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Clinical effectiveness of ultrasound guided subacromial-subdeltoid bursa injection of botulinum toxin type A in hemiplegic shoulder pain

A retrospective cohort study

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Abstract

Hemiplegic shoulder pain (HSP), which occurs in most patients with hemiplegia, causes considerable distress and worsens outcomes in rehabilitation. Although they have received the treatments such as anti-inflammatory drugs or physical therapy, many of the individuals remain suffering from shoulder pain 6 months after acute stroke event. In this retrospective study, we evaluated the effectiveness of ultrasound guided subacromial-subdeltoid (SASD) bursa injections with botulinum toxin type A (BoNT/A) compared to steroids for refractory HSP.

The data were collected retrospectively by reviewing the patient's medical records and pain questionnaires in our rehabilitation center. In total, 38 patients who received ultrasound guided SASD bursa injection (BoNT/A group, n = 18; corticosteroid group, n = 20) were included. The pain visual analog scale (VAS) score at rest and during arm passive abduction, Fugl-Meyer score of upper limbs (F-M score) were evaluated before, 2, 4, 8, and 12 weeks after injection.

Both 2 groups obtained a significant improvement of VAS score at rest or during arms passive abduction compared to baseline score (within group compare, $P < .05$). There were no significant differences of pain score improvement between two groups at week 2, 4, 8, and 12 after injection either at rest or during passive arm abduction (between 2 groups compare, $P > .05$). There were also no differences in results of the post treatment F-M score between 2 groups (between 2 groups compare, $P > .05$). Similarly, during the follow-up period no collateral effects were reported after BoNT/A injection.

SASD bursa BoNT/A injection can substantially reduce the pain as corticosteroid in patients with HSP. BoNT/A injection could be a useful strategy for replacing steroids as a treatment for refractory HSP especially in the patients who cannot tolerate the steroids injection.

Abbreviations: BoNT/A = botulinum toxin type A, F-M = Fugl-Meyer, HSP = Hemiplegic shoulder pain, SASD = subacromial-subdeltoid, VAS = visual analog scale.

Keywords: Botulinum toxin A, bursa, should pain, stroke

1. Introduction

Stroke is the most common cause of disability among elderly people. Incidence of the hemiplegic shoulder pain (HSP) is approximately 17% to 37% one month after stroke, thereafter increasing to 47% six months later.[1,2] HSP is one of the negative factors which affects daily activities, quality of life and could increase the duration of hospitalization.[3] About 20% to 30% of individuals remain suffering from shoulder pain 6 months after the acute stroke event, although most of them have received treatments such as anti-inflammatory drugs, diazepam, tizanidine, baclofen, or physical therapy.[4]

The associated factors of HSP include poor upper extremity function, shoulder motion limitation, shoulder subluxation, increased muscle tone around the shoulder, reflex sympathetic dystrophy, and rotator cuff injury.[5,6] Shoulder subluxation has been associated with rotator cuff tears, and thus it may be an indirect cause of HSP.[7] The most painful and limited shoulder movement direction is lateral (external) rotation, followed by abduction.[8] Inflammation of the subacromial-subdeltoid (SASD) bursa is a common cause of shoulder pain and functional disability.[9] Rah et al found that subacromial bursa corticosteroid injection showed improvement in pain, disability, and active range of motion in HSP

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patients.[10] Although immediate pain reduction can be significant by steroid injection, the long-term side effects including tissue degeneration and tendon rupture should be concerned.

The utilization of botulinum toxin A (BoNT/A) in clinical field has expanded beyond traditional cosmetic and anti-spasticity use in the last decades. BoNT/A intra-articular injection has beneficial effects of improved pain score in adult patients with refractory joint pain.[11] Animal experiments demonstrate that BoNT/A inhibits not only the acetylcholine at the neuromuscular junctions but also other pain related neurotransmitters such as glutamate, substance P and calcitonin gene related peptide.[12]

In our previous clinic practice, we used SASD BoNT/A injection for the HSP patients who cannot tolerate steroids injection. Most of the individuals also had pain and function improvement after treatment. Thus, the objective of our retrospective cohort study was to assess the benefit of SASD bursa BoNT/A injection for refractory HSP as compared to steroid injection. We also evaluate the efficacy and collateral effects of SASD bursa BoNT/A injection in patients with refractory HSP. Results of this study may help to devise new therapeutic and rehabilitation strategies for patients with HSP.

2. Materials and methods

2.1. Subjects

This is a retrospective cohort study. A total of 38 patients with refractory HSP patients in our rehabilitation center who underwent SASD bursa injection (BoNT/A or steroid) from January 2016 to May 2018 were included and followed up for 12 weeks (see study flow chart, Fig. 1). Based on the type of pharmaceutical injected, all patients were classified into 2 categories: BoNT/A treatment group and steroid treatment group. Patient demographics, treatment characteristics, and outcomes were collected prospectively. Clinical characteristics of the stroke patients were not significantly different between the experimental and control groups (see Table 1). All procedures were conducted by TW and HXS who were experienced in ultrasound-guided procedure. The description of our study is according to STROBE checklist.

All patients had severe shoulder pain after stroke on the paresis upper limb. The indications for SASD bursa injections were

(1) HSP duration at least 2 months,
(2) pain score >3 on a pain visual analog scale (VAS) of 0 to 10 cm (0 no pain, 10 worst possible pain) at rest, and/or pain score >5 on VAS during passive shoulder abduction,
(3) pain was not relieved by conventional treatment (common analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs; slings, strapping, and handling of the arm; physical therapy such as functional electrical stimulation of shoulder muscles or manual therapy),
(4) no significant spasticity in the upper shoulder joint, defined as a score of on the Modified Ashworth Scale score <2,
(5) ultrasonographically diagnosed rotator cuff disorder or SASD bursitis and
(6) no history of shoulder pain or shoulder diseases before stroke, other neurologic diseases, and BoNT/A treatment. Patients who had not been followed up for a minimum of 12 weeks post injection were also excluded from the study.

This retrospective study was approved by the Institution's Ethics Examination Committee of Human Research of our hospital and informed consent was obtained from all participants before SASD injection treatment.

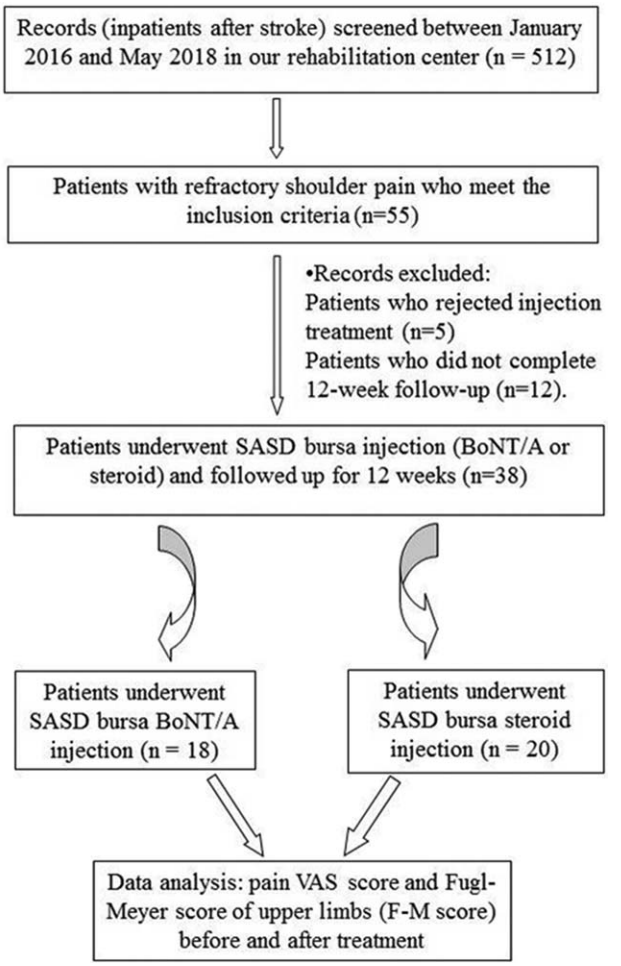

Figure 1. Flow chart and retention of participants.

2.2. Intervention and outcome measures

Before injection, all patients underwent a thorough neurologic examination. Pain scores at rest and during passive arm abduction up to 90° were evaluated by using a 0 to 10 cm VAS. The Fugl-Meyer score of upper limbs (F-M score) and pain VAS score were evaluated before, 2, 4, 8, and 12 weeks after injection.

Table 1

Clinical characteristics of the stroke patients in the BoNT/A and BD groups.

	BoNT/A group (n = 18)	BD-group (n = 20)
Age	61.4 ± 13.0	66.2 ± 9.8
Sex (male/female)	10/8	11/9
Stroke type (ischemic/hemorrhagic)	11/7	12/8
Time from stroke onset (months)	6.3 ± 4.7	4.9 ± 5.6
Duration of shoulder pain (months)	5.7 ± 3.8	4.4 ± 5.0

Clinical characteristics of the stroke patients were not significantly different between the BoNT/A and BD groups.
BD = betamethasone dipropionate, BoNT/A = botulinum toxin type A.

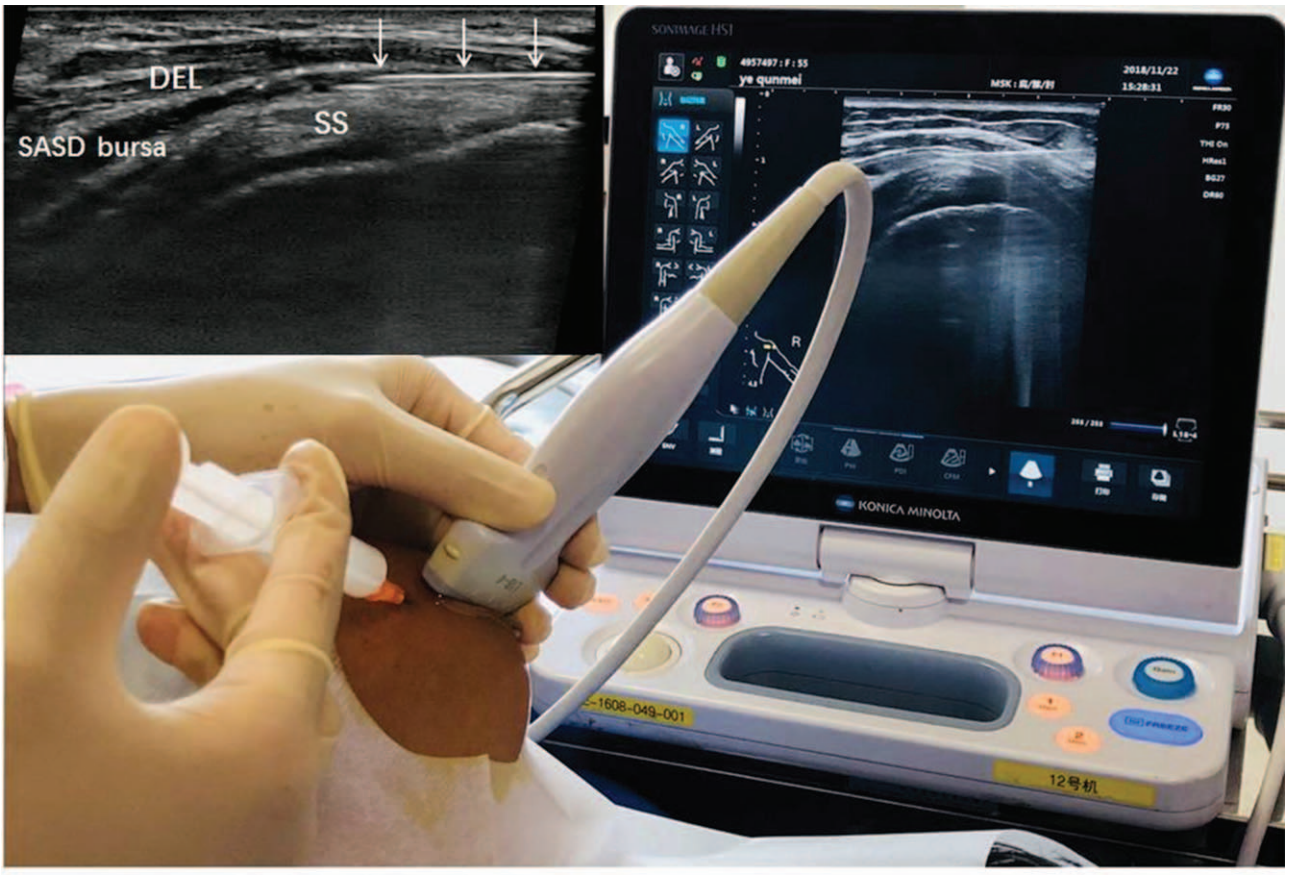

Figure 2. Procedure for ultrasound-guided SASD bursa injection. (↓: needle; DEL = deltoid, SASD = subacromial-subdeltoid, SS = supraspinatus tendon).

BoNT/A treatment group was carried out by using Onabotulinumtoxin A (Botox, Allergan Inc.) 100 units (BoNT/A group). BoNT/A was reconstituted with 2.0 mL of saline solution in all cases. Steroid injection group was carried out by using betamethasone dipropionate 1.0 mL reconstituted with 1.0 mL of saline solution and 2 ml 2% lidocaine (betamethasone dipropionate injection, BD group). SASD bursa injections were performed by using a standard lateral approach under ultrasound guidance in all patients (Fig. 2). A physical therapist (YZL) who was blinded to the interventions, evaluated the parameters (VAS and F-M score) before and after treatment. All patients continued their standard rehabilitation treatment after injection treatment.

2.3. Data analysis and statistics

The SPSS Version 12.0 statistical package was used for statistical analysis. Chi-square test was used to compare sex proportion, affected side (left or right) and the proportion of patients with successful results in VAS between 2 groups. Changes in pain VAS scores at rest and during passive 90° arm abduction, and Fugl-Meyer score of upper limbs (F-M score) before and 2, 4, 8, and 12 weeks after injection were compared between 2 groups by using unpaired Student *t* test. Results were considered as statistically significant at $P < .05$.

3. Results

Thirty-eight consecutive refractory HSP patients in our rehabilitation center who underwent SASD bursa injection were included (BoNT/A group, n = 18; BD group, n = 20). All the included individuals were finished following up for12 weeks (Flow chart and retention of participants, see Fig. 1). Clinical characteristics of the included individuals were not significantly different between the experimental and control groups (see Table 1).

As shown in Table 2, in BoNT/A treatment group, mean VAS scores before injection were 3.41 ± 0.51 and 5.92 ± 0.80 at rest and during passive arm abduction, respectively. VAS scores were lower 2 weeks after BoNT/A injection, both at rest and during passive arm abduction ($P < .05$). The beneficial effect persisted 12 weeks after BoNT/A injection ($P < .05$). In BD treatment group, we also found decreased pain score at each follow-up time point compared to baseline. There were no significant differences of pain improvement between 2 groups at week 2, 4, 8, and 12 after injection either at rest or during passive arm abduction ($P > .05$, Table 2). Although F-M score showed an increasing trend at week 2, 4, 8, and 12 weeks compared to baseline in both BoNT/A group and BD group, the differences were not significant ($P > .05$, Table 3). There were no differences in results of F-M score between 2 groups at each evaluation time point after treatment ($P > .05$, Table 3). During the follow-up period no collateral effects were reported after BoNT/A injection. In BD group, we found hyperglycemia in 5 patients after injection and lasted for 3 days.

4. Discussion

In our retrospective study, we found a strong correlation between SASD bursa BoNT/A injection and pain relief in patients with

Table 2

The changes of pain score after SASD bursa injection.

	VAS score at rest			VSA score during passive arm abduction		
	BoNT/A group (n = 18)	BD group (n = 20)	*P* value (between two groups)	BoNT/A group (n = 18)	BD group (n = 20)	*P* value (between two groups)
Before treatment	3.41 ± 0.51	3.21 ± 0.43	.268	5.92 ± 0.80	5.43 ± 0.65	.051
2 weeks after treatment	0.58 ± 0.52	0.43 ± 0.51	.529	2.10 ± 0.67	2.09 ± 0.54	.958
4 weeks after treatment	0.58 ± 0.51	0.50 ± 0.52	.758	1.92 ± 0.51	2.14 ± 0.66	.362
8 weeks after treatment	0.75 ± 0.45	0.79 ± 0.58	.899	2.25 ± 0.62	2.46 ± 0.78	.205
12 weeks after treatment	0.81 ± 0.44	0.82 ± 0.68	.937	2.77 ± 0.32	2.66 ± 0.88	.721
P value (within group)	0.000	0.000		0.000	0.000	

Both 2 groups obtained a significant improvement of VAS score at rest and arms passive abduction compared to baseline ($P < .05$). There were no significant differences of pain improvement between 2 groups at week 2, 4, 8, and 12 after injection either at rest or during passive arm abduction ($P > .05$).

BD = betamethasone dipropionate, BoNT/A = botulinum toxin type A, SASD = subacromial-subdeltoid, VAS = visual analog scale.

refractory HSP after stroke. All included patients had severe HSP with pain VAS score at rest of 3 to 10, lasting for at least 2 months. In all cases, pain score was still decreased 12 weeks after SASD bursa BoNT/A injection. During the 12 weeks follow-up period, we found no difference between BoNT/A and BD group with VAS and F-M score improvement.

BoNT/A has been used widely to cosmetic and anti-spasticity in clinical practice. Intramuscular injections of BoNT/A also have the effects of pain relief in HSP patients.[13] The mechanism by which intramuscular BoNT/A injection decreases pain may include a muscle relaxant effect and inhibition of the release of neurotransmitters by sensory neurons.[14]

The causative mechanism for shoulder pain after stroke was not fully understood. No single type of shoulder pathology could account for all shoulder pain in patients after stroke, and more than 1 type of shoulder pathology can cause pain in each individual.[15] In fact, during our ultrasound examination, we found that supraspinatus tear and SASD bursa fluids accumulation is a common coexistence phenomenon in our included HSP patients. So, rotator cuff injury may play an important role in HSP after stroke, and SASD bursa may be an original pain source in patients with HSP. Stroke patients with a flaccid shoulder also have a high likelihood of experiencing HSP during rehabilitation.[2] In our study, we also found the included individuals replicated shoulder pain during passive arm abduction and external rotation, which suggested the symptoms of subacromial impingement. In these patients, with high-grade sonographic screening, such as a rotator cuff tear or bursitis, were expected to be presented on sonography.[16] We hypothesize that subacromial bursitis (SB) or shoulder impingement syndrome (SIS) is common causes of pain or disability especially in HSP patients with symptoms deteriorated during shoulder abduction or external rotation. It is strongly suggested that SASD bursa may be an original pain source in these individuals.

To the best of our knowledge, no studies have explored the effects of SASD bursa BoNT/A injection in patients with HSP, or the treatment of rotator cuff tears in stroke patients with hemiplegia. Although immediate pain reduction can be significant by corticosteroid injection, the long-term side effects including tissue degeneration and tendon rupture[17] should be concerned. Meanwhile, other major concerns are hyperglycemia and the occurrence of infection especially in diabetes mellitus patients with corticosteroid treatment. In our study, hyperglycemia was found in 5 patients (BD group) after corticosteroid injection and lasted for 3 days.

BoNT/A intra-articular injection have beneficial effects of improved pain score in adult patients with refractory joint pain.[11] Recently ultrasound-guided injections show greater accuracy than landmark technology for all shoulder pain treatment, with the expectation of the target space.[18,19] Ultrasound-guided injections potentially offer a significantly greater clinical improvement over blind injection in adults with shoulder pain after stroke.[20] In our study, both groups (BoNT/A & BD group) with ultrasound guided injection showed pain improvement after treatment.

It is well known that BoNT/A can decrease muscular tone and associated symptoms of pain by inhibiting the release of acetylcholine at neuromuscular junctions.[21] However, there is little known about the temporality of its anti-nociceptive effect. Our study shows that the period of significant pain relief lasted 12 weeks after BoNT/A treatment. So, we need more study and long follow-up period to clarify this problem.

This study has some limitations. First, this is a retrospective study. Although the assessor (physiotherapist) was blinded to the

Table 3

The changes of F-M score after SASD bursa injection.

	F-M score (BoNT/A group, n = 18)	F-M score (BD-group, n = 20)	*P* value (between 2 groups)
Before treatment	22.5 ± 7.5	22.7 ± 11.8	.180
2 wk after treatment	28.6 ± 6.9	24.4 ± 11.9	.199
4 wk after treatment	28.8 ± 7.1	24.9 ± 9.5	.152
8 wk after treatment	29.3 ± 8.1	25.3 ± 9.0	.192
12 wk after treatment	28.3 ± 7.7	26.9 ± 11.0	.525
P value (within group)	.936	.686	

Although F-M score showed an increasing trend at week 2, 4, 8, and 12 weeks compared to baseline in BoNT/A group and BD group, the differences were not significant ($P > .05$). There were no differences in results of the post treatment FM score between 2 groups at each evaluation time point ($P > .5$).

BD = betamethasone dipropionate, BoNT/A = botulinum toxin type A, F-M = Fugl-Meyer, SASD = subacromial-subdeltoid.

interventions, both patients and physiatrists were not blind to the therapy, thus the possibility of selection bias and placebo effect should be considered in the interpretation of our results. Second, the dose of BoNT/A (for SASD bursa injection) was established somewhat arbitrarily because no previous research on the effect of BoNT/A in SASD bursa injection was available. Therefore, it is debatable that whether 100 U BoNT/A is the optimal dose to inject into the SASD bursa in treating HSP. In the future, multicenter studies with randomized, double-blind, placebo-controlled should be performed to explore the best strategy of SASD bursa BoNT/A injections in the treatment of HSP especially in the patients who cannot tolerate the corticosteroid injection.

5. Conclusions

To our knowledge, this is the first clinical study to assess the efficacy of SASD bursa BoNT/A injection in refractory shoulder pain after stroke. In conclusion, BoNT/A shows the same persistent clinical benefits in pain reduction as corticosteroid in patients with HSP. These results suggest that BoNT/A injection could be a useful strategy for replacing steroids as a treatment for refractory HSP, especially for the patients who cannot tolerate corticosteroid treatment.

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