Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double blind, placebo controlled study of botulinum toxin A

Alain P Yelnik, Florence M Colle, Isabelle V Bonan, Eric Vicaut

Objective: This randomised, double blind, placebo controlled, two parallel group study was conducted to assess the beneficial effect of injection of botulinum toxin A (Dysport) into the subscapularis muscle on shoulder pain in stroke patients with spastic hemiplegia.

Methods: A single dose of botulinum toxin A (500 Speywood units) or placebo was injected into the subscapularis muscle. Pain was assessed using a 10 point verbal scale. Subscapularis spasticity was assessed by the change in passive shoulder lateral rotation and abduction. Upper limb spasticity was assessed using the Modified Ashworth Scale for shoulder medial rotators, and elbow, wrist and finger flexors. Assessments were carried out at baseline and at weeks 1, 2 and 4.

Results: Twenty patients (10 patients per group), 11 with ischaemic stroke and 9 with haemorrhagic stroke, completed the study. Pain improvement with botulinum toxin A was observed from week 1; score difference from baseline at week 4 was 4 points versus 1 point with placebo (p = 0.025). Lateral rotation was also improved, with a statistically significant difference compared with placebo at week 1 (p = 0.05) and week 4 (p = 0.018). A general improvement in upper limb spasticity was observed; it was significant for finger flexors at week 4 (p = 0.025).

Conclusions: Subscapularis injection of botulinum toxin A appears to be of value in the management of shoulder pain in spastic hemiplegic patients. The results confirm the role of spasticity in post-stroke shoulder pain.

Pain and spastic shoulder are frequent in hemiplegia following a stroke. Shoulder pain is a major problem for these patients, interfering with physiotherapy, sleep and daily activities. It is usually due to local causes: algoneuropathy (shoulder–hand syndrome), capsulitis, glenohumeral subluxation and also spasticity because of the prolonged muscular contracture and possible tendinopathies. These causes can be associated, especially spasticity and algoneuropathy in severe hemiplegia, and patients exhibit the typical arm posture: adduction and medial rotation of the shoulder, and flexion of the elbow, wrist and finger.

Different approaches are used for treatment of pain in such patients, depending on the mechanism involved. Oral medications for pain, as those for spasticity, are usually ineffective or insufficient. Treatment of algoneuropathy and capsulitis mainly consists of corticosteroids, systemic treatment being more effective than local administration. To treat spasticity or its consequences, transection of the subscapularis tendon or subscapularis nerve block has been reported, but these treatments are not in common use. Botulinum toxin A has been shown to be effective in reducing spasticity and increasing the passive range of motion of the spastic upper limb in hemiplegic patients with a real functional benefit. The effect of botulinum toxin A on shoulder pain after a stroke has not been systematically studied. However, improvement of pain by the toxin has been reported in a placebo controlled study, although pain was not the main objective of the study. A beneficial effect has also been observed in an open study. Other controlled studies in which upper limb pain was assessed failed to show a significant reduction in pain.

No specific treatment of the spastic shoulder muscles has been studied. Supraspinator and infraspinator muscles are not involved in painful contracted shoulder, and among the muscles implicated in medial rotation, the subscapularis and pectoralis muscles undoubtedly play a major role, with apparent pre-eminence of the subscapularis muscle. In a recent study of three cases, injection of botulinum toxin A into the subscapularis muscle was shown to reduce pain and improve the passive range of motion.

Based on these observations, we formed the hypothesis that shoulder pain occurring in patients with spastic hemiplegia, even with limited range of motion compatible with capsulitis, can be relieved by reducing the spasticity of the main medial rotator muscle (ie, the subscapularis muscle). Therefore, we conducted the present study to further assess the beneficial effect of injection of botulinum toxin A (Dysport) into the subscapularis muscle on shoulder pain. An improvement in the passive range of motion was expected as a parameter of the efficacy of botulinum toxin on spasticity and as a possible secondary benefit.

PATIENTS AND METHOD

Study design and patients

The study was conducted according to a randomised, double blind, placebo controlled, parallel group design in hemiplegic patients of either sex presenting with upper limb spasticity related to cerebral stroke. Patients were included whatever the post-stroke stage. Spasticity was characterised by a score of at least 1+ on the Modified Ashworth Scale (MAS) for the medial rotators and elbow flexors, with limited range of passive motion of the shoulder; external rotation 10° or <30° related to the opposite side. Patients gave written informed consent before entering the study. The following criteria excluded patients from selection: previous traumatic or neurological...
disease of the hemiplegic shoulder; retraction of at least one muscle of the elbow, wrist or fingers in the hemiplegic upper limb; previous treatment with botulinum toxin A or alcohol in the subscapularis muscle of the hemiplegic shoulder; neuromuscular disease such as myasthenia gravis; pregnant or lactating female patients; other common exclusion criteria for clinical trials. Concomitant treatment with drugs affecting muscle tone was allowed when initiated at least 2 weeks before inclusion, and without changes in the doses; it was then continued through the follow-up post-injection period without any change. Five patients (one in the toxin group, four in the placebo group) were previously treated with botulinum toxin A for upper (never in the shoulder muscles) or lower limb spasticity, always with Dysport, and at least 3 months ago. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and prevailing amendments, and was formally approved by the Ethics Committee of Saint-Louis Hospital (Paris, France).

Treatment
Treatment was allocated by computerised randomisation. Patients were seated on the edge of their bed, with the arm against the trunk, the shoulder being slightly pushed backward by an assistant to produce as much winging of the scapula as possible. An 0.8 mm diameter, 100 mm needle coated with Teflon, except for the tip, was inserted in the medial scapular border, slightly below the level of the spine of the scapula, along its anterior face, pointing at the acromion, as previously described. Before the intramuscular injection, the needle was used as a stimulation electrode to detect the motor point where minimal stimulation induces maximum internal rotation, and then botulinum toxin A (Dysport, 500 Speywood units) or placebo (all constituents of Dysport solvent) was injected while pulling back the needle by 1–2 cm. In addition, all patients received after treatment, on weekdays—non-standardised physical therapy for stretching, spasticity inhibition and increasing active motion when possible.

Methods of assessment
Pain was assessed using a 10 point verbal scale or, for aphasic patients only (one in the placebo group, three in the toxin group), a visual analogue scale. Subscapularis muscle spasticity was assessed, with the patient sitting, by a range of motion. Assessor detected subscapularis muscle spasticity, always with Dysport, and at least 3 months ago. These assessments were carried out at baseline and at weeks 1, 2 and 4. In addition to the assessments of pain, consumption of analgesics at baseline and at week 4 was recorded. The change from baseline in pain associated with spasticity, as assessed by the patient, was calculated at each visit. The change in consumption of analgesics between baseline and week 4 was coded by the investigator as increased (increasing the dosage or changing to another analgesic), no change or decreased. The change in shoulder range of motion was assessed by the change from baseline in lateral rotation and in abduction values at week 1, week 2 and week 4 visits. Changes from baseline in MAS scores for each muscle group were calculated at each visit.

Statistical analyses
As the statistical distributions of the pain and range of motion parameters were a priori not Gaussian, non-parametric tests were used. As calculated according to the method of Noether, the population required to detect a difference in the distribution of values between the two groups with an 80% power and a two-sided 5% confidence level was 24 patients (ie, 12 per group). Characteristics of the patients in the two groups at baseline were compared using exact 95% confidence intervals (CI). Covariance analyses adjusted on values at baseline were used to compare pain reduction and change in range of motion between the two groups at each visit. A $\chi^2$ test was used for comparisons of differences in MAS scores.

RESULTS
Patient characteristics at baseline
Twenty patients, 10 in each group, were recruited and completed the study. This population fell short of the planned 24 patients because of the difficulty in recruitment, as explained in the discussion. The characteristics of the patients are shown in table 1. As determined from exact 95% CI, there were no statistically significant differences between groups for age or sex. The same was true for all parameters of disease history and for the time elapsed since cerebral stroke.

Clinical efficacy
Median pain scores and quartiles in the two treatment groups at baseline and at the post-treatment time points are summarised in table 2. There was no statistically significant difference in baseline pain scores between the two groups. As shown by the mean changes from baseline (fig 1), pain improvement was observed throughout the observation period following Dysport, while minimal post-treatment changes were observed after placebo administration. Pain improvement appeared as early as week 1 and was significantly different from baseline (4 points vs 1 point in the placebo group; p = 0.025) at week 4. Consumption of analgesics in the Dysport group was unchanged in 5/6 patients and increased in only 1/6 patients. In the placebo group, it was unchanged in 2/5 patients and increased in 3/5 patients. However, the difference in consumption between the two groups was not statistically significant.

Values for lateral rotation and abduction of the hemiplegic spastic shoulder are summarised by time point in table 2. Median baseline values for the two parameters were similar at baseline and showed wide individual variations. In the Dysport group, the amplitude of external rotation was improved as early as week 1, showing a change from a median of 0° at baseline to 10°. Change from baseline in external rotation became

Table 1  Demographic characteristics and disease history

<table>
<thead>
<tr>
<th>Placebo (n = 10)</th>
<th>Dysport (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>55.2 (8.3)</td>
</tr>
<tr>
<td><strong>Sex (n [%])</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (80%)</td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td></td>
</tr>
<tr>
<td>Central stroke (n/N [%])</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>Haemorrhage (n/N [%])</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>Cerebrovascular disease (n/N)</td>
<td>5/6</td>
</tr>
<tr>
<td>Cortical/subcortical (n/N)</td>
<td>1/6</td>
</tr>
<tr>
<td>Ischaemia (n/N [%])</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Middle cerebral artery (n/N)</td>
<td>4/4</td>
</tr>
<tr>
<td>Anterior cerebral artery (n/N)</td>
<td>0/4</td>
</tr>
<tr>
<td>Location of cerebral lesion (n/N %)</td>
<td></td>
</tr>
<tr>
<td>Right side</td>
<td>6/10 (60%)</td>
</tr>
<tr>
<td>Left side</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td><strong>Time between lesion and Dysport treatment (days)</strong></td>
<td>794 (1050)</td>
</tr>
</tbody>
</table>

*Values are mean (SD).
†One female patient with child bearing potential in the placebo group and two in the Dysport group.

www.jnnp.com
and pain thereafter, probably related to the injection process rather than to the placebo itself; another patient experienced somnolence.

**DISCUSSION**

Twenty patients were included in this randomised, double blind, placebo controlled study with the objective of assessing the efficacy of a single injection of botulinum toxin A into the subscapularis muscle to reduce pain associated with shoulder spasticity after stroke. The main finding was improvement in pain. A clinically significant improvement in passive lateral rotation was concurrently observed, resulting from a decrease in local spasticity. External rotation improved markedly, more than abduction, which is not surprising because the subscapularis muscle is a strong internal rotator with limited impact on abduction. At the same time as the improvement in shoulder pain and range of motion, spasticity of the upper limb muscles appeared to be reduced. The improvement was statistically significant for the finger flexors. This confirms clinical experience, suggesting that part of the spasticity of these muscles remote from the injection point is related to shoulder pain. Another interesting point is that, contrary to what would have been expected, the longer the time after stroke, the better were the results. This suggests that algoneurodystrophy and capsulitis, often associated with spasticity in severe hemiplegia but for which botulinum toxin is not a treatment, mainly occurred during the first months after the stroke, whereas pain remaining for longer was primarily caused by spasticity and thus could be treated by relieving spasticity with botulinum toxin A.

The population size may have hindered the evaluation of the efficacy of botulinum toxin A on the range of motion of the spastic shoulder. Sample size estimation was 24 patients based on an expected large effect size. However, the difficulty in recruitment limited the study population to 20. This difficulty was mainly because of the impossibility, in the time frame of

<table>
<thead>
<tr>
<th>parameter</th>
<th></th>
<th>Placebo</th>
<th>Dysport</th>
<th>p Value ±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral rotation</td>
<td>Week 1</td>
<td>7.5 (–5; 35)</td>
<td>10.0 (0; 40)</td>
<td>0.131</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>5.0 (–20; 25)</td>
<td>10.0 (0; 60)</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>7.5 (–20; 15)</td>
<td>15.0 (15; 45)</td>
<td>0.018</td>
</tr>
<tr>
<td>Abduction</td>
<td>Week 1</td>
<td>10.0 (–10; 35)</td>
<td>5.0 (0; 15)</td>
<td>0.588</td>
</tr>
<tr>
<td></td>
<td>Week 2</td>
<td>2.5 (–5; 35)</td>
<td>7.5 (0; 15)</td>
<td>0.654</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>2.5 (–5; 35)</td>
<td>7.5 (–5; 20)</td>
<td>0.894</td>
</tr>
</tbody>
</table>

*Values are median (min; max) in degrees.
†Non-parametric model adjusted to value at baseline.
REFERENCES


Treatment of shoulder pain in spastic hemiplegia by reducing spasticity of the subscapular muscle: a randomised, double blind, placebo controlled study of botulinum toxin A

Alain P Yelnik, Florence M Colle, Isabelle V Bonan and Eric Vicaut

J Neurol Neurosurg Psychiatry 2007 78: 845-848 originally published online November 6, 2006
doi: 10.1136/jnnp.2006.103341

Updated information and services can be found at:
http://jnnp.bmj.com/content/78/8/845

These include:

References
This article cites 23 articles, 5 of which you can access for free at:
http://jnnp.bmj.com/content/78/8/845#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Pain (neurology) (763)
- Drugs: CNS (not psychiatric) (1945)
- Neuromuscular disease (1311)
- Stroke (1449)
- Musculoskeletal syndromes (537)
- Editor's choice (140)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/