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Research paper

Phenol vs. botulinum toxin A injection for managing lower limb spasticity in adult patients with upper motor lesions: A randomized clinical trial

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ABSTRACT

Background: Phenol and botulinum toxin type A (BTX-A) injections are two options for treating spasticity with the ability to select a specific spastic muscle and determine the dosage based on spasticity degree. This study intends to compare the efficacy of BTX-A vs. phenol blockade in treating lower limb spasticity and to evaluate the performance improvement in gross motor functional outcomes among adult patients with upper motor neuron (UMN) lesions.

Methods: This randomized, double-blind clinical trial of 28 spastic lower limb adult patients with UMN was diagnosed between March 1, 2017, to April 30, 2019. Patients were randomized in a 1:1 ratio to a "BTX-A injections" or a "Phenol injections" group. The outcomes were measured through assessment spasticity by the Modified Ashworth Scale (MAS), active range of motion (AROM) of lower limb joint by a goniometer, Verbal Rating Scale (VRS), Visual Analog Scale (VAS), and Penn Spasm Frequency Scale (PSFS) as a baseline and post-injection follow-up at 24 hours, 3 weeks, and 3 months.

Results: All 28 randomized patients were analyzed. No significant difference between the two study arms, neither in demographic characteristics nor in MAS, AROM, VRS, VAS, and PSFS parameters prior to the procedures. AROM showed a significant decrease from baseline throughout the study in the phenol group. While in the BTX-A group, they improved significantly at 3 weeks; no more improvement was observed at 3 months, and the differences were statistically significant ($p < 0.05$). The reduction in MAS, VRS, VAS, and PSFS was statistically significant in each group at 24 hours, 3 weeks, and 3 months after the injection ($p < 0.05$). However, the differences were not significant between the phenol and BTX-A groups ($p > 0.05$), except for PSFS at the 3 months of follow-up in the Phenol group ($p = 0.01$). The need for re-injection at 6 months and 9 months was that 5 patients vs. 0 patients ($p = 0.01$) and 8 patients vs. 3 patients ($p = 0.04$) in the BTX-A and phenol groups, respectively, were statistically significant.

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Conclusion: Phenol injection showed superior treatment effects in AROM, decreased spasm degree based on PSFS at 3 months, and less-frequent re-injection rate compared to BTX-A injections in adult patients with UMN lesions. However, both phenol and BTX-A injections effectively reduce spasticity without significant differences in efficacy and adverse effects. Future studies must be conducted with a longer duration of follow-up, and larger sample sizes better to compare both drugs' effectiveness and side effects.
Trial registration: The study protocol was registered as a clinical trial under registration IRCT20170826035914N2 at the Iranian Registry of Clinical Trials (http://www.irct.ir).

Keywords: botulinum toxin type A, phenol, spasticity, lower limb, clinical trial

INTRODUCTION

Spasticity refers to muscle hypertonia caused by upper motor neuron (UMN) lesions. It causes pain and contracture in spastic limbs. Because of the restriction of motion in the lower limb joints, this condition may also interfere with gait and stability.[1] Incidence of spasticity was reported between 65% and 78% in traumatic spinal cord injury (SCI) and between 80% and 85% in Multiple Sclerosis.[2]

Many studies reported the efficacy of spasticity treatments by increasing articular range of motion (ROM), reduction in muscles Modified Ashworth Scale (MAS), and improving gait, self-care, and other activities of daily living.[3,4] Several treatment options are available, including; rehabilitation (e.g., physical therapy and occupational therapy), surgical interventions, and pharmacotherapy (e.g., oral antispasmodics, motor point block, and chemo-denervation).[4,5]

Motor-point block with phenol and botulinum toxin type A (BTX-A) injections are other treatment options for selecting a specific spastic muscle and determining the dosage based on spasticity degree.[6] BTX-A injection is a well-tolerated preferred option for spasticity, which acts locally by inhibiting the acetylcholine release, delaying the surgery, and improving the gait.[4] Additionally, phenol neurolysis and phenol motor point injection were used to treat spasticity with sustained effects for several months and up to 2 years.[3]

A direct comparison of BTX-A with the oral agent tizanidine has shown BTX-A to be superior in reducing upper limb spasticity with fewer side effects.[7] Neurolysis with phenol is preferable in treating moderate to severe hospitalized spastic patients, which is a low-cost, potent, rapid onset option. Still, it has a higher rate of complications, especially pain during the injection, local inflammation, hypotension, weakness, and cutaneous dysesthesia.[3]

Few studies have compared BTX-A efficacy, in treating lower limb spasticity, vs. phenol blocks.[4,6,8] This study aimed to compare the effectiveness of phenol and BTX-A injections on patients with lower limb spasticity and knee limitation of motion.

MATERIALS AND METHODS

Study Design and Participants

This study was approved by the ethics committees of Shiraz University of Medical Sciences (Approval code: IR.SUMS.MED.REC.1396.24) and conducted per the Declaration of Helsinki. This is a double-blinded, randomized clinical trial (RCT) study that was approved and registered at the Iranian Registry of Clinical Trial with ID: IRCT20170826035914N2. All patients were informed of the study's objectives, protocol, risks, and benefits, and informed written consent was obtained from all the participants. Participants were randomly selected from the physical medicine and rehabilitation clinics of Shiraz University between March 1, 2017, and April 30, 2019. We included 28 patients with UMN lesions who had spasticity of 2 or 3 on the MAS. The consort flowchart for selecting patients, allocation, and analysis of data is shown in Figure 1.

Inclusion Criteria

The study included all adult (age 20 to 70 years) patients, with UMN lesions and capable of providing informed consent, communicating, and filling out questionnaires. The study included patients diagnosed with SCI, traumatic brain injury, and non-traumatic brain injuries including cerebrovascular accidents, cerebral palsy (CP), transverse myelitis, and spastic paraplegia with knee ROM limitations. Their disease onset had to be at least 6 months before the commencement of the study without any clinical or subclinical evidence of defective neuromuscular transmission or other underlying neurological disorders that may affect the BTX-A injection.

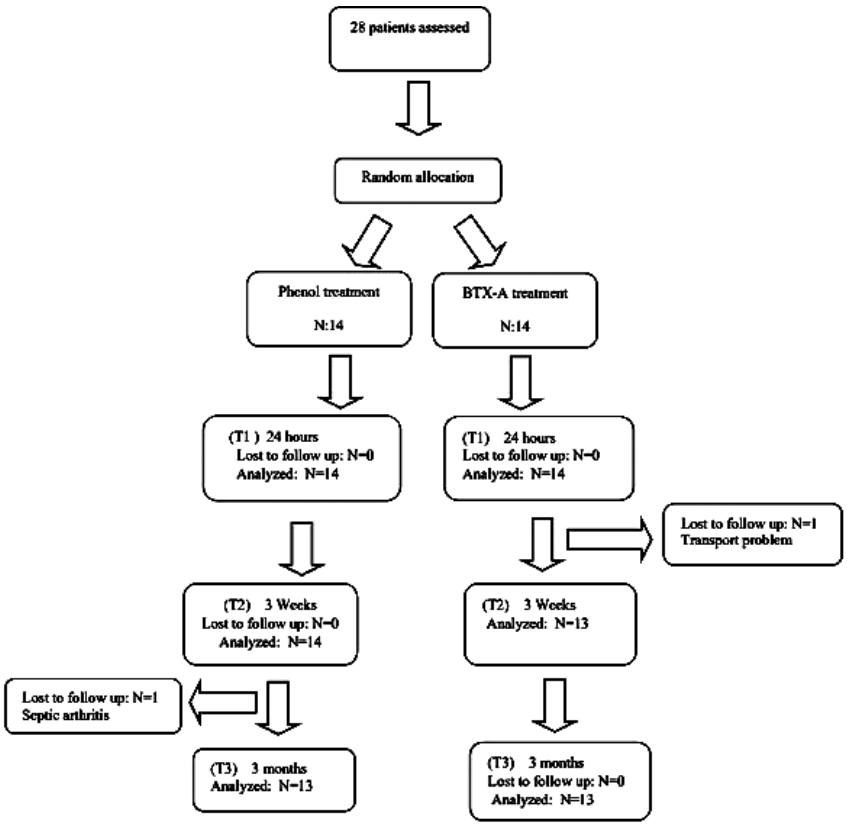


Figure 1. CONSORT flow chart for selecting patients, allocation, and analysis.

Exclusion Criteria

Patients with coagulopathy or on anticoagulants, patients with cardiovascular diseases, or fixed joint contracture were excluded. Patients who have had a history of an allergic reaction to phenol or BTX-A, treatment with BTX-A within the past 4 months, previous injection of phenol or alcohol in the targeted limb, taking aminoglycoside antibiotics, spectinomycin, or other neuromuscular blocking agents, infection at the injection site, previous selective rhizotomy, orthopedic surgery, or an intrathecal baclofen pump, and pregnant or breastfeeding women were also excluded from the trial.

Randomization and Blinding

In this work, 28 eligible participants were divided into two parallel groups at random. Phenol injection: (14 patients) group A and BTX-A injection: (14 patients) group B by the clinic's supervisor, who had been taught using a block randomization listing. A computer-generated non-stratified list with a block size of six was made. Also, statisticians, patients, questionnaires, and statistical analyzers were blinded to the distribution.

Sample Size

The sample size was measured at 8 study limbs in each group using NCSS statistical software version 9 (NCSS, Kaysville, Utah). By considering a 95% confidence interval (CI) and 80% power to show the significance of treatment effect according to the study by Kirazli et al.[9] (d: 0.7, S: 0.7).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right) \times S^2}{d^2}$$

Therefore, a total number of 14 spastic limb patients in each group were included in our study.

The Technique of Phenol Injection

In group A, a 1 cc phenol solution diluted in up to 6% distilled water was injected for each target site based on the spasticity degree and the muscle size, under aseptic precaution. The patients were positioned in a prone posture without local or general anesthesia, and a 22-gauge needle was used to inject 6% phenol, as a motor point block.

The phenol motor point injections were administrated following the identification of standardized anatomical landmarks of the gastrocnemius muscle, with ankle plantarflexion to identify the hamstrings and knee flexion and internal rotation to identify the semimembranosus muscles. Thereafter, the gastrocnemius muscle was palpated while being passively stretched, and the needle was inserted between the two upper quadrants as described previously.[10] This site has been originally used for phenol and alcohol blocks and corresponding to the motor points of the muscle.[8,11] To limit variability, the same investigator prepared the diluted injections, with no participation in patients' assessment, or interaction with either therapists or assessors.

The Technique of BTX-A Injection

In group B, after sterile preparation and similar prone positioning, BTX-A 500 unit (Dysport, Ipsen Biopharm, Wrexham, UK) was injected after identifying the anatomical landmark in the intended muscles such as gastrocnemius, hamstring, and semimembranosus muscles without anesthesia.

The final concentration was 10 units/0.1 mL. BTX-A dosage was chosen based on clinical practice guidelines, spasticity degree, muscle size, and participants' body weight.[4,9] The maximum dose of BTX-A administered to each hamstring muscle was 300 units. Since gastrocnemius spasticity affects knee ROM, we injected a mean dose of 150 unite BTX-A in 10 patients with both hamstrings and gastrocnemius spasticity. It should be pointed out that the maximum injected dose of BTX-A at each lower limb was 500 units.

Both groups received training for self-rehabilitation and in-home exercise. They were also committed to continuing physical therapy until the end of the study. Physical therapy was done at least four sessions a week. Each session lasted 40 minutes, focusing on muscular stretching, ROM training, and strengthening exercises. They were also strongly discouraged from over-stretching their muscles. Both groups were instructed and taught to check the injection site for any bleeding or infection signs**.**

Outcome Measures

The participants were evaluated for a total duration of 3 months. A baseline assessment was performed prior to any injection. The participants were reassessed in 24 hours, 3 weeks, and 3 months after the allocated treatment by a different investigator who was blinded to the injections' type, dose, and volume.

We measured the limitation of motion for the knee while the hip was on 90 degrees flexion and the catch angle in passive knee extension with a goniometer. Flexion contracture angle was also measured while the hip and knee were extended (inability to fully straighten or extend the knee).[8] MAS was applied to assess hamstrings tension, which ranges from 0 (no increase in muscle tone) to 4 (rigid in flexion or extension).[4] To increase the reliability of treatments, we used other scales, including the Penn Spasm Frequency Scale (PSFS) which rates the frequency of spasms in patients from 0 (no spasm) to 4 (spasms occurring more than 10 times per hour), the Verbal Rating Scale (VRS) that a 5-point scale and consists of a list of adjectives describing various levels of symptom intensity (0 = no itch, 1 = mild itch, 2 = moderate itch, 3 = severe itch, and 4 = very severe itch), and Visual Analog Scale (VAS), in which 0 means no pain and 10 represents maximum pain, were also self-reported.[12,13] Finally, the patients' satisfaction was recorded in the final follow-up.

Statistical Analysis

The descriptive data were evaluated using the mean, SD, frequency, and frequency percent. The analysis of inferential statistics was done using the chi-square test (assessment of correlation of the two categorical data), independent *t*-test (comparing mean of a quantitative factor between the two groups), Leven test (analysis of variance equation between the two groups), and the repeated measures ANOVA (RM ANOVA) (to determine the trend of regression of pain scores over the time). Friedman, a non-parametric test, was also used to compare variables inter-groups. A p-value < 0.05 was deemed statistically significant. All statistical analyses were done using SPSS software (IBM SPSS, version 18; Armonk, IBM Corp, Armonk, NY).

RESULTS

A total of 28 affected lower limbs patients were randomly allocated into the 1:1 group. One participant was lost to follow-up from the phenol group due to septic arthritis in the contralateral limb, which was unrelated to the procedure. Another participant from the BTX-A group left the trial due to transport limitations (Figure 1).

The mean age of patients was 38.31 ± 12.98 years in the phenol group and 40.6 ± 14.4 years in the BTX-A group (ranging from 24 to 67 years). The median time since their diagnosis was 6 years (range 1–10 years) in the phenol group and 2 years (range 1.5–4 years) in the BTX-A group.

No significant differences were noted in demographic characteristics between the two groups. The main characteristics of patients are shown in Table 1.

A significant improvement in knee ROM while the hip was flexed (passive ROM) was observed from the baseline assessment compared to 24 hours, 3 weeks, and 3 months follow-up in the phenol group ($p < 0.05$). However, BTX-A group improvement was noticed at 3 weeks and no more improvement was observed at 3 months. There were no statistically significant differences between the two groups ($p > 0.05$) (Figure 2).

Table 1. Baseline characteristics of the participants.

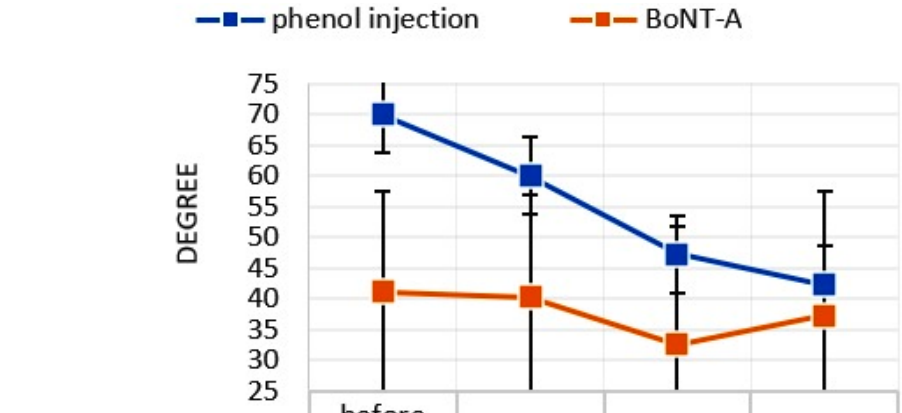
Variables*	Phenol group	BTX-A group
Age (years); mean ± SD	38.3 ± 12.9	40.6 ± 14.4
Male:Female	7:6	7:6
Study limb; *N* (%)		
Left	6 (46.2)	6 (46.2)
Right	7 (53.8)	7 (53.8)
Years since diagnosis; median [IQR]	6 [1–10]	2 [1.5–4]
Disease; *N* (%)		
Traumatic injuries**	9 (69.2)	7 (53.8)
Non-traumatic injuries***	4 (30.7)	6 (46.1)

Notes:

* Based on demographic data, there were no significant differences between the two groups ($p > 0.05$).

** Traumatic brain injuries include spinal cord injury and traumatic brain injury.

*** Non-traumatic brain injuries include cerebrovascular accidents, cerebral palsy, spastic paraplegia, and transverse myelitis.



	before injection	24h	3w	3m
phenol injection	70	60	47.31	42.31
BoNT-A	41.15	40.38	32.7	37.31
p value	0.01	0.027	0.046	0.574

Figure 2. The changing trend in knee ROM while the hip was flexed.

The knee flexion contracture while hip and knee were extended (active ROM) showed a significant decrease from baseline throughout the study in the phenol group. While in the BTX-A group, they improved significantly at 3 weeks; no more improvement was observed at 3 months, and the differences were statistically significant ($p < 0.05$) (Figure 3).

Changes in parameters including MAS, VRS, VAS, and PSFS in both groups over time are shown in Table 2. The reduction in MAS, VRS, VAS, and PSFS was statistically significant in each group at 24 hours, 3 weeks, and 3 months after the injection ($p < 0.05$). However, the differences were not significant between the phenol and BTX-A groups ($p > 0.05$), except for PSFS at the 3 months of follow-up in the phenol group ($p = 0.01$).

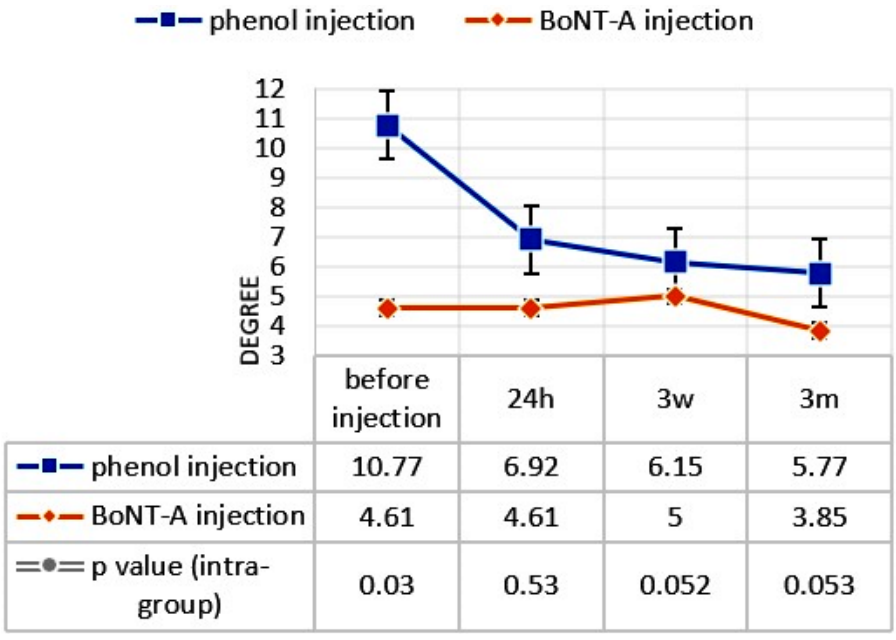


Figure 3. Changes in knee ROM over time while hip was extended.

Table 2. Comparison of mean (standard deviation) scores over time between and within phenol and BTX-A injected groups.

Parameter ($N = 26$)	Before injection	24 hours later	3 weeks later	3 months later	*p*-Value (intra-group)
MAS of hamstrings					
Phenol	3.0 ± 00	2.8 ± 0.37	2.0 ± 00	2.0 ± 00	<0.0001
BTX-A	2.8 ± 0.8	2.5 ± 0.78	1.7 ± 0.7	2.3 ± 0.7	<0.0001
p-Value (inter-group)	0.628	0.296	0.288	0.070	
VRS					
Phenol	1.3 ± 1.5	1.2 ± 1.5	0.9 ± 1.0	0.9 ± 1.0	0.008
BTX-A	1.3 ± 1.4	1.3 ± 1.4	0.8 ± 0.9	1.0 ± 1.2	0.002
p-Value (inter-group)	0.861	0.822	0.861	0.864	
VAS					
Phenol	4.4 ± 5.0	3.7 ± 4.4	2.2 ± 3.0	2.0 ± 2.7	0.001
BTX-A	3.3 ± 3.9	3.3 ± 3.9	2.5 ± 2.9	2.9 ± 3.4	0.001
p-Value (inter-group)	0.370	0.716	0.867	0.635	
PSFS					
Phenol	0.7 ± 1.0	0.6 ± 0.7	0.1 ± 0.3	0.1 ± 0.3	0.001
BTX-A	1.1 ± 1.4	1.1 ± 1.4	0.6 ± 0.7	1.0 ± 1.0	0.004
p-Value (inter-group)	0.40	0.37	0.07	0.01	

Abbreviations: BTX-A, botulinum toxin type A; MAS, Modified Ashworth Scale; VRS, Verbal Rating Scale; VAS, Visual Analog Scale; PSFS, Penn Spasm Frequency Scale.
Notes: *p*-Values < 0.05 were considered significant.

The reported adverse effects were as follows: one patient in the BTX-A group and five patients in the phenol group had temporarily mild pain after the injection, which was relieved by 500 mg Acetaminophen in the next 24–48 hours. In addition, three patients in the phenol group experienced bruising, and two patients had bruising and edema. There was no statistically significant difference between the phenol and BTX-A group ($p = 0.2$).

Six months after the injection, the subsequent follow-up showed no need for re-injection in the phenol group, and five re-injections were done in the BTX-A group ($p = 0.01$). All patients were also interviewed 9 months after the interventions, and three patients in the phenol group and eight in the BTX-A group were re-injected (3 vs. 8, $p = 0.04$).

DISCUSSION

Spasticity is among the most debilitating symptoms in adult patients with UMN lesions. The associated excruciated pain, progressive muscle deconditioning, and shortening contribute to disability worsening.[1] Alleviation of the distressing symptoms, attenuation of spasticity-related deforming force, functional improvement, and secondary complications prevention are the main goals of treatment.[14]

In this study, we assessed the efficacy of phenol and BTX-A injections for knee ROM and hamstrings spasticity. There is no clinical consensus regarding the approach of spasticity management; however, various physical, pharmacological, and invasive intervention as BTX-A, chemical neurolytic agents like phenol and alcohol, and surgical methods can be used.[15]

Physical modalities have been commonly used in the management of spasticity, including basic ROM activities, prolonged stretching, orthoses with splinting and casting, icing and brushing, biofeedback, and electrical stimulation. These modalities, however, are labor-intensive and provide temporary relief with limited long-term effects.[16] Invasive interventions are also used to reduce spasticity, including chemical neurolytic agents (e.g., ethyl alcohol and phenol) or surgical interventions (e.g., peripheral neurectomy, or tendon lengthening and release).[17] Surgical interventions, however, are reserved for selected patients with contractures or severe deformities. In addition, the cost of such interventions reduces their utilization.[4,16,17]

Chemical neurolytic agents have been historically used in the management of UML spasticity. Phenol has protein-denaturing, demyelinating, and cytotoxic properties by precipitation and dehydration of protoplasm in a concentration of 3% or more.[18] It is readily available; nevertheless, there are many disadvantages associated with phenol injection including skin irritation or necrosis, which can involve adjacent muscles, irreversible peripheral denervation, and dysesthesia that can be worse than the initial pain.[19]

Botulinum toxin, a *Clostridium botulinum* derivative, has been effective in managing localized spasticity. As a neuromuscular junction-blocking agent, botulinum toxin exerts a paralytic effect by the degradation of synaptosomal proteins (e.g., synaptosomal-associated protein 25). Thus, it rapidly and strongly inhibits the presynaptic cholinergic nerve terminals' release of acetylcholine.[8] The motor effect of the toxin is typically seen within a few days of the administration, lasting between 3 and 4 months.[5]

Current knowledge on the direct comparison of phenol and BTX-A is based on previous studies with different methodologies and targeting different muscles. The effects of phenol injections and BTX-A were evaluated in several studies.[4,6,8,9] These agents have been used in the treatment of lower limb spasticity in patients with CP and adults.[4,20]

Our result showed that instead of more improvement in AROM with phenol injection and less-frequent re-injection rate compared to BTX-A injections, both phenol and BTX-A injections effectively reduce spasticity without significant differences in efficacy and adverse effects except for PSFS at the 3 months of follow-up in the phenol group. AROM showed a significant decrease over time in the phenol group. While in the BTX-A group, they improved significantly at 3 weeks; no more improvement was observed at 3 months.

Different studies with different outcomes were published comparing BTX-A injection with other products in the treatment of UMN lesions spasticity. For example, Kirazli et al.[9] examined the effects of phenol vs. BTX-A injection in the poststroke spastic foot. Interestingly, BTX-A injection showed superior results with a greater reduction in the meantone and improvement in foot movement and function including dorsiflexion and walking velocity at 2 and 4 weeks as compared to phenol injection. These effects, however, were not significant at weeks 8 and 12 between groups.[9] Furthermore, Kaishou et al. showed a significant functional and spasticity improvement with BTX-A

injection combined with electrical stimulation guidance and physiotherapy when compared to physiotherapy solely in children with CP.[21] In contrast, a recent article reviewed by Blumetti et al.[22] mentioned low or very low evidence of the quality of BTX-A injections compared to other agents or placebo in children with CP. Additionally, BTX-A did not show superior outcomes in managing ankle contractures compared to serial ankle casting. But it was more effective that orthotics in attenuating spasticity and improving ROM.[22] Our explanation for these discrepancies between our result and previously mentioned studies is the small number of patients, heterogenicity of patients feature, different doses and technique of the injected drugs, and the short follow-up duration in our study compared with the previous studies. Further studies with more patients with more inclusion criteria and longer follow-ups are recommended.

In our study, the maximum effects of BTX-A injection were seen in the third week following the injection, with minimal diminished effects on the third month of follow-up. In contrast, phenol efficacy did not diminish at 3 weeks post-injection. This is in line with previous studies' findings that BTX-A takes several days to generate its benefit. Its effects last 3 months due to the physiologic repair of the neuromuscular junction. Therefore, patients receiving BTX-A should repeat their injection every 3–4 months with a remaining concern about its long-term effects on muscles and possible resistance to BTX-A.[13,23] Contrary to BTX-A, phenol acts immediately on smaller nerve fibers, which manifests within minutes and may last up to 6 months depending on the used dose.[18,19]

Our results also showed that spasm degree based on PSFS was significantly reduced at month 3 post-injection in the phenol group than BTX-A group. Similarly, Manca et al.[6] evaluated the use of BTX-A compared to phenol nerve blocks in patients with spastic paresis to alleviate the ankle clonus. Their study displayed a significant and constant improvement of clonus in the phenol group throughout the study period.[6] A systematic review conducted in 2015 reported a low level of evidence regarding phenol or BTX-A injections to use in the spasticity treatment, with limited to no functional improvement. However, it is important to highlight that this study assessed these outcomes in SCI patients and it did not negate the possibility of different outcomes in different populations.[24]

Adverse events reported with BTX-A included weakness and localized muscle pain after the injection. Phenol injections are associated with worse adverse events profile, including pain, swelling and inflammation, dysesthesia, hypotension, and fibrosis.[19,24] In our study, the observed adverse effects in the phenol group were temporary pain, bruises, and edema, but no one experienced dysesthesia due to the motor point method of injection.

Phenol injection requires accurate needle placement to maximize its effectiveness, often associated with increased risks of damaging the nearby tissues and necrosis of surrounding muscles.[18,19] However, such side effects can be minimized with the appropriate dosing and techniques performed by experienced staff.[18] On the other side, BTX-A coupled with physical modalities and at-home exercises can be considered another effective option with mild and localized adverse effects.[19,25,26] A major advantage of phenol is its relatively low price compared to BTX-A.[27] According to the British Medical Association cost of 1 unit of BTX-A is significantly higher than other treatment options for spasticity.[28] In a low-income country like Iran, 500 U of BTX-A costs about 600 times greater than phenol. Considering insurance coverage limitations and multiple re-injections, BTX-A treatment is associated with higher costs.[29]

This study has some limitations. First, the dose of phenol and BTX-A, administration, frequency, method, and duration were not entirely the same as in previous articles, which may influence the results. Second, the sample size was small. Third, the heterogeneity of patients' characteristics according to their underlying disease and the inability of patients from other cities to participate in the study and complete the follow-ups may influence the results. Fourth, change in walking distance and the value and change of VAS with motion may be biased by selecting different assessment methods compared with previous trials. Another limitation of our study was that we didn't evaluate lower limb function during follow-ups, especially gait and standing. It is also worth mentioning that there is a scarcity of comparative studies of the clinical outcomes of phenol and BTX-A injections in spastic muscles, therefore, making this study a unique trial. It should be noted that these interventions must be in the appropriate clinical context, considering the importance of proper patient selection and the appropriate injection technique. Moreover, thorough patient assessment, decent knowledge and experience regarding the peripheral functional anatomy, combination therapy, and an understanding of how these treatments work and how to administer them properly (dosing, dilution, injection guidance) is required prior to any of these interventions are required.[13,23]

CONCLUSION

Phenol injection showed superior treatment effects in AROM, decreased spasm degree based on PSFS at 3 months, and less frequent re-injection rate compared to BTX-A injections in adult patients with UMN lesions. However, both phenol and BTX-A injections effectively reduce spasticity without significant differences in efficacy and adverse effects. Future studies must be conducted with a longer duration of follow-up, and larger sample sizes better to compare both drugs' effectiveness and side effects.

List of Abbreviations

BTX-A, botulinum toxin type A; UMN, upper motor neuron; MAS, Modified Ashworth Scale; AROM, active range of motion; VRS, Verbal Rating Scale; VAS, Visual Analog Scale; PSFS, Penn Spasm Frequency Scale.

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Authors' Contributions

Hamid Reza Farpour and Seyedeh Yasamin Parvar participated in the design of this study; they both performed the statistical analysis and collaborated in the discussion. Faisal Ahmed, Azadeh Hajihosseini, and Hossein-Ali Nikbakht carried out the study and collected important background information. Narges Ghamari and Mohamed Badheeb participated in drafting the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors of this study declined to declare any competing interests.

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