spasticity is concerned.

Muscle hypertonia develops as a result of impaired reflexes and secondary changes in rheological muscle properties, such as fibrosis, stiffness, and atrophy [60,61]. One previous study revealed no significant changes in the neurophysiological parameters (e.g., F-wave response and H-reflex to the maximum M-response ratio) after the application of ESWT [62]. Comparing the effectiveness of ESWT applied to the myotendinous junction and the muscle belly using ultrasound guidance, Yoon et al. found no significant differences between the effectiveness at each of the two sites, regardless of the density of motor points [38]. These findings indicate that ESWT plays no role in the alteration of spinal excitability or neuromuscular blockade. Modification of non-neurological factors, such as the elastic and viscous properties of the muscles, has been proposed as a mechanism for spasticity reduction. Increased production of nitric oxide (a neurotransmitter promoting muscle relaxation), stimulation of the muscle spindle, and recovery of muscle extensibility may contribute to the decrease in hypertonic muscle tension after the use of ESWT [63,64]. In our meta-analysis, most of the enrolled patients had chronic stroke and their affected limbs were speculated to have developed changes in muscular properties [13]. The direct effect of ESWT on the spastic muscles might also contribute to its better efficiency (than BoNT injections) which heavily relies on neuromuscular junction conditions.

In the present meta-analysis, we found that RSW was superior to FSW in terms of anti-spasticity efficacy. The maximal energy of FSW on the tissue is limited to a certain depth, leading to a smaller targeted area than that obtained with RSW. Furthermore, if the depth for FSW is set at a region where the muscle is fibrotic, the anti-spasticity effects are expected to be poor. In contrast, the energy generated in RSW disperses through the spastic muscle, and the muscle volume covered by RSW is greater than that covered by FSW. Moreover, the striking of the metal projectile in RSW results in a stronger vibration effect than in FSW. The vibration of shockwaves can potentially improve the tension of targeted muscle by breaking the link between actin and myosin [15,65].

Energy flux density and dosage of ESWT varied significantly among the included trials. Because the primary purpose of this meta-analysis was to compare the effectiveness of BoNT injections and the different modes of ESWT; the influences of treatment sessions, targeted muscles and ESWT machine settings were beyond the scope of this study. In a review of nine studies, Oh et al [66] reported that differences in the number of ESWT shocks and application sites (e.g., upper vs. lower limbs) had a negligible influence on the anti-spasticity effect. Therefore, we believe that the heterogeneity across the ESWT protocols had little impact on the comparability of ESWT with other treatments in our network comparisons.

Regarding the safety of ESWT and BoNT injections, the enrolled studies did not report severe adverse effects. However, the major

concern for BoNT injections is the formation of neutralizing antibodies (ranging from 0 to 3.6 %) after repeated treatments, which may jeopardize its therapeutic effects [67]. Alteration of muscle mechanics and intramuscular connective tissue contents were observed in the rat model following BoNT injections [68]. Unintended botulism-like syndrome is possible when hematogenic systemic spread occurs, particularly using a high injection dose [69]. On the contrary, the side effects of ESWT are usually mild, encompassing skin petechial or transient localized pain.

With regard to the effectiveness of BoNT injections, studies probing BoNT injections appeared to be more numerous than those using FSW or RSW. The effectiveness and safety of BoNT injections for spasticity reduction have been investigated in more details than those of ESWT. Furthermore, there was only one therapeutic arm with head-to-head comparison between ESWT and BoNT injections. The majority of BoNT injection vs. ESWT comparisons were derived from indirect comparisons performed through control treatments. Therefore, based on our meta-analysis, although the effectiveness of ESWT seemed comparable to BoNT injections, more RCTs directly comparing BoNT injections and ESWT are needed to confirm our preliminary observations.

The present study had some limitations. First, MAS (the most widely used method for spasticity assessment) was chosen as the main outcome. Our meta-analysis did not include studies using other assessment tools (e.g., the Tardieu scale) because of concerns regarding comparability. However, in the pertinent literature, there are only a few trials that have used non-MAS scales for spasticity evaluation; therefore, this would have had a minimal impact on our results. Herewith, Modified Modified Ashworth Scale (MMAS) can be considered for spasticity assessment in future studies due to better reliability [70]. Second, to facilitate the analysis, we treated MAS as a continuous variable. Accordingly, the pooled mean differences derived from our analysis could only be used to represent the direction and association between the treatment and its effect, but they might be insufficient to reflect the true effectiveness of the treatment. Third, long-term outcomes are lacking in our meta-analysis. The majority of the enrolled trials only followed patients for up to three months. As such, whether the effectiveness of BoNT injections and ESWT persists after the post-treatment third month requires further investigation. Fourth, the control groups included various therapies, including placebo injection, oral medication, and physical therapy. This may have caused high uncertainty, expressed by an enlarged 95% CI of the effect size in the control treatment. However, the effectiveness of the control groups was not our primary focus of investigation, and we believe that the intra-group heterogeneity would have a low influence on the interpretation of comparisons between BoNT injections and ESWT. Fifth, although previous studies reported insignificant influence on the anti-spasticity effects of ESWT regarding the amount of shock impulses per session and the application sites [66], the number of muscles needed to be treated could be another issue worth further investigation.

In conclusion, BoNT injections and ESWT are effective in alleviating post-stroke spasticity for at least 12 weeks. The effectiveness of ESWT was comparable to that of BoNT injections, whereas our meta-analysis indicated that RSW had the best potential among the three therapeutic options. More prospective trials incorporating head-to-head comparisons of BoNT injections vs. ESWT are needed to consolidate the use of ESWT for treating spasticity in chronic stroke.

#### Author Contributions

P.C.H. and K.V.C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: P.C.H., K.V.C. and Y.H.C.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: P.C.H.

Critical revision of the manuscript for important intellectual content: K.V.C. and L.Ö.

Statistical analysis: P.C.H. and W.T.W

Obtained funding: K.V.C

Administrative, technical, or material support: K.V.C. and Y.H.C.

Supervision: L.Ö.

#### Declaration of Competing Interest

Each author certifies that he or she has no commercial associations

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#### Data sharing statement

All data of the current study would be available upon reasonable request to the corresponding author.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.eclinm.2021.101222](https://doi.org/10.1016/j.eclinm.2021.101222).

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