MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 8160-8171
DOI: 10.12659/MSM.911296

Received: 2018.05.23
Accepted: 2018.07.02
Published: 2018.11.13

Efficacy and Safety of Botulinum Toxin Type A in Spasticity Caused by Spinal Cord Injury: A Randomized, Controlled Trial

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: This study was supported by the National Natural Science Foundation of China (No: 81472140)

Background: Baclofen is approved by the US FDA to treat spasticity, but its sustained use may cause drug addiction. The objective of this study was to compare the efficacy and safety of botulinum toxin type A versus baclofen in spasticity.

Material/Methods: A total of 336 patients who had spasticity caused by spinal cord injury were enrolled in a randomized (in 1: 1: 1: ratio) for placebo, controlled trial. Patients had received baclofen (BA group, n=112), local intramuscular injection of 500 U Botulinum toxin type A (BTI group, n=112), or physical therapies alone (placebo group, n=112). Modified Ashworth scale (mAS) score, disability assessment scale (DAS) score, modified medical research council (mMRC) score, the Barthel Index (BI) score, and treatment-emergent adverse effects were evaluated during the follow-up period. Wilcoxon test or one-way ANOVA/Tukey post hoc tests were performed at 95% of confidence level.

Results: Baclofen (1.504±0.045 *vs.* 1.53±0.06, p=0.003, q=4.068) and botulinum toxin type A (1.49±0.09 *vs.* 1.528±0.15, p=0.0224, q=3.5541) had improved mAS scores after 2 weeks. Baclofen had a more strongly improved DAS score than botulinum toxin type A at 4 (p=0.0496, q=3.48) and 6 (p<0.0001, q=6.48) weeks. Baclofen and botulinum toxin type A had consistently improved BI scores. Baclofen caused asthenia and sleepiness, while botulinum toxin type A caused bronchitis and elevated blood pressure.

Conclusions: Botulinum toxin type A may be an effective therapeutic option for spasticity caused by spinal cord injury.

MeSH Keywords: **Baclofen • Botulinum Toxins, Type A • Disabled Persons • Motor Activity • Muscle Spasticity • Spinal Cord Injuries**

Abbreviations: **US FDA** – The Food and Drug Administration of the United States; **CONSORT** – Consolidated Standards of Reporting Trials; **mAS** – modified Ashworth scale; **mMRC** – modified medical research council; **BI** – the Barthel Index; **ANOVA** – analysis of variance; **EMG** – electromyograph; **DAS** – disability assessment scale; **k** – Cohen kappa coefficient, ***q*** – critical value for Tukey *post hoc* test

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/911296

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Background

Motor neuron dysfunction is defined as spasticity. Spasticity due to spinal cord injury is difficult to manage and needs a multispecialty team [1]. The principal mechanism for the development of spasticity is disruptions in inhibitory descending motor pathways of the spinal cord, exaggerated tendon jerks, increase in muscle tone by velocity, and a stretch reflex hyperexcitability [2]. Pathologically, spasticity is increased skeletal muscle tone [3].

The treatment for spasticity is focused on rehabilitation of patients to improve daily activities and relieve pain [2]. Muscle relaxants are good options for spasticity caused by spinal cord injury because they work by acting on polysynaptic reflex mechanisms [4]. Spasticity caused by spinal cord injury is treated with oral and injectable medications. The strategy for treatment depends on the level of functional failure of the spasticity and its location. At present, baclofen (gamma-aminobutyric acid b agonist, a central muscle relaxant) [5] is used in systematic spasticity [6] and local intramuscular injection of botulinum toxin type A (acetylcholine inhibitor, a peripheral muscle relaxant) [7] in conjunction with appropriate physical therapy is used in focal dystonia and rigidity in hemiplegic or diplegic spasticity [1].

Baclofen is approved by the US FDA for treatment of spasticity caused by spinal cord injury [5]. It decreases muscle tone contractions of paralyzed muscles and hyperreflexia within 1 week of interventions [2]. However, it is a systemic, not a focal, treatment. It can cause weakness of the spastic limbs, sedation, dizziness, fatigue, headache, and ataxia [6]. Its sustained use may cause drug addiction, and sudden withdrawal can cause hallucinations and seizures [5].

Botulinum toxin is derived from *Clostridium botulinum* [8]. It takes a long time (100–115 days) for significant improvement in spasticity, and repeated treatment is also required [6]. Moreover, it can produce dose-related weakness of skeletal muscles by decreasing the release of acetylcholine at the neuromuscular junction [6].

The primary aim of the present study was to treat Chinese patients with spasticity caused by spinal cord injury using oral baclofen or local intramuscular injection of botulinum toxin type A. The secondary endpoint of the study was to compare efficacy and safety of botulinum toxin type A with baclofen at level 1a of evidence without conflict of interest.

Material and Methods

Drugs

Baclofen-10 mg (scored tablet) was purchased from Actavis-UK, Ltd. Baclofen-20 mg (Lioresal-20 mg) was purchased from Novartis (China), Ltd. Botulinum toxin type A (BTXA™) for injection was purchased from HUGH, China.

Ethics approval and consent to participate

This study had been registered in research registry (*www.researchregistry.com*), UID No. researchregistry4118 dated 3 December 2012. The protocol (SI/TJ/24/12, dated 28 November 2011) was approved by the Tianjin Hospital review board. The study adhered to CONSORT (Consolidated Standards of Reporting Trials) guidelines, the 2013 Declarations of Helsinki [9], and the laws of China. All enrolled patients signed an informed consent form regarding interventions and publication of the study, including images of the patients (if any) in all formats of dissemination (hard and/or electronic) irrespective of time and language.

Inclusion criteria

We included patients who had experienced spasticity caused by spinal cord injury and who were admitted to the Department of Neurosurgery and Rehabilitation of Tianjin Hospital, China from 15 December 2012 to 15 March 2017. Only patients aged 18 years and above and who signed an informed consent form were included in the study. Patients who had hip adductors muscle and medial hamstring muscle spasticity, chronic spastic hypertonia in the lower limbs (6 months or more history), 2 or lower modified Ashworth scale (mAS) score [10], 2 or lower modified medical research council (mMRC) score [11], and 50 or lower Barthel Index (BI) functional outcomes score [12] were included in the final enrollment.

Demographic characteristics of patients at the time of enrollment are presented in Table 1. There were no significant differences in demographical parameters between groups at the time of enrollment ($p>0.01$ for all).

Exclusion criteria

Patients aged under 18 years and who did not sign an informed consent form were excluded from the trial. Patients who had an orthopedic fracture or concomitant neurological disease, women patients with pregnancy or lactation period, patients who had not been tested for sensitivity to botulinum toxin type A injection (performed with diluted transdermal injection) were excluded from the trial. Patients who had been taking spasticity-modifying drug(s) and loss of locomotion other than spasticity were excluded from the final enrollment.

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Table 1. The demographic characteristics of the enrolled patients.

Characters		Groups			Comparison between groups
		Physical therapies alone	BA	BTI	
Interventions*		No medications	Baclofen	Botulinum toxin type A	
Sample size		112	112	112	*p*-Value
Gender	Male	30 (27)	40 (36)	36 (32)	0.353
	Female#	82 (73)	72 (64)	76 (68)	
Age (years)		35.47±2.21	36.55±3.42	36.95±7.12	0.055
Body weight (kg)		56.12±6.45	54.42±9.45	55.45±8.47	0.3
Height (cm)		151.52±6.45	153.54±7.89	152.89±8.45	0.132
Duration of illness (days)		205.98±16.45	211.45±25.47	207.45±20.49	0.136
Side affected	Dominant side	79 (71)	76 (68)	81 (72)	0.76
	Non-dominant side	33 (29)	36 (32)	31 (28)	
mAS score		1.48±0.08	1.504±0.045	1.49±0.09	0.053
mMRC score		1.84±0.03	1.83±0.05	1.82±0.09	0.055
BI functional outcomes score		37.12±3.11	35.95±4.12	36.58±3.45	0.052

Categorial data were represented as a number (percentage) and continuous data were presented as mean ±SD. *Chi-square* independence test and one-way ANOVA were performed for statistical analysis of Categorial data and Continuous data respectively. A $p<0.01$ was considered significant. * All patients were subjected to physical therapies without any kind of extra intervention(s). mAS – modified Ashworth Scale; mMRC – modified Medical Research Council; BI – Barthel Index. All patients were belonging to P.R. China. # No any female with pregnancy or lactation period.

Experimental Design

A total of 336 patients who had spasticity caused by spinal cord injury were subjected to randomization (simple randomization, 1: 1: 1 ratio). The sample size was calculated by OpenEpi 3.01-English (Open Source Epidemiologic Statistics for Public Health, USA), with 112 in each group. For the other parameters, 2-sided confidence intervals were 95%, risk ratio detected was 1, and normal approximation was 1.073%. The CONSORT flow diagram of the study is shown in Figure 1. The randomization code was prepared by the institute and it was kept blind until the trial was completed.

Interventions

Patients in the BA group received a half tablet (5 mg) of baclofen 3 times in a day for 1 week, 1 tablet (10 mg) of baclofen 3 times in day for 1 week in the second week, one and a half tablets (15 mg) of baclofen 3 times a day for 1 week in the third week, and 1 tablet (20 mg) of baclofen 3 times a day for 1 week in the fourth week [13]. Patients in the BTI group received a local intramuscular injection of 500 U of botulinum toxin type A. An electromyograph (EMG) was used for identification of exact muscles [14]. All enrolled patients were subjected to physical therapies such as locomotor training (e.g., body weight-supported treadmill training, stepping practice, walking practice on a treadmill or over the ground, walking practice within and between exercise stations) [15], and intensive task-specific training (motor learning, e.g., walking, sit-to-stand transfers, and standing) [16] for rehabilitation under the supervision of physiotherapists for 6 weeks. The patients who had not received any interventions but who received physical therapies were included in the placebo group.

Outcome measures

Outcome measures were evaluated at 2 weeks, 4 weeks, and 6 weeks from the start of the intervention at level 1a (Table 2) of evidence [17].

mAS score

Muscle tone of thumb, wrist, and fingers were measured as shown in Table 3 [2].

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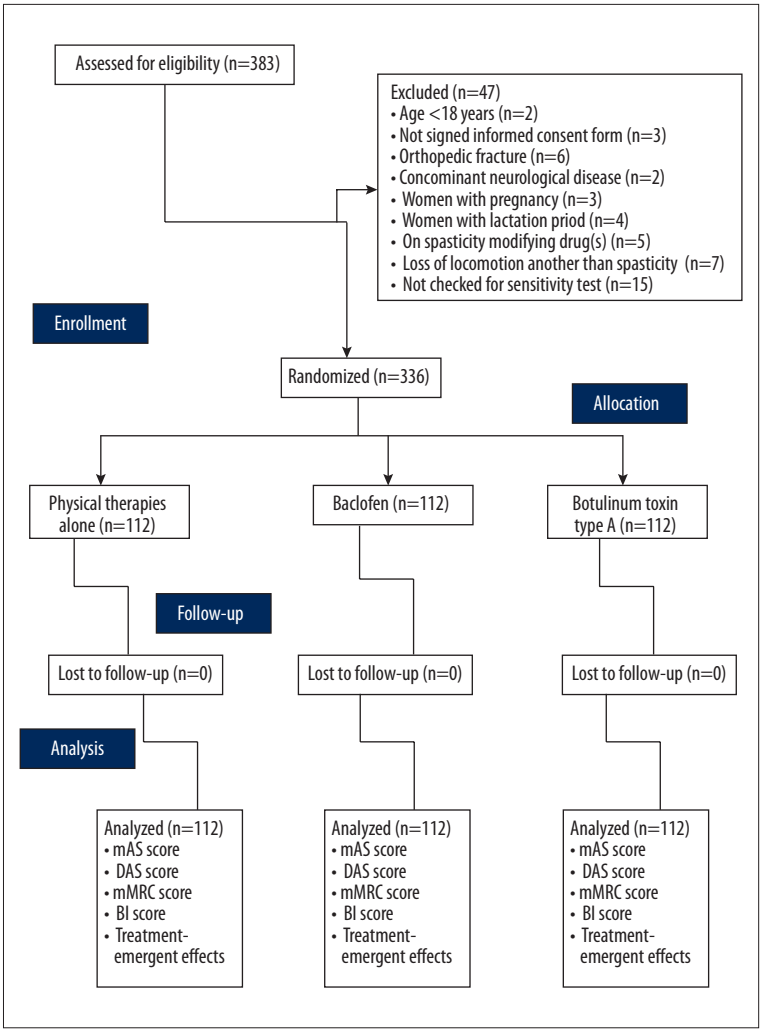

Figure 1. CONSORT flow diagram of the trial. mAS – modified Ashworth Scale; mMRC – modified Medical Research Council; BI – Barthel Index functional outcomes. Two-sided confidence intervals: 95%, risk ratio detected: 1, and normal approximation: 1.073%. Intention-to-treat analysis method was preferred.

Table 2. Level of evidence.

Level	Treatment study	Sub-level	Quality of evidence
1	RCT with adequate statistical power	a	Strong
2	RCT with improper randomization	b	Moderate
3	A case study with analysis	c	Low
4	Case study without analysis		
5	Expert opinion		

RCT – randomized controlled trial. Source: *https://www.elsevier.com/journals/journal-of-shoulder-and-elbow-surgery/1058-2746/guide-for-authors*.

Disability Assessment Scale (DAS) score

DAS score was accessed as 0: no disability, 1: slight disability, 2: moderate disability, 3: severe disability, and 4: extreme disability [14].

Muscle strength

Muscle strength was measured as mMRC score (as shown in Table 4) [11].

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Table 3. Modified Ashworth scale grading.

Condition	Grading
No improvement	0
Small improvement	1
Improvement manifested by a catch, the affected part is not easily moved	2
Improvement manifested by a catch, the affected part is easily moved	3
A significant increase in muscle tone, no passive movement	4
A significant increase in muscle tone with passive movement	5

Table 4. Modified medical research council grading.

Condition	Grading
No contraction	0
Trace of contraction	1
Movement with gravity	2
The movement against gravity but against resistance	3
The movement against gravity and with weak resistance	4
The movement against gravity and with strong resistance	5
Normal power	6

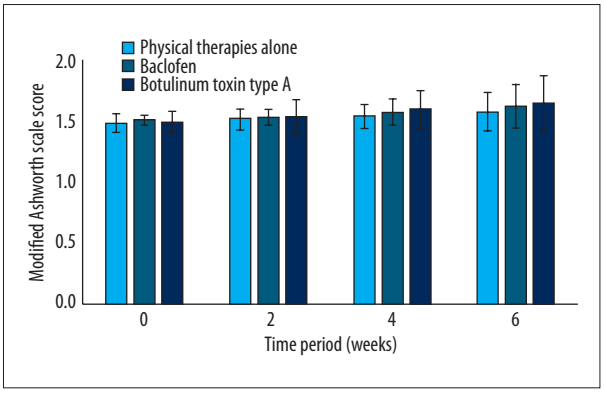

Figure 2. Modified Ashworth scale score during follow-up study. Compared to baseline, at 2 weeks, physical therapies alone had no effect (p=0.063), baclofen (1.504±0.045 *vs.* 1.53±0.06, p=0.003, q=4.068) and botulinum toxin type A (1.49±0.09 *vs.* 1.528±0.15, p=0.0224, q=3.5541) had improved mAS score. At 4 weeks, physical therapies alone (1.535±0.1 *vs.* 1.48±0.08, p<0.0001, q=6.44) baclofen (1.57±0.11 *vs.* 1.504±0.045, p<0.0001, q=9.087), and botulinum toxin type A (1.59±0.16 *vs.* 1.49±0.09, p<0.0001, q=7.732) had improved mAS scores. After 6 weeks, baclofen (1.62±0.18 *vs.* 1.57±0.16, p=0.02, q=2.75) had not improved and botulinum toxin type A (1.64±0.23 *vs.* 1.57±0.16, p=0.02, q=3.85) had improved mAS score compared to physical therapies alone. mAS – modified Ashworth scale. One-way ANOVA following Tukey post hoc test were performed for statistical analysis. A p<0.05 and q>3.332 were considered as significant. 0 week: Baseline. Data are represented as mean ±SD of all, n=112.

Functional outcomes

Functional outcomes were measured by BI functional outcome scores of 10 activities (toilet use (score: 0–5–10), bladder care (score: 0–5–10), bowels (score: 0–5–10), ambulation (score: 0–5–10–15), feeding (score: 0–5–10), bathing (score: 0–5), dressing (score: 0–5–10), grooming (score: 0–5), stair climbing (score: 0–5–10), and transfers (score: 0–5–10–15)). The code was made as 0: totally dependent and 100: totally independent. The maximum score in each activity was only given when patients performed it without the help of human or electronic evaluator(s) [12].

Safety study

Treatment-emergent effects were monitored daily up to 12 weeks from enrollment by evaluators who were blind to the study [2].

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Table 5. Disability Assessment Scale score.

Characters		Groups			Comparison between groups			
		Physical therapies alone	BA	BTI				
Interventions		No medications (1)	Baclofen (2)	Botulinum toxin type A (3)	*p*-Value	*q*-Value		
Sample size		112	112	112		1 *vs.* 2	1 *vs.* 3	2 *vs.* 3
BL (I)		3.10±0.11	3.085±0.12	3.12±0.09	0.0514	N/A	N/A	N/A
2 weeks (II)		3.08±0.2	3.054±0.18	3.1±0.1	0.116	N/A	N/A	N/A
4 weeks (III)		3.07±0.15	3.045±0.18	3.095±0.12	0.0496	1.74	1.74	3.48
6 weeks (IV)		3.059±0.195	2.99±0.15	3.09±0.14	<0.0001	4.468	2.01	6.48
Statistical analysis within the group	*p*-Value I *vs.* II	0.355	0.131	0.117	N/A	N/A	N/A	N/A
	p-Value I *vs.* III	0.0893	0.052	0.079	N/A	N/A	N/A	N/A
	p-Value I *vs.* IV	0.054	<0.0001	0.058	N/A	N/A	N/A	N/A
	q-Value I *vs.* IV	N/A	6.615	N/A	N/A	N/A	N/A	N/A
	p-Value II *vs.* III	0.673	0.709	0.735	N/A	N/A	N/A	N/A
	p-Value II *vs.* IV	0.427	0.0042	0.539	N/A	N/A	N/A	N/A
	q-Value II *vs.* IV	N/A	4.456	N/A	N/A	N/A	N/A	N/A
	p-Value III *vs.* IV	0.637	0.014	0.774	N/A	N/A	N/A	N/A
	q-Value III *vs.* IV	N/A	3.412	N/A	N/A	N/A	N/A	N/A

Wilcoxon test (within the group) or one-way ANOVA (between group) following Tukey *post hoc* tests were performed for statistical analysis. A $p<0.05$ and $q>3.332$ were considered as significant. BL – baseline. Data were represented as mean ±SD of all, n=112. N/A – not applicable. 0: No disability, 1: slight disability, 2: moderate disability, 3: severe disability, and 4: extreme disability.

Statistical analysis

InStat (GraphPad, USA) was used for statistical analysis. The independent-samples chi-square test and one-way analysis of variance (ANOVA) were performed for categorical and continuous data of demographic characteristics at the time of enrollment (99% of confidence level) [6]. All data were evaluated twice for reliability. Kendall Tau-b (considering <0.5: weak relationship, 0.5–0.7: moderate relationship, and >0.7: strong relationship) and Cohen kappa (k) statistics (considering k values as 0.81–1: very good reliability, 0.61–0.80: good reliability, 0.41–0.60: moderate reliability, and <0.21: poor reliability) were used for inter-rater reliability for continuous and categorical data, respectively [10]. Wilcoxon test following Tukey post hoc test (considering critical value (q) >3.332) was performed within the group, and one-way ANOVA following Tukey post hoc test (considering $q>3.332$) was performed between groups. Results during the follow-up period were considered significant at 95% confidence level. Intention-to-treat analysis method was preferred.

Results

Evaluators had a strong relationship (Kendall Tau-b results=0.76) and very good reliability (k=0.85) for continuous and categorical data during the trial.

Physical therapies alone showed improved mAS scores after 4 weeks of exercise (1.48±0.08 *vs.* 1.535±0.1, $p<0.0001$, $q=8.05$). Baclofen (1.504±0.045 *vs.* 1.53±0.06, $p=0.003$, $q=4.068$) and botulinum toxin type A (1.49±0.09 *vs.* 1.528±0.15, $p=0.0224$, $q=3.5541$) showed improved mAS scores after 2 weeks of intervention. There was significant improvement in mAS scores at 6 weeks compared to 4 weeks for baclofen (1.62±0.18 *vs.* 1.57±0.11, $p=0.013$, $q=3.462$) but there was no significant improvement in mAS score at 6 weeks compared to 4 weeks for botulinum toxin type A (1.64±0.23 *vs.* 1.59±0.16, $p=0.06$). However, after 6 weeks, baclofen (1.62±0.18 *vs.* 1.57±0.16, $p=0.02$, $q=2.75$) did not show improvement and botulinum toxin type A (1.64±0.23 *vs.* 1.57±0.16, $p=0.02$, $q=3.85$) did show improvement of mAS score for physical therapies alone (Figure 2).

Baclofen showed a more improved DAS score than botulinum toxin type A at 4 weeks ($p=0.0496$, $q=3.48$) and 6 weeks ($p<0.0001$, $q=6.48$, Table 5).

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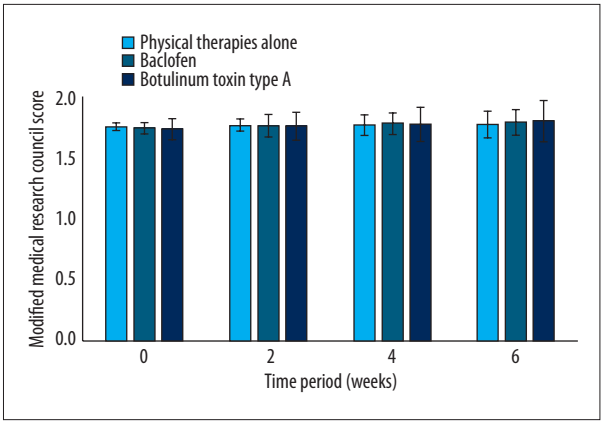

Figure 3. Modified medical research council score during follow-up study. After 6 weeks, physical therapies alone failed to improve mMRC score (p=0.053). From 4 weeks onwards, baclofen and botulinum toxin type A had succeeded in improvement of mMRC score compared to baseline. mMRC: Modified medical research council. One-way ANOVA following Tukey post hoc test was performed for statistical analysis. A p<0.05 and q>3.332 were considered as significant. 0 week: Baseline. Data are represented as mean ±SD of all, n=112.

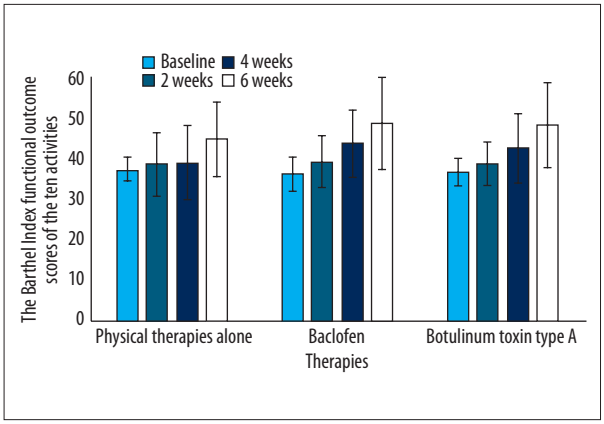

Figure 4. The Barthel Index functional outcome scores of the 10 activities during follow-up study. After 6 months, physical therapies alone started to show improved BI functional outcome scores (37.12±3.11 *vs.* 44.51±9.11, p<0.0001, q=10.113). Baclofen (35.95±4.12 *vs.* 39.15±6.15, p<0.0001, q=5.42) and botulinum toxin type A (36.58±3.45 *vs.* 38.54±5.45, p=0.0015, q=4.03) began to show improved BI scores within 2 weeks. Effects of baclofen and botulinum toxin type A for improvement in BI score were the same (p=0.007, q=0.42) after 6 weeks of intervention(s). BI – Barthel Index. One-way ANOVA following Tukey post hoc test was performed for statistical analysis. A p<0.05 and q>3.332 were considered as significant. Data are represented as mean ±SD of all, n=112. 0: Total dependent and 100: Total independent. Activities: Toilet use (score: 0–5–10), bladder care (score: 0–5–10), bowels (score: 0–5–10), ambulation (score: 0–5–10–15), feeding (score: 0–5–10), bathing (score: 0–5), dressing (score: 0–5–10), grooming (score: 0–5), stair climbing (score: 0–5–10), and transfers (score: 0–5–10–15).

Physical therapies alone failed to improve mMRC score during the follow-up period. After 4 weeks, baclofen (1.83±0.05 *vs.* 1.87±0.09, p<0.0001, q=5.362) and botulinum toxin type A (1.82±0.09 *vs.* 1.86±0.15, p=0.0163, q=3.727) were successful in improving mMRC scores. Consistency in improvement of mMRC score lasted up to 2 weeks for baclofen (1.85±0.1 *vs.* 1.87±0.09, p=0.117) and consistent improvement with botulinum toxin type A lasted up to 4 weeks (1.86±0.15 *vs.* 1.89±0.18, p=0.12, Figure 3).

Physical therapies alone were required at least 6 weeks for improvement of BI functional outcome scores (37.12±3.11 *vs.* 44.51±9.11, p<0.0001, q=10.113). However, baclofen (35.95±4.12 *vs.* 39.15±6.15, p<0.0001, q=5.42) and botulinum toxin type A (36.58±3.45 *vs.* 38.54±5.45, p=0.0015, q=4.03) showed improved BI scores of functional outcomes within 2 weeks. After 6 weeks, baclofen (48.52±11.45 from 35.95±4.12) and botulinum toxin type A (48.11±10.54 from 36.58±3.45) had the same effects on BI score of functional outcomes (p=0.007, q=0.42) and consistently improved BI functional outcome scores during the follow-up period (Figure 4).

During 12-week follow-up, asthenia (p<0.0001, q=10.27) and sleepiness (p=0.0002, q=5.06) were produced by baclofen, while botulinum toxin type A produced muscle soreness (p=0. 0002, q=5.06), bronchitis with difficulty swallowing (p=0.006, q=3.95), elevated blood pressure (p=0.017, q=3.51), and elevated blood creatine phosphokinase level (p=0.006, q=3.95, Table 6).

Discussion

We found that baclofen had an intervention-dependent effect and botulinum toxin type A had a sustained effect of improving mAS score during the follow-up period (Table 7). Physical therapies alone do not improve muscle tone [16]. Baclofen has a short-term effect on spasticity [2,4] and the body can quickly develop resistance against it [18]. However, botulinum toxin type A has persistent inhibition of neurotransmitter release [19]. The mAS score shows that botulinum toxin type A administration in conjunction with physical rehabilitation therapy is an effective treatment option for spasticity caused by spinal cord injury.

Baclofen and botulinum toxin type A had improved mMRC scores after 2 weeks and 4 weeks of interventions, respectively (Table 8). Baclofen has been reported to have a negative effect on muscle strength of patients with spasticity caused by spinal cord injury [20]. The mMRC score showed that baclofen has a

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Table 6. Treatment-emergent effects during follow-up study of 12 weeks.

Characters	Groups			Comparison between groups			
	Physical therapies alone	BA	BTI				
Interventions	No medications (1)	Baclofen (2)	Botulinum toxin type A (3)	*p*-Value	*q*-Value		
Sample size	112	112	112		1 *vs.* 2	1 *vs.* 3	2 *vs.* 3
Epigastric pain	0 (0)	3 (3)	0 (0)	0.048	3.03	0.0	3.03
Amenorrhea	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Headache	1 (1)	1 (1)	1 (1)	N/A	N/A	N/A	N/A
Anorexia	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Hypochondrial pain	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Asthenia*	1 (1)	31 (28)	2 (2)	<0.0001	10.27	0.34	9.93
Hyposthenia	2 (2)	7 (6)	4 (4)	0.22	N/A	N/A	N/A
Cramps	0 (0)	1 (1)	0 (0)	0.369	N/A	N/A	N/A
Paresthesia	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Sweating	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Sciatica	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Vertigo	0 (0)	2 (2)	0 (0)	0.1345	N/A	N/A	N/A
Sleepiness*	0 (0)	8 (7)	0 (0)	0.0002	5.06	0.0	5.06
Nausea	0 (0)	3 (3)	0 (0)	0.048	3.03	0.0	3..03
Muscle soreness#	0 (0)	0 (0)	8 (7)	0.0002	0.0	5.06	5.06
Pain at site of injection#	0 (0)	0 (0)	9 (8)	<0.0001	0.0	5.39	5.39
Epilepsy	0 (0)	0 (0)	1 (1)	0.369	N/A	N/A	N/A
Bronchitis with swallowing trouble#	0 (0)	0 (0)	5 (4)	0.006	0.0	3.95	3.95
Musculoskeletal stiffness	2 (2)	0 (0)	4 (4)	0.1313	N/A	N/A	N/A
High blood pressure#	0 (0)	0 (0)	4 (4)	0.017	0.0	3.51	3.51
Increased blood creatine phosphokinase#	0 (0)	0 (0)	5 (4)	0.006	0.0	3.95	3.95

One-way ANOVA following Tukey *post hoc* test was performed for statistical analysis. A $p<0.05$ and $q>3.332$ were considered as significant. Data were represented as number (percentage). N/A – not applicable. For statistical analysis, the treatment-emergent effect was considered as 1 and absent of event was considered as 0. * Significant treatment-emergent effect with baclofen.
The significant treatment-emergent effect with botulinum toxin type A.

temporary effect on spasticity and further trials are required to determine the mechanism of action.

Unlike mAS and mMRC scores, baclofen and botulinum toxin type A both had consistent improvement in BI scores of functional outcomes during the follow-up period (Table 9). Baclofen and botulinum toxin type A both improved BI functional outcomes [18]. With respect to the selection of medications for treatment, a high the level of functioning in activities of daily living in patients with spasticity can be achieved with oral baclofen or local injection of botulinum toxin type A.

Physical therapies alone and botulinum toxin type A did not improve physical disability of patients, but baclofen improved

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Table 7. Modified Ashworth scale score during the follow-up study.

Characters		Groups			Comparison between groups			
		Placebo	BA	BTI				
Interventions		No medications (I)	Baclofen (II)	Botulinum toxin type A (III)	*p*-Value	*q*-Value		
Sample size		112	112	112		I vs. II	I vs. III	II vs. III
BL (1)		1.48±0.08	1.504±0.045	1.49±0.09	0.053	N/A	N/A	N/A
2 weeks (2)		1.51±0.09	1.53±0.06	1.528±0.15	0.305	N/A	N/A	N/A
4 weeks (3)		1.535±0.1	1.57±0.11	1.59±0.16	0.005	2.94	4.62	1.68
6 weeks (4)		1.57±0.16	1.62±0.18	1.64±0.23	0.02	2.75	3.85	1.1
Statistical analysis within the group	*p*-Value 1 *vs.* 2	0.063	0.0003	0.0224	N/A	N/A	N/A	N/A
	q-Value 1 *vs.* 2	N/A	4.068	3.5541	N/A	N/A	N/A	N/A
	p-Value 1 *vs.* 3	<0.0001	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value 1 *vs.* 3	6.44	9.087	7.732	N/A	N/A	N/A	N/A
	p-Value 1 *vs.* 4	<0.0001	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value 1 *vs.* 4	8.05	8.225	9.343	N/A	N/A	N/A	N/A
	p-Value 2 *vs.* 3	0.0505	0.0009	0.0031	N/A	N/A	N/A	N/A
	q-Value 2 *vs.* 3	N/A	4.57	4.715	N/A	N/A	N/A	N/A
	p-Value 2 *vs.* 4	0.0007	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value 2 *vs.* 4	5.261	7.522	6.46	N/A	N/A	N/A	N/A
	p-Value 3 *vs.* 4	0.059	0.013	0.06	N/A	N/A	N/A	N/A
	q-Value 3 *vs.* 4	N/A	3.462	N/A	N/A	N/A	N/A	N/A

N/A – not applicable. One-way ANOVA following Tukey post hoc test was performed for statistical analysis. A $p<0.05$ and $q>3.332$ were considered as significant. BL – 0 weeks (baseline). Data were represented as mean ±SD of all, n=112.

physical disability during follow-up. The failure of botulinum toxin type A to improve DAS scores may be due to the low dose (only 500 U), improper technique for objective-muscle identification [21], and improper procedure for different diluent volumes [22]. A further trial is required for objective-muscle identification technique for local injection of botulinum toxin type A.

Abnormal physical weakness and sleepiness during the day were major adverse effects reported by patients receiving baclofen, and inflammation of the lining of bronchial tubes and elevated blood pressure were major adverse effects found in patients receiving botulinum toxin type A. There are several medications available for treatment of spasticity but the tolerability of medications is the main issue for selection of the optimal treatment [23]. Oral baclofen has poor outcomes for ability to perform activities of daily living and for quality of life because of its adverse effects [20]. In seizure disorders and patients with cardiovascular history, baclofen should be used with caution [24]. Subclinical and systemic adverse effects of botulinum toxin type A are not commonly reported [25]. With respect to adverse effects of interventions, botulinum toxin type A has selectivity for spasticity caused by spinal cord injury.

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Table 8. Modified medical research council score during the follow-up study.

Characters		Groups			Comparison between groups			
		Physical therapies alone	BA	BTI				
Interventions		No medications (I)	Baclofen (II)	Botulinum toxin type A (III)	*p*-Value	*q*-Value		
Sample size		112	112	112		1 vs. 2	1 vs. 3	2 vs. 3
BL (I)		1.84±0.03	1.83±0.05	1.82±0.09	0.055	N/A	N/A	N/A
2 weeks (II)		1.85±0.05	1.85±0.1	1.845±0.12	0.901	N/A	N/A	N/A
4 weeks (III)		1.857±0.09	1.87±0.09	1.86±0.15	0.67	N/A	N/A	N/A
6 weeks (IV)		1.861±0.11	1.88±0.11	1.89±0.18	0.277	N/A	N/A	N/A
Statistical analysis within the group	*p*-Value I *vs.* II	0.071	0.0596	0.08	N/A	N/A	N/A	N/A
	q-Value I *vs.* II	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-Value I *vs.* III	0.059	<0.0001	0.0163	N/A	N/A	N/A	N/A
	q-Value I *vs.* III	N/A	5.362	3.727	N/A	N/A	N/A	N/A
	p-Value I *vs.* IV	0.053	<0.0001	0.0003	N/A	N/A	N/A	N/A
	q-Value I *vs.* IV	N/A	5.609	5.595	N/A	N/A	N/A	N/A
	p-Value II *vs.* III	0.473	0.117	0.41	N/A	N/A	N/A	N/A
	q-Value II *vs.* III	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	p-Value II *vs.* IV	0.337	0.034	0.029	N/A	N/A	N/A	N/A
	q-Value II *vs.* IV	N/A	2.858	3.15	N/A	N/A	N/A	N/A
	p-Value III *vs.* IV	0.767	0.457	0.177	N/A	N/A	N/A	N/A
	q-Value III *vs.* IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A

N/A – not applicable; BL – 0 weeks (baseline). Data were represented as mean ±SD of all, n=112. One-way ANOVA following Tukey *post hoc* test was performed for statistical analysis. A $p<0.05$ and $q>3.332$ were considered as significant.

Our study has certain limitations. The effect of the combination baclofen and botulinum toxin type A was not evaluated. The trial had a short follow-up. We performed titration in the baclofen intervention, but standardization was not performed in botulinum toxin type A obtrusion. The mechanisms of action of muscle relaxants vary (central muscle relaxant *vs.* peripherical muscle relaxant). Both interventions are safe in pediatric patients, but the study did not enroll children.

Conclusions

This evidence-based, randomized, controlled trial with 1a level of evidence concluded that baclofen and botulinum toxin type A were effective in treating spasticity caused by spinal cord injury. However, botulinum toxin type A in conjunction with appropriate physical therapy might be an effective therapeutic option with acceptable treatment-emergent adverse effects.

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Table 9. The Barthel Index functional outcome scores of the ten activities during the follow-up study.

Characters		Groups			Comparison between groups			
		Physical therapies alone	BA	BTI				
Interventions		No medications (I)	Baclofen (II)	Botulinum toxin type A (III)	*p*-Value	*q*-Value		
Sample size		112	112	112		1 vs. 2	1 vs. 3	2 vs. 3
BL (I)		37.12±3.11	35.95±4.12	36.58±3.45	0.052	N/A	N/A	N/A
2 weeks (II)		38.51±7.89	39.15±6.15	38.54±5.45	0.714	N/A	N/A	N/A
4 weeks (III)		38.91±9.2	43.51±8.47	42.43±8.54	0.0003	5.57	4.22	1.31
6 weeks (IV)		44.51±9.11	48.52±11.45	48.11±10.54	0.007	4.08	3.66	0.42
Statistical analysis within the group	*p*-Value I *vs.* II	0.084	<0.0001	0.0015	N/A	N/A	N/A	N/A
	q-Value I *vs.* II	N/A	5.42	4.03	N/A	N/A	N/A	N/A
	p-Value I *vs.* III	0.052	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value I *vs.* III	N/A	10.26	8.57	N/A	N/A	N/A	N/A
	p-Value I *vs.* IV	<0.0001	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value I *vs.* IV	10.173	15.16	13.26	N/A	N/A	N/A	N/A
	p-Value II *vs.* III	0.723	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value II *vs.* III	N/A	6.58	5.21	N/A	N/A	N/A	N/A
	p-Value II *vs.* IV	<0.0001	<0.0001	<0.0001	N/A	N/A	N/A	N/A
	q-Value II *vs.* IV	7.25	10.82	11.73	N/A	N/A	N/A	N/A
	p-Value III *vs.* IV	<0.0001	0.0002	<0.0001	N/A	N/A	N/A	N/A
	q-Value III *vs.* IV	6.46	5.43	6.37	N/A	N/A	N/A	N/A

N/A – not applicable; BL – 0 weeks (baseline). Data were represented as mean ±SD of all, n=112. One-way ANOVA following Tukey post hoc test was performed for statistical analysis. A $p<0.05$ and $q>3.332$ were considered as significant. Toilet use (score: 0–5–10); bladder care (score: 0–5–10); bowels (score: 0–5–10); ambulation (score: 0–5–10–15); feeding (score: 0–5–10); bathing (score: 0–5); dressing (score: 0–5–10); grooming (score: 0–5); stair climbing (score: 0–5–10); transfers (score: 0–5–10–15). 0: Total dependent and 100: Total independent.

Acknowledgments

The authors are thankful for all medical, non-medical, and physiotherapists staff of Tianjin Hospital, Tianjin, China for their valuable contributions to this study.

Conflict of interests

None.

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