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Duration of Treatment Effect of Extracorporeal Shock Wave on Spasticity and Subgroup-Analysis According to Number of Shocks and Application Site: A Meta-Analysis

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Objective To investigate duration of the treatment effect of extracorporeal shockwave therapy (ESWT) on spasticity levels measured with Modified Ashworth Scale (MAS) regardless of the patient group (stroke, multiple sclerosis, and cerebral palsy) and evaluate its spasticity-reducing effect depending on the number of shocks and site of application.

Methods PubMed, EMBASE, the Cochrane Library, and Scopus were searched from database inception to February 2018. Randomized controlled trials and cross-over trials were included. All participants had spasticity regardless of cause. ESWT was the main intervention and MAS score was the primary outcome. Among 122 screened articles, 9 trials met the inclusion criteria.

Results The estimate of effect size showed statistically significant MAS grade reduction immediately after treatment (standardized mean difference [SMD]=-0.57; 95% confidence interval [CI], -1.00 to -0.13; p=0.012), 1 week after (SMD=-1.81; 95% CI, -3.07 to -0.55; p=0.005), 4 weeks after (SMD=-2.35; 95% CI, -3.66 to -1.05; p<0.001), and 12 weeks after (SMD=-1.07; 95% CI, -2.04 to -0.10; p=0.03). Meta-regression and subgroup analysis were performed for the 'immediately after ESWT application' group. The prediction equation obtained from meta-regression was -1.0824+0.0002* (number of shocks), which was not statistically significant. Difference in MAS grade reduction depending on site of application was not statistically significant either in subgroup analysis (knee and ankle joints vs. elbow, wrist, and finger joints).

Conclusion ESWT effectively reduced spasticity levels measured with MAS regardless of patient group. Its effect maintained for 12 weeks. The number of shocks or site of application had no significant influence on the therapeutic effect of ESWT in reducing spasticity. Ongoing trials with ESWT are needed to address optimal parameters of shock wave to reduce spasticity regarding intensity, frequency, and numbers.

Keywords Extracorporeal shockwave therapy, Muscle spasticity, Meta-analysis

INTRODUCTION

Spasticity is a motor disorder that is characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks. It results from hyperexcitability of the stretch reflex as one component of the upper motor neuron syndrome [1]. The upper motor neuron (UMN) syndrome is due to parapyramidal fiber [2] dysfunction with some contribution from pyramidal fibers. Various conditions can cause UMN syndrome or spasticity.

Spasticity has been measured clinically and neurophysiologically to explain how the integrity of various segmental, plurisegmental pathways and rheological properties of muscles could be altered in the spastic state. Neurophysiological measurements provide quantitative indicators of alterations in various pathways—e.g., tibial F max/M max ratio [3,4], H-reflex latency [5], H-reflex recovery curve [6]. Clinical measurements could be used to evaluate the resistance to passive movement of the limb: Modified Ashworth Scale (MAS), Tardieu scale [7], and composite spasticity score [8]. However, major limitations concerning these neurophysiological and clinical measurements are the paucity of literature reporting its use and difficulties in incorporating these measurements into a meta-analysis model. In this meta-analysis, we used the MAS which remained the primary clinical measure of spasticity and proved to have good inter-rater reliability. The MAS is a 6-grade scale, ranging from 0 (normal muscle tone) to 4 (limb rigid in flexion or extension) [9].

Extracorporeal shockwave therapy (ESWT) was first applied in the treatment of kidney stones in 1980 [10]. Since then, it has shown therapeutic effect for pain relief in musculoskeletal disorders [11]. Its therapeutic effect in reducing spasticity has also been proven in stroke patients [12,13], children with cerebral palsy [14,15], and patients with multiple sclerosis [16]. Recent meta-analyses have demonstrated that its therapeutic effect can be maintained for up to 4 weeks [17,18]. However, there is no consensus about how long its treatment effects will last, how many times ESWT should be administered, or how treatment effects may differ depending on application sites.

Thus, the objective of this study was to investigate the duration of treatment effect of ESWT in reducing spasticity levels measured with MAS regardless of patient group (stroke, multiple sclerosis, and cerebral palsy) and valuate its spasticity-reducing effect depending on the number of shocks and the site of application.

MATERIALS AND METHODS

Literature search

Two reviewers performed a systematic search up to February 2018 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [19]. The study design was restricted to randomized controlled trials (RCTs) and cross-over trials. Other conditions were not restricted. To include all relevant studies, we used databases of PubMed, EMBASE, the Cochrane Library, and Scopus. The search strategy was based on MeSH or Emtree. Search terms were as follows: ('spasticity'/exp OR spasticity OR (('muscle'/exp OR muscle) AND ('spasticity'/exp OR spasticity)) OR 'rigidity'/exp OR rigidity OR (('muscle'/exp OR muscle) AND ('rigidity'/exp OR rigidity)) OR 'muscle tone'/exp OR 'muscle tone' OR (increased AND ('muscle'/exp OR muscle) AND ('tone'/exp OR tone)) OR 'muscle hypertonia'/exp OR 'muscle hypertonia' OR 'hypertonia'/exp OR hypertonia) AND ('shock'/exp OR shock) AND ('wave'/exp OR wave) AND ('therapy'/exp OR therapy).

Study selection

After duplicate articles were excluded using EndNote X8 (EndNote, Philadelphia, PA, USA), two reviewers independently selected articles. We included cross-over trials that had neither carry-over nor period effects. Cross-over trials had some advantages in that each participant acted as her or his control and fewer participants were needed to obtain the same power [20]. Any discrepancy was resolved by discussion. If discrepancies could not be resolved, a third author joined the discussion. The selection criteria were as follows: (1) study designs were RCTs and cross-over trials; (2) All participants had spasticity regardless of cause (stroke, multiple sclerosis, and cerebral palsy); (3) ESWT was the intervention and the outcome measure was the MAS; (4) MAS was evaluated at least twice (baseline and post-treatment) and expressed as a mean and standard deviation (SD). Only full report articles were included. Abstracts, books, letters, and posters were excluded.

Data extraction

Two reviewers independently extracted data from the included studies and made an extraction data table. The third person reviewed this table to make sure there was no error. The table had the following data extracted from included studies: author name, publication year, participants (lesion, numbers [treated/control], and duration of illness [treated/control]), intervention (ESWT energy, mode, application focus, treated muscle, and total counts), comparison (tested muscles and MAS at baseline), and outcomes (follow-up time points and MAS at follow-up time points).

Assessment of methodological quality

To assess methodological quality of included studies, analysis was performed with 'risk-of-bias tool' recommended by the Cochrane Handbook for Systematic Reviews of Intervention. It is a two-part tool addressing six specific domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias). Each domain includes one or more specific entries. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry [21]. Two reviewers conducted quality assessment independently. Disagreement was resolved by discussion.

Statistical analysis

All statistical analyses were performed using Comprehensive Meta-Analysis version 3.0 (Biostat Inc., Englewood, NJ, USA). Individual outcome measures are expressed as mean±SD. Standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated as effect sizes. Forest plot was generated depending on the follow-up period. Funnel plot was generated to evaluate publication bias. Additional trim-and-fill method was used to interpret the funnel plot objectively.

Heterogeneity refers to any kind of variability among studies due to clinical diversity or methodological diversity or both. An I^2 test was performed to measure heterogeneity of intervention effects. The I^2 test describes the percentage of variability in effects that are due to heterogeneity rather than to sampling error. A rough guide of I^2 thresholds of interpretation is as follows [22]: 0%–40%, negligible heterogeneity; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity. To address heterogeneity, a random-effects meta-analysis was performed to
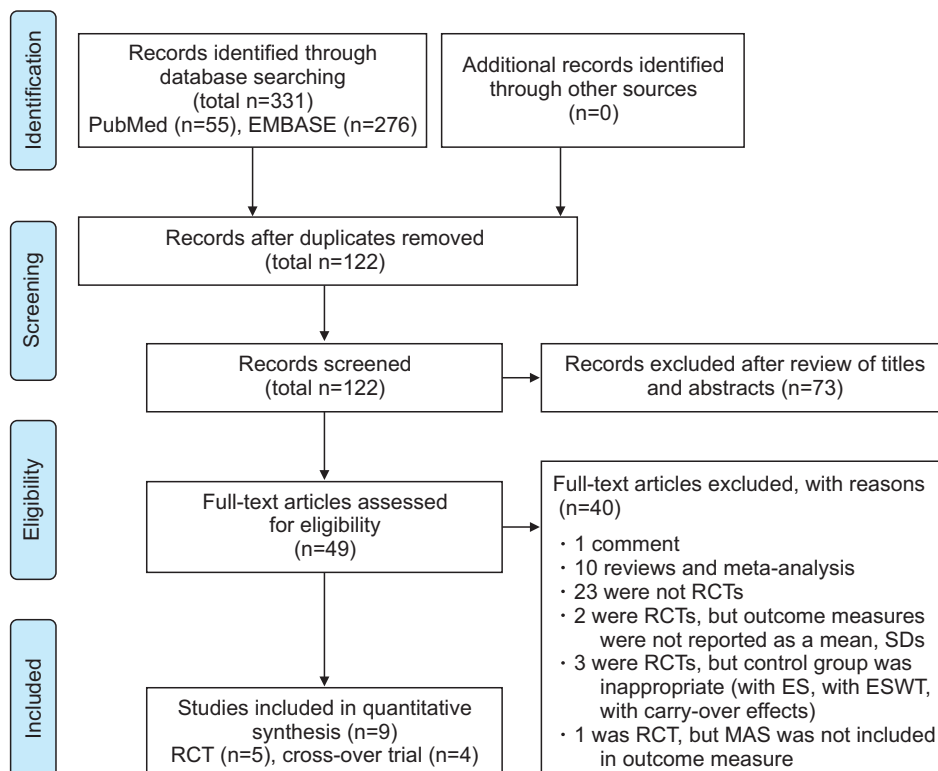
Fig. 1. Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) flow chart. RCT, randomized controlled trial; ES, electrical stimulation; ESWT, extracorporeal shockwave therapy; MAS, Modified Ashworth Scale.

Table 1. Detailed characteristics of individual studies (randomized controlled trials)

Study (year)	Participants				Intervention					Comparison			Outcome		
	Lesion	No. of patients (treated/control)	Duration of illness (mo) Treated	Control	ESWT energy (mJ/mm²)	Mode	Application focus	Treated muscle	Total counts (shots)	Tested muscle	MAS (baseline) Treated	Control	MAS Treated	Control	Follow-up time points (after the end of sessions)
Taheri et al. [23] (2017)	Stroke	14/14	33±21.4	25.8±9.9	0.1	NA	Myotendinous junction	GCM	4500	GCM	2.6±0.5	2.5±0.5	1.8±0.5 (immediately after)	2.1±0.7 (immediately after)	Immediately after, 9 weeks after
Yoon et al. [24] (2017)	Stroke	54/26 (elbow flexor)	100.3±98.3[a] 66.8±51.9[b]	63.5±94.1[c]	0.068–0.093	NA	Muscle belly, myotendinous junction	BB, semi-tendinosus	4500	BB	2.8±0.7[a] 2.9±0.5[b]	2.6±0.6[c]	2.6±0.8[a] 2.7±0.6[b]	2.6±0.6[c]	Immediately after
		26/28 (knew flexor)	99.1±85.1[d] 51.1±36.0[e]	38.7±30.2[f]						Semi-tendinosus	2.9±1.0[d] 2.9±0.6[e]	2.4±0.7[f]	2.4±0.8[d] 2.3±0.6[e]	2.4±0.7[f]	Immediately after
Dymarek et al. [13] (2016)	Stroke	30/30	51.30±25.46	51.53±26.13	0.03	Radial	Muscle belly	FCR, FCU	1500	Elbow	1.5±0.5	1.6±0.7	1.3±0.7 (immediately after)	1.6±0.8 (immediately after)	Immediately after, 1 hr after, 24 hr after
										RC	1.7±0.7	1.8±0.9	1.3±0.5 (immediately after)	1.7±0.8 (immediately after)	
										FF	2.1±0.9	1.7±0.7	1.5±0.8 (immediately after)	1.7±0.7 (immediately after)	

Continued on the next page.

Table 1. Continued

Study (year)	Lesion	Participants			Intervention					Comparison					Outcome
		No. of patients (treated/control)	Duration of illness (mo) Treated	Control	ESWT energy (mJ/mm²)	Mode	Application focus	Treated muscle	Total counts (shots)	Tested muscle	MAS (baseline) Treated	Control	MAS Treated	Control	Follow-up time points (after the end of sessions)
Marinelli et al. [16] (2015)	Multiple sclerosis	34/34	NA	NA	NA	Radial	Muscle belly, myotendinous junction	GCM, soleus, achilles tendon	8000	Ankle extensor	2.7±0.8	2.6±1.0	2.6±0.9	2.5±1.1 (4 weeks after)	1 week after, 4 weeks after
Tirbisch [25] (2015)	Stroke	4/4	0.75–6		0.03	NA	Myotendinous junction	GCM, soleus	18000	GCM	3.0±0.8	1.8±0.9	1.4±0.5	1.5±1.7	Immediately after
										Soleus	2.9±1.0	1.5±1.2	1.5±1.3	1.1±1.4	Immediately after

Values are presented as mean±standard deviation.

ESWT, extracorporeal shockwave therapy; MAS, Modified Ashworth Scale; NA, not applicable; GCM, gastrocnemius; PT, physiotherapy; BB, biceps brachii; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; RC, radio-carpal joint; FF, finger flexor joint.
[a]Belly group, [b]junction group, [c]control group for elbow flexor, [d]belly group, [e]junction group, and [f]control group for knee flexor.

Table 2. Detailed characteristics of individual studies (cross-over trials)

Participants				Intervention					Comparison		Outcome	
Study (year)	Lesion	No. of patients	Duration of illness	ESWT energy (mJ/mm²)	ESWT mode	Application focus	Treated muscle	Total counts (shots)	Tested muscle	MAS (baseline)	MAS	Follow-up time points
Moon et al. [26] (2013)	Stroke	30	80.5±46.5 days	0.089	NA	Myotendinous junction	GCM	4500	GCM	2.5±0.7	1.8±0.6 (4 weeks after)	Immediately after, 1 week after, 4 weeks after
Gonkova et al. [14] (2013)	Cerebral palsy	25	4.84±3.11 years	NA	Radial	Muscle belly	GCM, soleus	1500	Ankle extensor	2.7±0.1	2.2±0.1 (4 weeks after)	Immediately after, 2 weeks after, 4 weeks after
Amelio and Manganotti [15] (2010)	Cerebral palsy	12	8.0±2.31 years	0.03	NA	Muscle belly	GCM, soleus	1500	Ankle extensor	3.3±0.5	2.8±0.6 (12 weeks after)	Immediately after, 1 week after, 4 weeks after, 12 weeks after
Manganotti and Amelio [12] (2005)	Stroke	20	Stroke ≥9 months	0.03	NA	Muscle belly, myotendinous junction	Hypertonic forearm muscles, interosseus of hands	4700	Wrist flexors	3.4±0.7	3.0±0.5 (12 weeks after)	Immediately after, 1 week after, 4 weeks after, 12 weeks after
									Finger flexors	3.2±0.6	1.8±0.7 (12 weeks after)	

Values are presented as mean±standard deviation.
ESWT, extracorporeal shockwave therapy; MAS, Modified Ashworth Scale; NA, not applicable; GCM, gastrocnemius.

incorporate heterogeneity into a model and a sensitivity analysis was performed as a means of investigating heterogeneous results. Residual heterogeneity (heterogeneity not explained by subgrouping) was allowed by using the meta-regression technique [22].

Sensitivity analysis was also conducted to investigate the influence of each study on the overall outcome. Sample sizes, relative weights, residuals, and p-value are presented. Mean effect size after excluding studies one by one was then calculated. From sensitivity analysis, statistically significant outlier was excluded. Statistical analyses were performed using 95% CIs. The level of statistical significance was set at $p < 0.05$.

RESULTS

Eligible studies and characteristics

A flow chart displaying the study selection process is shown in Fig. 1. A total of 331 articles were identified from databases according to predetermined strategies without language restriction. After removing duplicates, 120 articles remained. After title and abstract review, 73 articles were excluded. After full-text review, 9 articles were finally included in the meta-analysis, including 5 RCTs [13,16,23-25] and 4 cross-over trials [12,14,15,26]. Detailed characteristics of included articles are described in Tables 1 and 2.

Risk-of-bias assessment

To ensure transparency in how judgments of risk of bias were made, we followed the table which provided criteria for making judgments about the risk of bias from each of the six domains in the tool. A judgment of 'Yes' indicated a low risk of bias, 'No' indicated a high risk of bias, and "Unclear" indicated unclear or unknown risk of bias. A 'Risk of bias graph' figure illustrated the proportion of studies with each judgement ('Yes', 'No', or 'Unclear') for each entry in the tool. A 'risk of bias summary' figure presented all judgements in a cross-tabulation of study by entry. Detailed information about six domains is shown in Figs. 2 and 3 [22]. We did not use scales or checklists. The use of scales or checklists was discouraged because
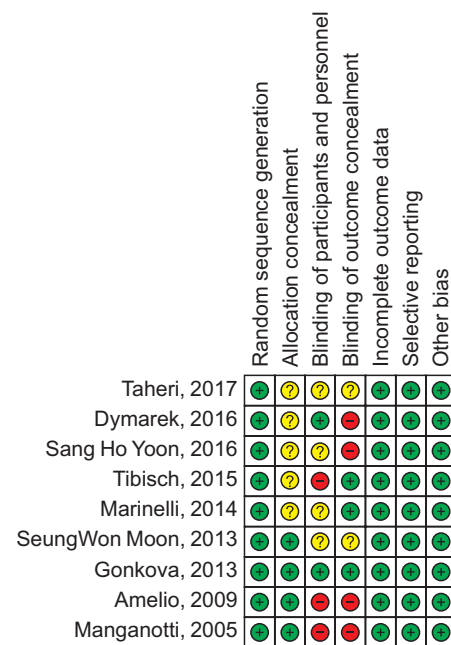

Fig. 3. Risk of bias summary. It presented all judgements in a cross-tabulation of study by entry of + (Yes), – (No), and ? (Unclear).
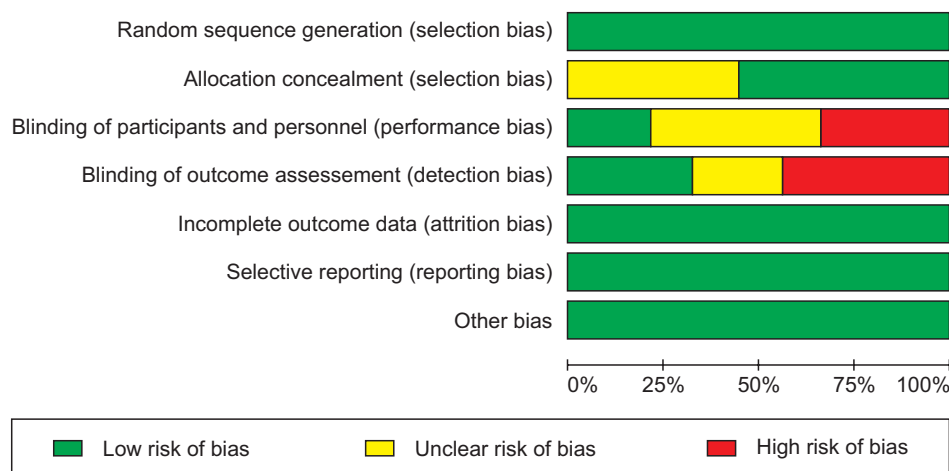

Fig. 2. Risk of bias graph illustrating the proportion of studies with each judgement ('Yes', 'No', or 'Unclear') for each entry in the tool.

many items in instruments were not directly related to internal validity [21].

Publication bias

Sensitivity analysis was performed for every result to exclude a small-study effect (a tendency for intervention effects estimated in smaller studies to differ from those estimated in larger studies). Studies showing statistically significant residuals were regarded as having a small study effect and excluded. All adjusted effect estimates from the trim-and-fill method were the same as the observed effect estimates. Because there was little difference between results obtained and the trim-and-fill adjusted estimates, it could be concluded that publication bias was unlikely to change conclusions of this meta-analysis [27] (Fig. 4).

Treatment effects depending on periods

Immediately after ESWT application

Fifteen groups from eight studies were evaluated to show the effect of ESWT on MAS grade immediately after application. The estimate of effect size showed statistically significant MAS grade reduction after ESWT (SMD=-1.22; 95% CI, -1.95 to -0.49; p=0.001; I^2=93.66) (Fig. 5A).

Sensitivity analyses revealed that Gonkova's and Manganotti-F's studies had statistically significant greater effects (Fig. 6A). After excluding each study one by one, Gonkova's and Manganotti-F's studies showed the greatest difference from the original results (Fig. 6B). Thus, it was reasonable to exclude Gonkova's and Manganotti-F's studies as outliers. As a result, the pooled estimate of the effect size was -0.57 (SMD=-0.57; 95% CI, -1.00 to -0.13; p=0.012; I^2=81.18) (Fig. 5B)
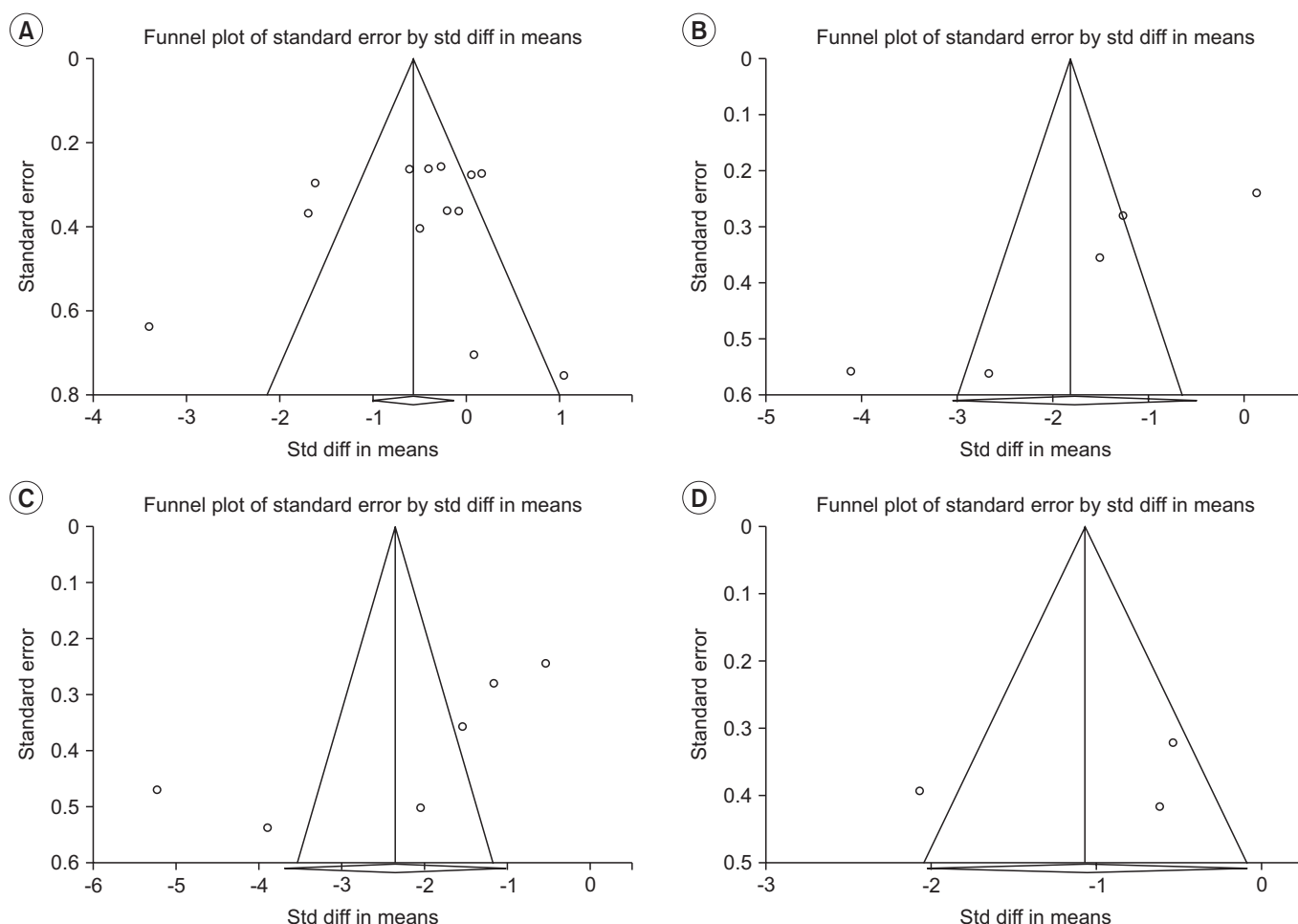

Fig. 4. Funnel plot to evaluate publication bias at (A) immediately after ESWT application, (B) 1 week after ESWT application, (C) 4 weeks after ESWT application, and (D) 12 weeks after ESWT application. Std diff, standard difference. ESWT, extracorporeal shockwave therapy.
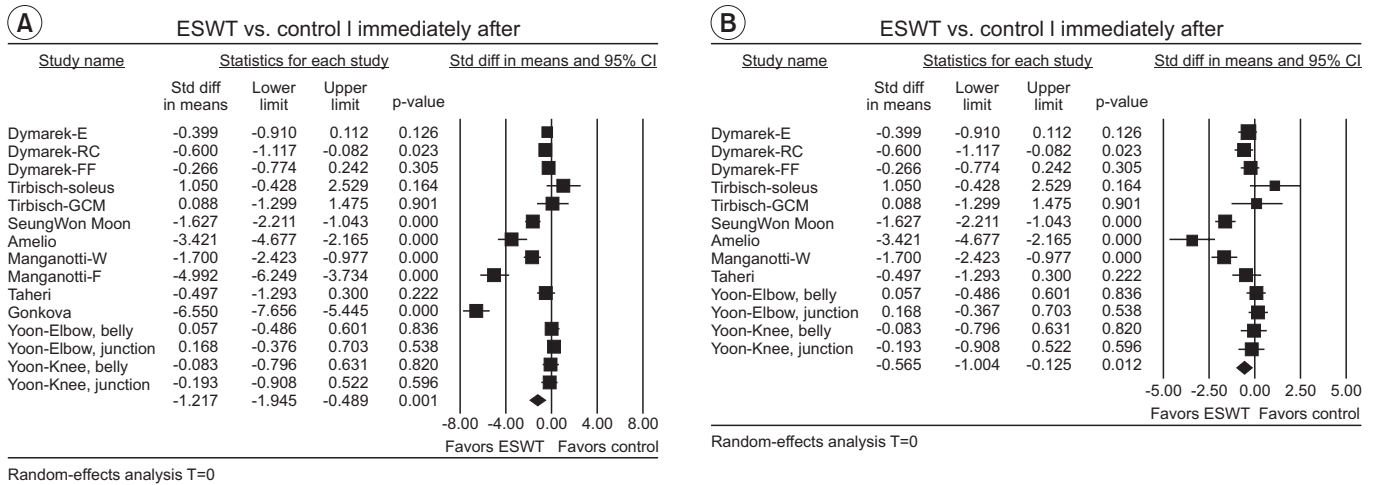
A ESWT vs. control I immediately after

Study name	Std diff in means	Lower limit	Upper limit	p-value
Dymarek-E	-0.399	-0.910	0.112	0.126
Dymarek-RC	-0.600	-1.117	-0.082	0.023
Dymarek-FF	-0.266	-0.774	0.242	0.305
Tirbisch-soleus	1.050	-0.428	2.529	0.164
Tirbisch-GCM	0.088	-1.299	1.475	0.901
SeungWon Moon	-1.627	-2.211	-1.043	0.000
Amelio	-3.421	-4.677	-2.165	0.000
Manganotti-W	-1.700	-2.423	-0.977	0.000
Manganotti-F	-4.992	-6.249	-3.734	0.000
Taheri	-0.497	-1.293	0.300	0.222
Gonkova	-6.550	-7.656	-5.445	0.000
Yoon-Elbow, belly	0.057	-0.486	0.601	0.836
Yoon-Elbow, junction	0.168	-0.376	0.703	0.538
Yoon-Knee, belly	-0.083	-0.796	0.631	0.820
Yoon-Knee, junction	-0.193	-0.908	0.522	0.596
	-1.217	-1.945	-0.489	0.001

Std diff in means and 95% CI
-8.00 -4.00 0.00 4.00 8.00
Favors ESWT Favors control

Random-effects analysis T=0

B ESWT vs. control I immediately after

Study name	Std diff in means	Lower limit	Upper limit	p-value
Dymarek-E	-0.399	-0.910	0.112	0.126
Dymarek-RC	-0.600	-1.117	-0.082	0.023
Dymarek-FF	-0.266	-0.774	0.242	0.305
Tirbisch-soleus	1.050	-0.428	2.529	0.164
Tirbisch-GCM	0.088	-1.299	1.475	0.901
SeungWon Moon	-1.627	-2.211	-1.043	0.000
Amelio	-3.421	-4.677	-2.165	0.000
Manganotti-W	-1.700	-2.423	-0.977	0.000
Taheri	-0.497	-1.293	0.300	0.222
Yoon-Elbow, belly	0.057	-0.486	0.601	0.836
Yoon-Elbow, junction	0.168	-0.367	0.703	0.538
Yoon-Knee, belly	-0.083	-0.796	0.631	0.820
Yoon-Knee, junction	-0.193	-0.908	0.522	0.596
	-0.565	-1.004	-0.125	0.012

Std diff in means and 95% CI
-5.00 -2.50 0.00 2.50 5.00
Favors ESWT Favors control

Random-effects analysis T=0

Fig. 5. Forest plot of effect sizes at (A) immediately after ESWT application, (B) after excluding outliers (Manganotti-F and Gonkova). ESWT, extracorporeal shockwave therapy; Std diff, standard difference; CI, confidence interval; E, elbow joint; RC, radio-carpal joint; FF, finger joints; GCM, gastrocnemius; W, wrist flexors; F, finger flexors.
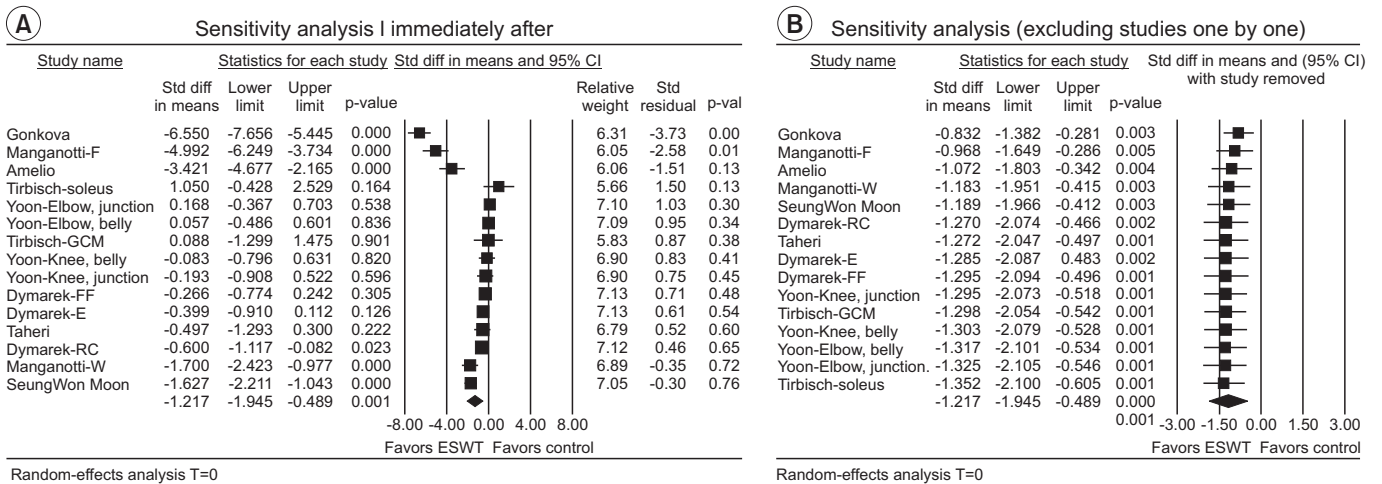
A Sensitivity analysis I immediately after

Study name	Std diff in means	Lower limit	Upper limit	p-value	Relative weight	Std residual	p-val
Gonkova	-6.550	-7.656	-5.445	0.000	6.31	-3.73	0.00
Manganotti-F	-4.992	-6.249	-3.734	0.000	6.05	-2.58	0.01
Amelio	-3.421	-4.677	-2.165	0.000	6.06	-1.51	0.13
Tirbisch-soleus	1.050	-0.428	2.529	0.164	5.66	1.50	0.13
Yoon-Elbow, junction	0.168	-0.367	0.703	0.538	7.10	1.03	0.30
Yoon-Elbow, belly	0.057	-0.486	0.601	0.836	7.09	0.95	0.34
Tirbisch-GCM	0.088	-1.299	1.475	0.901	5.83	0.87	0.38
Yoon-Knee, belly	-0.083	-0.796	0.631	0.820	6.90	0.83	0.41
Yoon-Knee, junction	-0.193	-0.908	0.522	0.596	6.90	0.75	0.45
Dymarek-FF	-0.266	-0.774	0.242	0.305	7.13	0.71	0.48
Dymarek-E	-0.399	-0.910	0.112	0.126	7.13	0.61	0.54
Taheri	-0.497	-1.293	0.300	0.222	6.79	0.52	0.60
Dymarek-RC	-0.600	-1.117	-0.082	0.023	7.12	0.46	0.65
Manganotti-W	-1.700	-2.423	-0.977	0.000	6.89	-0.35	0.72
SeungWon Moon	-1.627	-2.211	-1.043	0.000	7.05	-0.30	0.76
	-1.217	-1.945	-0.489	0.001			

Std diff in means and 95% CI
-8.00 -4.00 0.00 4.00 8.00
Favors ESWT Favors control

Random-effects analysis T=0

B Sensitivity analysis (excluding studies one by one)

Study name	Std diff in means	Lower limit	Upper limit	p-value
Gonkova	-0.832	-1.382	-0.281	0.003
Manganotti-F	-0.968	-1.649	-0.286	0.005
Amelio	-1.072	-1.803	-0.342	0.004
Manganotti-W	-1.183	-1.951	-0.415	0.003
SeungWon Moon	-1.189	-1.966	-0.412	0.003
Dymarek-RC	-1.270	-2.074	-0.466	0.002
Taheri	-1.272	-2.047	-0.497	0.001
Dymarek-E	-1.285	-2.087	0.483	0.002
Dymarek-FF	-1.295	-2.094	-0.496	0.001
Yoon-Knee, junction	-1.295	-2.073	-0.518	0.001
Tirbisch-GCM	-1.298	-2.054	-0.542	0.001
Yoon-Knee, belly	-1.303	-2.079	-0.528	0.001
Yoon-Elbow, belly	-1.317	-2.101	-0.534	0.001
Yoon-Elbow, junction.	-1.325	-2.105	-0.546	0.001
Tirbisch-soleus	-1.352	-2.100	-0.605	0.000
	-1.217	-1.945	-0.489	0.001

Std diff in means and (95% CI) with study removed
-3.00 -1.50 0.00 1.50 3.00
Favors ESWT Favors control

Random-effects analysis T=0

Fig. 6. (A) Sensitivity analysis with effect sizes, sample size, weight, and residual (immediately after ESWT application). (B) Sensitivity analysis with effect sizes after excluding studies one by one (immediately after ESWT application). ESWT, extracorporeal shockwave therapy; Std diff, standard difference; CI, confidence interval; E, elbow joint; RC, radio-carpal joint; FF, finger joints; GCM, gastrocnemius; W, wrist flexors; F, finger flexors.
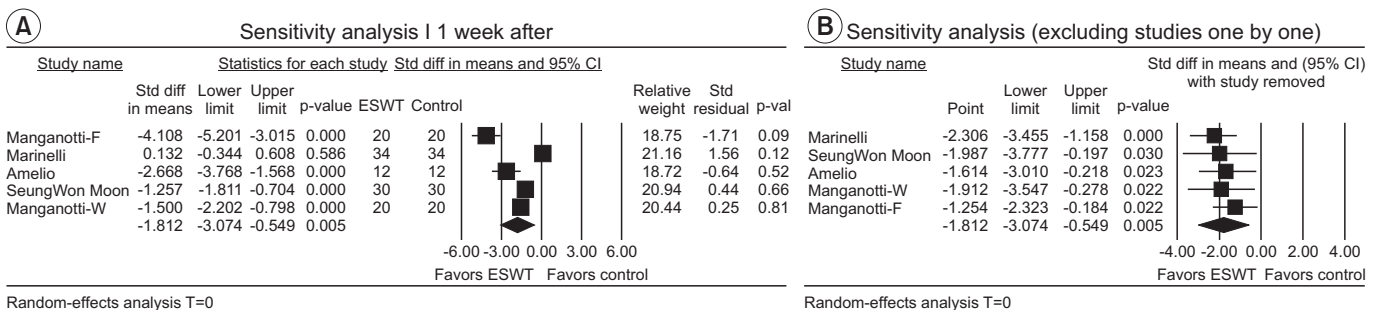
A Sensitivity analysis I 1 week after

Study name	Std diff in means	Lower limit	Upper limit	p-value	ESWT	Control	Relative weight	Std residual	p-val
Manganotti-F	-4.108	-5.201	-3.015	0.000	20	20	18.75	-1.71	0.09
Marinelli	0.132	-0.344	0.586	0.586	34	34	21.16	1.56	0.12
Amelio	-2.668	-3.768	-1.568	0.000	12	12	18.72	-0.64	0.52
SeungWon Moon	-1.257	-1.811	-0.704	0.000	30	30	20.94	0.44	0.66
Manganotti-W	-1.500	-2.202	-0.798	0.000	20	20	20.44	0.25	0.81
	-1.812	-3.074	-0.549	0.005					

Std diff in means and 95% CI
-6.00 -3.00 0.00 3.00 6.00
Favors ESWT Favors control

Random-effects analysis T=0

B Sensitivity analysis (excluding studies one by one)

Study name	Point	Lower limit	Upper limit	p-value
Marinelli	-2.306	-3.455	-1.158	0.000
SeungWon Moon	-1.987	-3.777	-0.197	0.030
Amelio	-1.614	-3.010	-0.218	0.023
Manganotti-W	-1.912	-3.547	-0.278	0.022
Manganotti-F	-1.254	-2.323	-0.184	0.022
	-1.812	-3.074	-0.549	0.005

Std diff in means and (95% CI) with study removed
-4.00 -2.00 0.00 2.00 4.00
Favors ESWT Favors control

Random-effects analysis T=0

Fig. 7. (A) Sensitivity analysis with effect sizes, sample size, weight, and residual (1 week after ESWT application). (B) Sensitivity analysis with effect sizes after excluding studies one by one (1 week after ESWT application). ESWT, extracorporeal shockwave therapy; Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.

One week after ESWT application

Six groups from five studies were evaluated to show an effect of ESWT on MAS grade one week after the application. Because no study had a statistically significant residual in sensitivity analysis (Fig. 7A) and effect sizes were similar after excluding each study one by one (Fig. 7B), all studies were included. The pooled estimate of effect size showed statistically significant MAS grade reduction (SMD=-1.81; 95% CI, -3.07 to -0.55; p=0.005; I^2=93.77) (Fig. 8).

Four weeks after ESWT application

Six groups from five studies were evaluated to show an effect of ESWT on MAS grade 4 weeks after the application. Because no study had a statistically significant residual in sensitivity analysis (Fig. 9A) and effect sizes were similar after excluding each study one by one (Fig. 9B), all studies were included. The pooled estimate of effect size showed statistically significant MAS grade reduction (SMD=-2.35; 95% CI, -3.66 to -1.05; p<0.001; I^2=94.96)

(Fig. 10).

Twelve weeks after ESWT application

Three groups from two studies were evaluated to show an effect of ESWT on MAS grade 12 weeks after the application. Because no study had a statistically significant residual in sensitivity analysis (Fig. 11A) and effect sizes were similar after excluding each study one by one (Fig. 11B), all studies were included. The pooled estimate of an effect size showed statistically significant MAS grade reduction (SMD=-1.07; 95% CI, -2.04 to -0.10; p=0.03; I^2=80.60) (Fig. 12).

Meta-regression (treatment effects depending on the number of shocks)

The regression coefficient obtained from a meta-regression analysis can describe how the intervention effect changes with a unit increase in the explanatory variable. Because of a small number of subgroups, meta-regression applied only for outcomes immediately after
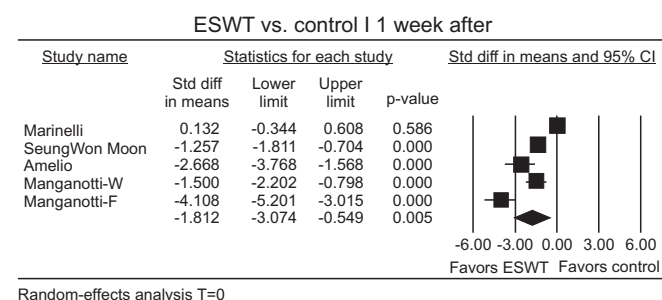
Fig. 8. Forest plot of the effect sizes 1 week after extracorporeal shockwave therapy (ESWT). Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.
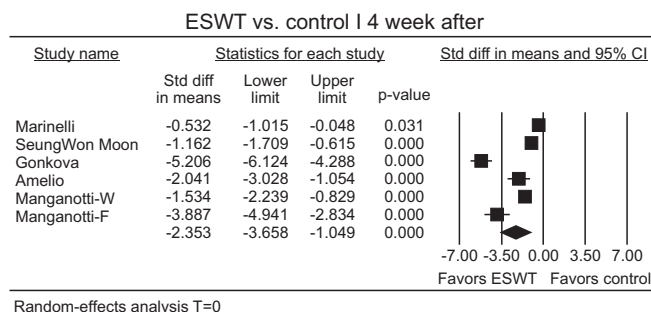
Fig. 10. Forest plot of effect sizes 4 weeks after extracorporeal shockwave therapy (ESWT). Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.
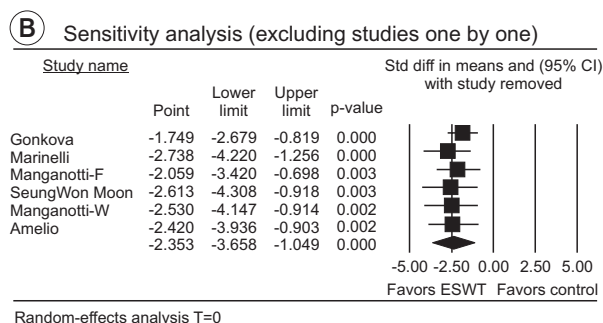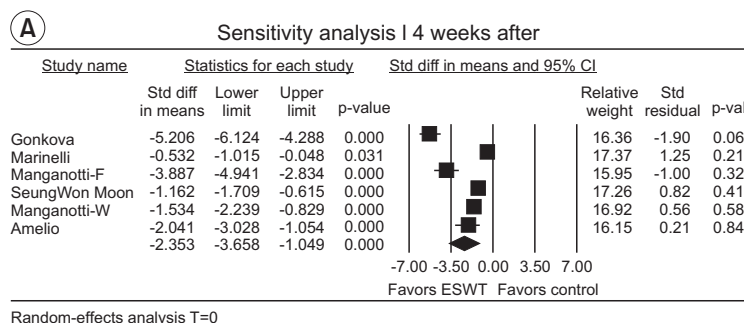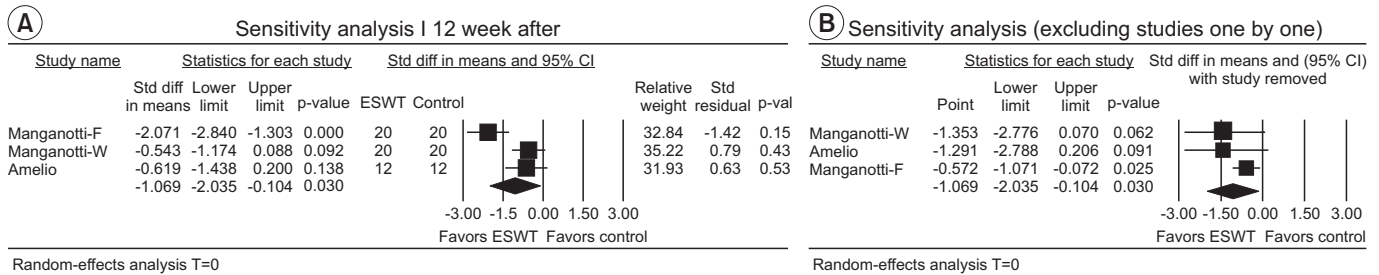

Fig. 9. (A) Sensitivity analysis with effect sizes, sample size, weight, and residual (4 weeks after the ESWT application). (B) Sensitivity analysis with effect sizes after excluding studies one by one (4 weeks after the ESWT application). ESWT, extracorporeal shockwave therapy; Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.
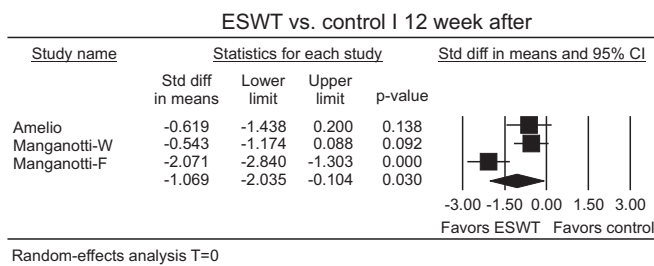
Fig. 11. (A) Sensitivity analysis with effect sizes, sample size, weight, and residual (12 weeks after ESWT application). (B) Sensitivity analysis with effect sizes after excluding studies one by one (12 weeks after ESWT application). ESWT, extracorporeal shockwave therapy; Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.

Fig. 12. Forest plot of the effect sizes 12 weeks after extracorporeal shockwave therapy (ESWT). Std diff, standard difference; CI, confidence interval; W, wrist flexors; F, finger flexors.

Fig. 13. Scatterplot of meta-regression under the random-effects model (immediately after ESWT application). ESWT, extracorporeal shockwave therapy.

ESWT application [22]. The prediction equation was -1.0824+0.0002* (number of shocks), which was not statistically significant (test of the model, p=0.28). R^2 analog was 0.00, meaning that a proportion of true variance in effects explained by total numbers was 0%. Effect sizes from the group immediately after ESWT application did not relate to the total number of shocks (Fig. 13).

Subgroup analysis (treatment effects depending on application site)

Depending on ESWT application site, we divided 'immediately after ESWT application' studies into two groups: 'knee and ankle joint' and 'wrist, elbow and finger joints'. The knee and ankle joint group had an effect (SMD=-0.71; 95% CI, -1.35 to -0.06; p=0.031). The elbow, wrist, and finger joints group also had an effect (SMD=-0.44; 95% CI, -1.05 to 0.18; p=0.16) (Fig. 14). Difference in SMD between the two groups was not statistically significant (total between Q value=0.35, degree of freedom=1, p=0.55).
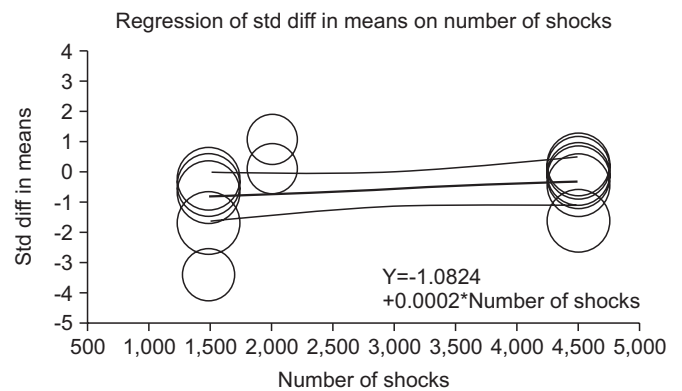
DISCUSSION

This study demonstrates that ESWT could effectively reduce spasticity levels measured with MAS regardless of patient group. Its effect could be maintained for 12 weeks. It has been proven that the effect of ESWT can be maintained for four weeks for patients with stroke or cerebral palsy in other meta-analyses [17,18]. Except for Manganotti's [12] and Amelio's [15] studies, all follow-up periods of previous meta-analyses [14,26,28-30] were within 6 weeks. To confirm duration of treatment effects of ESWT, future research follow-up period should be designed to be 12 weeks or more.

There was no relationship between the number of shocks and the therapeutic effect to reduce spasticity levels measured with MAS immediately after ESWT application. In studies included in this paper, ESWT was performed 1,500 to 18,000 times with an intensity of 0.03 mJ/mm^2 or within a range that did not cause pain. At-
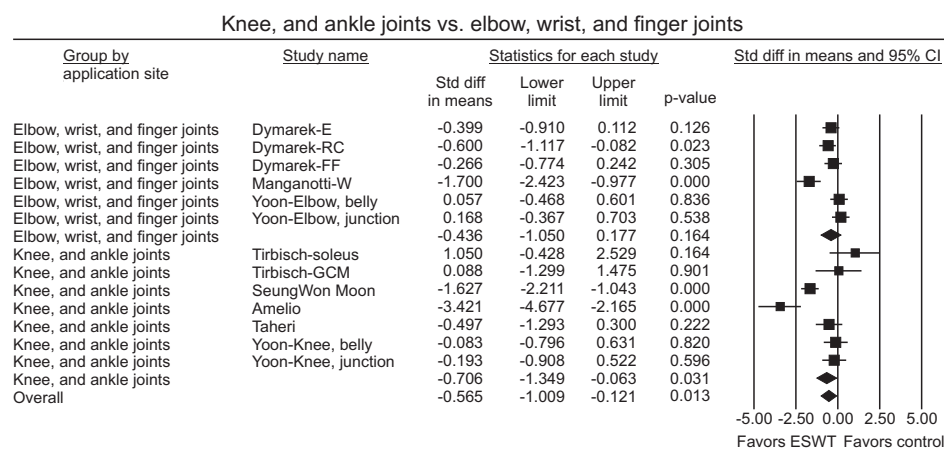
Knee, and ankle joints vs. elbow, wrist, and finger joints

Group by application site	Study name	Statistics for each study				Std diff in means and 95% CI
		Std diff in means	Lower limit	Upper limit	p-value	
Elbow, wrist, and finger joints	Dymarek-E	-0.399	-0.910	0.112	0.126	
Elbow, wrist, and finger joints	Dymarek-RC	-0.600	-1.117	-0.082	0.023	
Elbow, wrist, and finger joints	Dymarek-FF	-0.266	-0.774	0.242	0.305	
Elbow, wrist, and finger joints	Manganotti-W	-1.700	-2.423	-0.977	0.000	
Elbow, wrist, and finger joints	Yoon-Elbow, belly	0.057	-0.468	0.601	0.836	
Elbow, wrist, and finger joints	Yoon-Elbow, junction	0.168	-0.367	0.703	0.538	
Elbow, wrist, and finger joints		-0.436	-1.050	0.177	0.164	
Knee, and ankle joints	Tirbisch-soleus	1.050	-0.428	2.529	0.164	
Knee, and ankle joints	Tirbisch-GCM	0.088	-1.299	1.475	0.901	
Knee, and ankle joints	SeungWon Moon	-1.627	-2.211	-1.043	0.000	
Knee, and ankle joints	Amelio	-3.421	-4.677	-2.165	0.000	
Knee, and ankle joints	Taheri	-0.497	-1.293	0.300	0.222	
Knee, and ankle joints	Yoon-Knee, belly	-0.083	-0.796	0.631	0.820	
Knee, and ankle joints	Yoon-Knee, junction	-0.193	-0.908	0.522	0.596	
Knee, and ankle joints		-0.706	-1.349	-0.063	0.031	
Overall		-0.565	-1.009	-0.121	0.013	

-5.00 -2.50 0.00 2.50 5.00
Favors ESWT Favors control

Random-effects analysis T=0

Fig. 14. Forest plots of knee and ankle-joints group and elbow, wrist, and finger joints group depending on the application site (immediately after ESWT application). ESWT, extracorporeal shockwave therapy; E, elbow joint; RC, radio-carpal joint; FF, finger joints; GCM, gastrocnemius.

tention should be drawn to this result and interpretation because of considerable heterogeneity and small number of participants included in this study. Previous studies have reported a dose-response relationship between ESWT intensity and its effects regarding pain reduction [31] and healing promotion [32-34]. However, research on the relationship between the number of shocks and its therapeutic effects in reducing spasticity is lacking. Thus, further studies are required to ascertain the relationship.

The chief issue unresolved by this study is the potential mechanism of ESWT underlying the relationship between the number of shocks and its effects. Spasticity is a multidimensional problem. It is an untenable assumption to believe that MAS is an exclusive measure of spasticity (as defined by Lance [1]). Many studies have focused on increased spinal excitability as the primary cause of spasticity [35] and reported that amplitude of the F-wave, F-M ratio, latency of H-reflex, and H-M ratio can be used as tools for measuring spasticity electrophysiologically [36-38]. In a study of Sohn et al. [30], 10 healthy subjects and 10 hemiplegic stroke patients with plantar flexor spasticity received one session of EWST on the medial head of gastrocnemius. Although MAS of the plantar flexor improved significantly after the treatment, other variables (F-wave latency, H-reflex latency, and H-M ratio) were not changed. In studies included in this meta-analysis, examinations of the F-wave amplitude, H-reflex [24], H-max/M-max ratio, post-activation depression [16] were conducted. However, they had no significant changes after ESWT. These findings would support the idea that ESWT can reduce spasticity by directly affecting rheological properties and fibrosis of spastic muscles rather than

affecting spinal excitability [12,28,30,39].

Another result obtained in this study was that there was no significant difference in MAS values between lower and upper extremities' joints groups immediately after ESWT application. The knee and ankle joints group included soleus, gastrocnemius, and semitendinosus muscles while the elbow, wrist, and finger joints group included flexor carpi radialis, flexor carpi ulnaris, biceps brachii, interosseous of hands, and forearm muscles. This infers that ESWT has similar efficacy on any muscle with spasticity.

Because various patients and many treatment modes (ESWT energy, number of shocks, treated muscle) were included in this study, these study-level covariates could induce heterogeneity. In other meta-analyses, fixed-effects model was applied based on I^2 value (=0), assuming that stroke patients were the common population. However, the purpose of this study was to determine the overall effectiveness of ESWT regardless of the type or duration of illness. Thus, heterogeneous groups were included in this study. All I^2 values were greater than 80. We applied the random-effects model to incorporate heterogeneity into a model.

The present study had several limitations. First, publication bias could be a threat to the validity of findings from a meta-analysis. In this study, funnel plots showed asymmetrical appearance with a gap. The trim-and-fill method was used to adjust the results. However, funnel plot asymmetry may be caused by some factors other than publication bias. It is impossible to discern publication bias from any other possible cause of asymmetry [22]. Second, considering the inclusion of cross-over trials in

meta-analysis, the question of whether it is a suitable method for the condition should be addressed. Because all cross-over trials included in this study had sufficient washout periods to reduce carry-over (a type of period-by-intervention interaction), these were judged to be appropriate for meta-analysis [20]. Third, because many articles did not describe specific information on ESWT energy, mode, or combined therapy, we could not draw more conclusions through additional subgroup analysis and meta-regression.

In conclusion, ESWT effectively reduced spasticity levels measured with MAS regardless of patient group. Its effect maintained for 12 weeks. The number of shocks or the site of application had no significant influence on the therapeutic effect of ESWT in reducing spasticity. Thus, ESWT as a non-invasive, non-painful method could improve quality of life and facilitate rehabilitation by reducing spasticity. Further trials with ESWT are needed to address optimal parameters of the shock wave to reduce spasticity regarding its intensity, frequency, and numbers.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTION

Conceptualization: Oh JH, Park HD. Methodology: Oh JH, Han SH. Formal analysis: Oh JH. Funding acquisition: none. Project administration: Shim GY, Choi KY. Visualization: Oh JH. Writing - original draft: Oh JH. Writing - review and editing: Oh JH, Park HD. Approval of final manuscript: all authors.

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