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REVIEW ARTICLE

TREATMENT OF UPPER EXTREMITY SPASTICITY IN STROKE PATIENTS BY FOCAL NEURONAL OR NEUROMUSCULAR BLOCKADE: A SYSTEMATIC REVIEW OF THE LITERATURE

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Studies published from January 1966 until October 2000 on the clinical effects of focal neuronal and neuromuscular blockade in post stroke upper limb spasticity were identified. Twelve studies were included and evaluated on 13 methodological criteria. Ten studies on Botulinum toxin type A (BTX-A) treatment were found (of which 4 were randomised controlled trials (RCTs) and 6 were uncontrolled observational studies) as well as one uncontrolled observational study on phenol blockade of the subscapular muscle and one on alcohol blockade of the musculocutaneus nerve. The homogeneity of the patient groups with regard to diagnosis and their comparability with regard to functional prognosis and other sources of bias were generally unsatisfactory. Only two RCTs met predetermined criteria of minimal validity. There is evidence of effectiveness of BTX-A treatment on reducing muscle tone (varying between 0.8 and 2.0 points on the modified Ashworth scale) and improving passive range of motion at all arm-hand levels in chronic stroke patients for approximately 3–4 months. There is also preliminary evidence of a synergistic effect of concomitant electrostimulation. Taking into account a critical maximum dose of 100 MU Botox® (300–500 MU Dysport®) for preserving active finger flexion, BTX-A treatment seems to be a safe focal spasmolytic treatment. Effectiveness of BTX-A treatment on improving functional abilities could not be convincingly demonstrated, although two subgroups may be identified that might specifically benefit at a functional level: (1) patients with mild spasticity and a potential for voluntary extensor activity and (2) patients with severe spasticity suffering from problems with positioning and taking care of the affected arm and hand. Larger controlled studies are needed to compare the effectiveness of BTX-A with other focal spasmolytic techniques paying special attention to individual goal assessment, the (duration of) functional benefits, co-treatment and aftercare, side-effects and cost-effectiveness.

Key words: stroke, cerebrovascular accident, upper extremity spasticity, treatment, neuromuscular blockade, neurolysis, phenol, Botulinum toxin.

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INTRODUCTION

Spasticity is a characteristic component of the upper motor neuron syndrome that complicates the rehabilitation process of many stroke patients. It is usually defined as a velocity-dependent increase in muscle resistance against passive lengthening due to a supraspinal disinhibition of both tonic and phasic stretch reflexes (1). However, spasticity is also characterised by efferent symptoms such as delayed and disrupted muscle synergies (e.g. co-contractions) or remote involuntary (associated) muscle activity during active movements as well as by afferent symptoms such as massive flexion or extension reactions to touch or pain stimuli (2, 3). Spasticity can greatly interfere with the functional use of the affected body parts, in particular when spastic antagonists counteract selective voluntary muscle activity. In the long term, untreated spasticity may lead to secondary complications such as muscle stiffness, contractures and pain. In the upper extremity of stroke patients, spasticity most frequently emerges in a predominant flexion pattern. It may cause great difficulty with arm or hand positioning in space, grasping, self-care and many other activities of daily living (ADL) (4, 5).

The management of spasticity remains a major challenge in rehabilitation medicine. The available treatment options include various physical methods (e.g. muscle lengthening, splinting, electrostimulation), systemic use of spasmolytic drugs, soft-tissue surgery (e.g. muscle-tendon lengthening or transposition, tenotomy, neurectomy) as well as several invasive procedures for focal neuronal or neuromuscular blockade (4–13). The ideal treatment strategy would be to achieve a long-lasting relief of disabling hypertonia in selected groups of muscle fibres without causing impairment of sensation, deterioration of motor skills, or other local or systemic side-effects (14). Because spasticity in most stroke patients is a variable phenomenon in time and apparent only in certain muscle groups, the application of low-

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Table I. *Methodological evaluation*

		Randomised controlled trials				Observational studies							
		Hesse 1998	Simpson 1996	Bakheit 2000	Smith 2000	Lagalla 2000	Reiter 1996	Sampaio 1997	Bhakta 1996	Rodriquez 2000	Pierson 1996	Kong 1999	Hecht 1992
	Internal validity												
V1	Homogeneity with regard to definition of stroke and spasticity	+/−	+/−	+/−	−	+/−	−	+/−	−	+/−	−	+/−	−
V2	Control of bias related to functional prognosis before intervention	+/−	+/−	−	+/−	+/−	+/−	+/−	+/−	+/−	−	−	−
V3	Control for confounders during the study	+	+/−	+/−	−	+	−	+/−	−	+/−	−	+/−	+/−
V4	Description and adequacy of technical aspects of the therapeutic intervention	+	+	+/−	−	+	+	+/−	−	+	+	+	+
V5	Adequacy of study design	+	+	+	+	+/−	+/−	−	−	−	−	−	−
V6	Adequacy of effect parameters	+	+	+	+	+/−	+/−	+/−	−	+	−	+/−	−
	Data extraction												
D1	Description of inclusion and exclusion criteria	+	+/−	+/−	+/−	+	+/−	+/−	+/−	+	+/−	+	+
D2	Adequacy of statistical and quantitative analysis	+/−	+/−	+	+/−	+	+/−	+	+	+/−	−	+/−	+
D3	Length of follow-up	12 weeks	16 weeks	16 weeks	12 weeks	2 years	6 months	3 months	4–47 weeks	variable	4–24 months	6 months	0
D4	Loss to follow-up	0	2	1	0	6	?	0	6	12	7	0	0
D5	Intention to treat analysis	0	−	+	0	−	−	0	−	−	−	0	0
D6	Description of adverse effects	+	+	+	+	+	+	+	+	−	+	+	+
D7	Sample size	24	37	83	19 2 TBI	34	15 2 TBI	19	17	14	11	20	11 2 TBI
	Minimal criteria of validity	yes	yes	no	no	no	no	no	no	no	no	no	no

TBI = traumatic brain injury.
+ = sufficient; +/− = moderate; − = insufficient; 0 = criterion not applicable.
V = internal validity; D = data extraction. For number explanation see “Methodological evaluation”.

threshold and "reversible" focal treatment techniques seems to be the preferable first option. Besides peripheral and intramuscular neurolysis (e.g. with phenol), intramuscular administration of Botulinum toxin type A (BTX-A) is increasingly applied in stroke patients.

Phenol has two different actions on nerve tissue. The first immediate and reversible effect is a local anaesthetic nerve conduction blockade (15, 16). The second long-term effect is demyelination and axonal degeneration by denaturation of proteins (17–21). Through the same mechanism, phenol causes atrophy within muscle tissue (22, 23). Although phenol blocks act non-selectively across nerve fibres, the extent of the blocks may depend on the injection technique (e.g. perineural or intraneural) and the phenol concentration used. The reported duration of neurolytic blocks with phenol varies between 6 weeks and 6 months, depending probably on the technique as well as on the time required for remyelination and axonal regeneration. Dysaesthesia and neuralgia are among the most frequently reported side effects of neurolytic blocks (21, 24–40).

Recently, neuromuscular blockade with BTX-A has been introduced as an alternative to focal neurolysis in the management of spasticity (41–43). BTX-A weakens the activation of spastic muscles by selectively blocking the release of acetylcholine at the neuromuscular junction of both extrafusal and intrafusal muscle fibres. Its effect seems to be to some extent dose-dependent and usually lasts 2–4 months (44–49). An important advantage of motor point blockade over neurolysis is the absence of sensory disturbances.

At present, there is no consensus about the preferred strategy, precise method of administration and optimal dosage in the focal treatment of upper limb spasticity following stroke. Valid comparisons of studies concerning the efficacy of different methods for focal neuronal or neuromuscular blockade in stroke are complicated because of differences in selected patients, treatment goals and functional evaluations. The goal of this study was to provide preliminary clinical guidelines and suggestions for future research by conducting a systematic literature review.

METHODS

Study selection

Material for the review was selected from a systematic search in the databases of Medline (January 1966–October 2000), Current Contents (January 1996–October 2000), Cinahl (January 1982–October 2000) and the Cochrane Library. This search was conducted using the following combinations of search terms: spasticity, chemical neurolysis, intramuscular neurolysis, chemical denervation, neuromuscular blockade, nerve block, motor point block, phenol, alcohol/ethanol, Botulinum toxin, thermocoagulation, cryotherapy and neurotomy/neurectomy. Identifying relevant references from the retrieved articles extended the search. Only studies concerning the treatment of upper extremity spasticity by focal neuronal or neuromuscular blockade in adult stroke patients and published in the English, German, French or Dutch languages were considered. After the primary search the papers were subjected to a preliminary screening based on the following exclusion criteria: (1) studies not primarily addressing aspects of clinical efficacy, (2) reviews, (3) comments or letters to the editor, (4) preliminary reports or abstracts, (5) heterogeneous patient samples in which the stroke patients could not be identified, (6) sample sizes smaller than 10 patients, (7) papers not available in medical libraries in the Netherlands. Ultimately, the remaining studies were selected for detailed methodological evaluation.

Methodological evaluation

Both internal validity (V) and data extraction (D) were assessed. We established adapted V and D criteria based on a system that was originally developed for evaluating randomised controlled trials (RCTs) (50). Adaptation of these criteria was necessary to be able to also evaluate other study designs than RCTs. Each criterion was scored according to three levels: sufficient (+) (all subcriteria fulfilled), moderate (+/−) (all but one subcriterion fulfilled), or insufficient (−) (other). When a specific criterion was not applicable, it was scored as such (0). Criteria V5, D3, D5, and D6 had no subcriteria. Hence, these were scored only with sufficient (+) or insufficient (−). All selected studies were independently assessed by 3 referees (A.K., A.G., B.B.). In the case of disagreement between referees, consensus was established in second instance.

Internal validity. V1: The homogeneity of the study sample with regard to stroke and spasticity was tested. (1) A diagnosis of stroke by clinical standards was accepted, preferably confirmed by CT or MRI scanning. (2) Spasticity, being a velocity-dependent increase in muscle resistance on passive stretching, should clearly be distinguished from other types of hypertonia, muscle stiffness and contracture.

V2: Control of bias related to functional prognosis *before* exposure to the therapeutic intervention was judged for the controlled trials. Based on the literature, three such potential confounders were identified: (1) the severity of stroke judged by its sensorimotor and cognitive consequences, (2) the chances of neurological recovery based on the time post stroke (51, 52), and (3) co-morbidity with a possible effect on the outcome of the therapeutic event (e.g. concomitant rheumatic or neuromuscular disease). As for the observational studies, the homogeneity of the (sub)group(s) with respect to these factors was judged. Furthermore, a minimal time interval post stroke of 6 months was considered appropriate to assume a relatively stable clinical situation (51, 52).

V3: This criterion tested whether there had been sufficient control for potential confounding *during* the study. More specifically, (1) paramedical co-interventions (e.g. physiotherapy) and (2) concurrent use of medication (e.g. spasmolytic drugs) should have been reported and taken into account. As for the observational studies, all co-interventions should have been kept stable during the follow-up period.

V4: Adequacy of technical aspects of the therapeutic intervention was assessed. Studies should have indicated: (1) concentration and volume of substance applied, (2) whether a fixed or individualised treatment algorithm was used, and (3) how target muscles were localised. Only injections guided by internal electrical stimulation or electromyography were considered appropriate (53–55).

V5: The selected study design was evaluated in relation to the study aim. Randomised controlled trials were accepted as was any other design with the ability to control for confounding e.g. a cohort study making within-subjects comparisons of experimental and control interventions allowing sufficient wash-out periods.

V6: The (1) reliability, validity, and responsiveness of the selected outcome measures were assessed in relation to the study aim (56). Also, (2) blinding of the outcome assessor was considered an absolute prerequisite for unbiased observations.

Data extraction. D1: This criterion tested (1) whether the inclusion and exclusion criteria were sufficiently reported as well as (2) whether the base population was identified from which the study sample was selected.

D2: It was judged whether treatment effects were adequately reported in terms of (1) statistical (e.g. *F*- and *p*-values or confidence intervals) and (2) quantitative measures (e.g. absolute or relative differences).

D3: The length of the total follow-up period was assessed.

D4: This criterion tested the numbers of patients lost to follow-up.

D5: It was determined whether intention-to-treat analysis was done in the case of any loss to follow-up, non-compliance or unplanned crossovers.

D6: Description of adverse effects was assessed.

Table II. *Study-goal and outcome measures*

Author	Primary goal	Outcome measures		
		Technical/Impairment	Functional	Caregiver/patient objective
Hesse et al. (60)	Efficacy of combined BTX-A and ES on spasticity and related disabilities	• MAS • Limb position at rest	• 3 ADL activities • Global pain assessment score	
Simpson et al. (57)	Efficacy of BTX-A on spasticity and related disabilities	• Ashworth Scale • Grip strength • Arm/forearm circumference • Global assessment of spasticity scale (subjective)	• Fugl-Meyer Scale • FIM • Motor task/function rating scale • Caregiver dependency scale • Function and pain assessment	Rand 36-Item Health survey
Bakheit et al. (58)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM	• Rivermead motor assessment (arm section) • Barthel Index • Caregiver/patient assessment of three functional activities • Severity of muscle pain	
Smith et al. (59)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM • Postural alignment	• Frenchay arm test • Time to dress the upper half of the body • Video assessment of gait quality	
Lagalla et al. (PhD Thesis) (61)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Rest position	• Frenchay arm test • Patient/caregiver goals assessment	
Reiter et al. (62)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • MRC-scale	• FIM • Frenchay arm test • Motricity index • VAS	Nothingham Health profile
Sampaio et al. (65)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Grip strength • Frequency of spasm	• Frenchay arm test • Severity of pain	Degree of satisfaction of the patient
Bhakta et al. (63)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • PROM • Finger position at rest	• Patient defined ADL goal assessment • Presence and location of pain	
Rodriquez et al. (64)	Efficacy of BTX-A on spasticity	• MAS • Clonus scale • Grip strength • Videotaping finger extension		
Pierson et al. (66)	Efficacy of BTX-A on spasticity and related disabilities	• MAS • AROM/PROM	• Brace tolerance measure • Ambulation score • Pain rating scale	Patient satisfaction report
Kong et al. (67)	Efficacy of alcohol neurolysis on spasticity	• MAS • PROM • MRC-scale		
Hecht (68)	Efficacy of phenol neurolysis on spasticity	• PROM	• Pain subjectively rated by therapist	

BTX-A = Botulinum toxin type A; ES = electrical (neuromuscular) stimulation; MAS = modified Ashworth scale; ADL = activities of daily living; FIM = functional independence measure; AROM = active range of motion; PROM = passive range of motion; MRC-scale = Medical Research Council scale; VAS = visual analogue scale.

D7: The total number of included stroke patients at baseline was determined.

Criteria of minimal validity

Based on the scores for all criteria mentioned above, those studies were identified that were able to meet the following minimal criteria of validity: (1) no negative scores on the internal validity items, and (2) at least half of the items scored positive (+). These studies were primarily used for establishing clinical evidence. All other studies were considered to yield merely secondary evidence.

RESULTS

The primary search yielded 116 papers, including preliminary reports and abstracts. After the preliminary assessment, 12 studies were included for detailed methodological evaluation (57–68). Ten studies focused on the treatment of upper limb spasticity with BTX-A (57–66), one focused on alcohol neurolysis (67) and one study dealt with phenol neuromuscular blockade (68). No studies were found concerning the treatment of upper limb spasticity with neuromuscular blockade using thermocoagulation or cryotherapy. Studies addressing neurectomy consisted of combined treatment procedures including soft-tissue surgery. For this reason these studies were excluded from further evaluation. The BTX-A treatment studies included 4 RCTs and 6 uncontrolled observational studies. Both the study on alcohol neurolysis and the one dealing with phenol nerve blockade were observational studies. The results of the assessment of both V- and D-criteria for all 12 studies are given in Table I. Here, the RCTs will first be critically reviewed in more detail, whereas some of the methodological issues related to the observational studies will only be globally highlighted.

Randomised clinical trials

Three trials (57–59) studied the efficacy (and safety) of different dosages of BTX-A in the reduction of upper limb spasticity in stroke patients using a randomised, triple-blind (patient, physician, and outcome-assessor), placebo-controlled design. Both Simpson et al. (57) and Bakheit et al. (58) presented multicentre studies. Only Smith et al. (59) included two patients with head injury. Although Smith et al. claimed to have excluded patients with fixed contractures, the reported results on joints range of motion (ROM) suggested the existence of contractures in their study sample. No study explicitly differentiated between spasticity and other types of increased muscle tone. The control for the influence of sensorimotor and cognitive functioning on outcome was considered insufficient in all three studies. In the study of Bakheit et al. (58), the control for the influence of spontaneous recovery was also considered moderate, because patients were allowed to enter the study already 3 months after their stroke, whereas the other RCTs used minimal post-stroke intervals of 9 (57) and 12 months (59). As for co-morbidity, only Simpson et al. (57) explicitly excluded other neuromuscular disease. Ongoing spasticity treatments (medication, physiotherapy) were maintained during the trial by Simpson et al. (57), but could differ between patients. Bakheit et al. (58) did not allow de novo treatment with spasmolytic drugs, whereas Smith et al. (59) did not control for any type of concurrent intervention. Bakheit et al. (58) determined the injection sites only by using anatomical landmarks. Smith et al. (59) used a partially individualised treatment algorithm, which was insufficiently specified. Moreover, no specifications of the localisation technique or of injected volumes were given.

In none of the three RCTs mentioned above were the base populations from which the study samples had been selected clearly identified. Both Simpson et al. (57) and Smith et al. (59) primarily analysed within-group changes from baseline for different aspects of spasticity, where the preferable analysis should have consisted of between-group comparisons of changes from baseline. No statistical corrections were made for multiple testing of similar hypotheses. Although Bakheit et al. (58) mentioned a follow-up period of 16 weeks, the main analysis was performed using changes from baseline at 4 weeks after the intervention. Simpson et al. (57) lost 2 patients to follow-up without specifying the precise reasons for drop out or the group to which these patients had been allocated. Although Smith et al. (59) had no dropouts, 4 patients (of which 3 were stroke patients) crossed over who had been originally allocated to placebo treatment and these patients were re-randomised to one specific dosage of BTX-A. As a result, there was a source of selection bias for which the analysis was not adjusted. Considering the small sample sizes in four parallel groups, there should be a major concern about lack of statistical power in the studies by Simpson et al. (57) and Smith et al. (59).

Hesse et al. (60) conducted a randomised, triple-blind, placebo-controlled trial on the efficacy of combining BTX-A with electrical stimulation (ES) in the reduction of upper limb spasticity in stroke patients compared to single treatments using a four-arm parallel design (BTX-A + ES, BTX-A, placebo + ES, placebo). All patients received additional treatment consisting of physiotherapy and home exercises. There was no explicit differentiation between spasticity and other types of increased muscle tone. The possible influence of sensorimotor and cognitive functioning and the influence of co-morbidity on outcome were not controlled for. As for the data analysis, the primary outcome measures at 2, 6, and 12 weeks were averaged and the mean post-injection value was used to determine the treatment effect on different aspects of spasticity. As a result, no adjustments were made for the (small) differences in outcome measures at baseline. Moreover, by averaging effects over time, relatively small and temporary effects may have been obscured by false negative statistical tests (type II error) especially in view of the small group sizes ($n = 6$) and the correction of alpha (chance of type I error) to 1%.

Observational studies

No study explicitly differentiated spasticity from other types of increased muscle tone. In (almost) all observational studies the study samples were heterogeneous with regard to patient characteristics related to diagnosis, severity of stroke, chance of neurological recovery, and co-morbidity. Only few studies

Table III. *Treatment algorithm and main outcome*

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Author	Product	Treatment algorithm	Muscle/Nerve	Main outcomes
Hesse et al. (60)	Dysport	Fixed regime (4 arms): • 1000 BTX-A + ES • 1000 BTX-A • placebo + ES • placebo	• Biceps, Brachialis • FCR, FCU • FDP, FDS	• Tone reduction most prominent in group receiving BTX-A and ES; mean reduction in MAS at 6 weeks at the elbow 1.3 points, at the wrist 1.7 and at the fingers 1.5 points • Position at rest better in group receiving BTX-A and ES • Cleaning the palm of the affected hand significantly better in group receiving BTX-A and ES
Simpson et al. (57)	Botox	Fixed regime (4 arms): 75, 150, 300 MU and placebo Biceps: 50 100 200 FCR: 15 30 60 FCU: 10 20 40 75 150 300	• Biceps • FCR, FCU	• Significant tone reduction in BTX-A treated groups compared to placebo; mean reduction in Ashworth score at 6 weeks 0.8 points at the elbow and wrist • Significant tone reduction in wrist and elbow flexors in high BTX-A dosage group; mean reduction in Ashworth score at 6 weeks 1.1 points at the elbow and 1.2 points at the wrist • Peak effect 2–6 weeks post injection; return to baseline by 10 weeks
Bakheit et al. (58)	Dysport	Fixed regime (4 arms): 500, 1000, 1500 MU and placebo Biceps: 200 400 600 FCR: 75 150 225 FCU: 75 150 225 FDP: 75 150 225 FDS: 75 150 225 500 1000 1500	• Biceps • FCR, FCU • FDP, FDS	• Significant tone reduction at week 4 in BTX-A treated groups compared with placebo • Significant tone reduction during 16 weeks follow-up at the wrist and elbow; less clear at the fingers • Effect most prominent in high dosage group • Significant improvement in PROM at all joints, no differences between doses
Smith et al. (59)	Dysport	Individualised treatment algorithm (4 arms): 500, 1000, 1500 MU and placebo. 2/3 above elbow; 1/3 beneath elbow If only elbow, wrist, or finger flexors: 2/3 of total dosage was used.	• not specified	• Significant tone reduction in BTX-A treated groups compared with placebo, mean reduction in MAS at week 6 1 point at the elbow, 2 points at the wrist and fingers • Significant improvement in PROM at wrist, and finger curl distance at week 6 in BTX-A treated groups compared with placebo; mean increase in PROM 9° at the elbow and 14° at the wrist • Significant improvement in PROM at the elbow in 1500 MU group at 6 weeks (mean increase 19°); tendency for dose-related tone reduction • 6/9 patients improvement in gait quality • Effects lost by 12 weeks except for PROM elbow in 1500 MU dose
Lagalla et al. (61)	Botox	Individualised treatment algorithm: Total dosages 50–300 MU. Total dosage per muscle 25–75 MU.	• Biceps, Brachialis • FCR, FCU • FDP, FDS • FPL	• Significant tone reduction after first injection; mean reduction in MAS globally 1 point • Significant improvement in rest position and PROM; mean increase in PROM at the elbow 5.2°, at the wrist 19.0°, fingers MCP 13.7°, IP 7.1° • FAT increase of 1 to 3 points in 8/28 patients • Steady improvement in patient ad caregiver satisfaction • No changes in doses injected over time, intervals between BTX-A injections significantly lengthened • Cost of treatment solely influenced by basal Ashworth
Reiter et al. (62)	Botox	Individualised treatment algorithm: 3–5 upper limb flexors were treated with total dosages BTX-A ranging from 100 to 210 MU.	• Biceps • FCR, FCU • FDP, FDS • FPL	• Significant tone reduction after 1 month; mean reduction in MAS 1.2 points at the elbow, 1.4 at the wrist, and 1.0 at the fingers • Significant improvement in PROM; at the elbow 36.1°, at the wrist 36.5° and at the fingers 27° • Increased wrist and finger extension force in 4/12 patients • VAS score changed significantly • Effect apparent after 1 week; peak effect within 30 days; steady for an average of 3.58 months

Table III. *Continued*

Sampaio et al. (65)	Botox	Individualised treatment algorithm: Restricted to 6 prior defined muscles. Max dosage 25 MU per muscle, 150 MU in total.	• FCR, FCU • FDP, FDS • FPL, FPO	• Significant tone reduction at 1 month; mean reduction in MAS 1 point • Significant improvement in passive joint mobility score at 1 month; mean improvement 1 point • Improvement of mean FAT value from 0 to 1 point • Frequency of spasm decreased in 4 patients to 0 • Severity of pain decreased in 2 patients to 0 • Effect apparent after 1 week; peak effect 1 month post-injection; persisted up to 3 months
Bhakta et al. (63)	Dysport Botox	Individualised treatment algorithm: Allergan 100 MU/2.5 ml Dysport 500 MU/2.5 ml Total dosages ranging from 130-1000 MU	• Biceps, • FCR, FCU, • FDP, FDS	• Significant tone reduction post injection; mean reduction in MAS globally 2 points at the elbow and 1 point at the fingers • Significant PROM improvement post injection; mean increase of PROM at the shoulder 17°, at the elbow 16°, and at the wrist 31° • Functional benefit reported in 14/17 patients • Shoulder pain in 9/17 patients, reduction in 6/9 patients; pain at the elbow in 3/17 patients, reduction in 3/3; at the wrist in 6/17patients, reduction in 5/6 • Effect apparent after 2–3 weeks after injection, lasting for 4–47 weeks • Beneficial effects on distance
Rodriquez et al. (64)	Botox	Fixed regime: 50 MU into long finger flexors	• FDP, FDS	• Significant reduction in tone; mean reduction in MAS globally 1 point • Significant reduction of clonus; and improvement in finger extension • Significant decrease in grip strength • Comparison of changes between two injections in tone and clonus not significant; finger extension significant increased
Pierson et al. (66)	Botox	Individualised treatment algorithm	• Biceps • FCR, FCU • FDP, FDS, FPL • abductor digiti minimi quinti	• Significant reduction in tone; mean reduction in MAS globally 1 point • Significant improvement in AROM (mean 17°), PROM (mean 18.4°), and brace wear • Beneficial effect on pain, subjective functional improvement, satisfaction with treatment outcome • Duration of effect lasted up to 4–5 months
Kong et al. (67)	Alcohol	Until abolition of muscle contracture	• n. musculocutaneous	• Significant reduction in tone at 4 weeks; mean reduction in MAS 1 point • Significant improvement in PROM (mean 17°) at 4 weeks • Improved walking balance in 7/14 patients • Relief of shoulder pain reported • Effect lasted up to 6 months
Hecht (68)	Phenol	Motor point block subscapularis muscle	• m. subscapularis	• Immediate improvements ROM in flexion, abduction., and exorotation. Greatest improvement in exorotation (42%), next flexion (22%) and abduction (12%) • Pain subjectively evaluated diminished in original arc of motion, but still present at extremes of end rage • Effect lasted for 3–6 months

FCR = flexor carpi radialis; FCU = flexor carpi ulnaris; FDP = flexor digitorum profundus; FDS = flexor digitorum superficialis; FPL = flexor pollicis longus; FPO = flexor pollicis opponens; BTX-A = Botulinum toxin type A; ES = electrical (neuromuscular) stimulation; MU = mouse units; ROM = range of motion; PROM = passive range of motion; MCP = metacarpophalangeal joint; IP = interphalangeal joint; AROM = active range of motion; FAT = Frenchay arm test; VAS = visual analogue scale; MAS = modified Ashworth scale.

controlled for ongoing spasticity treatments (61, 64–67). Small sample sizes were common and in some studies (63, 64, 66) loss to follow-up was unacceptable (>33%). Therefore, no detailed methodological evaluation of the observational studies will be given. Instead, the reader is referred to Table I.

DISCUSSION

Although focal neuronal and neuromuscular blocks are increasingly used in clinical practice for the treatment of post stroke upper limb spasticity, the number and quality of the traced publications investigating the efficacy of these treatments is as yet limited. Four randomised clinical trials were identified (57–60), whereas other studies reported uncontrolled observations (61–68). Of all selected studies, only two met the predetermined criteria of minimal validity (57, 60) and these studies will be primarily used for discussing clinical effectiveness. Nevertheless, the outcomes of several other studies will still be considered because they may yield secondary (supportive) evidence of effectiveness and/or safety and provide important perspectives for further research. The treatment goals and outcome measures of each selected study are given in Table II. The applied treatment protocols and main clinical outcomes are summarised in Table III.

Alcohol or phenol

Kong et al. (67) reported a case series on the effectiveness of neurolysis of the musculocutaneous nerve with alcohol on post-stroke elbow flexion spasticity. Although patients with fixed elbow flexion contractures were included, significant improvements in tone and PROM were found with effects lasting up to 6 months. Hecht (68) reported a case series of patients with therapy-resistant shoulder pain due to spasticity. Patients were given a motorpoint block of the subscapularis muscle with phenol and the immediate post-injection effects were determined. Although immediate improvements in PROM were seen, the authors did not use an adequately measure for determining shoulder pain (patient observation during passive shoulder examination). In both studies the most common reported side effect was a transient soreness over the injection side. In the study on alcohol neurolysis (67), 3 patients (15%) suffered from temporary dysaesthetic pain, which could be reasonably treated with amitriptyline or non-steroidal anti-inflammatory drugs. The only conclusion one can draw based upon these uncontrolled studies is that phenol or alcohol may be used as a potential agent for reducing spasticity and improving PROM in the upper extremity of stroke patients by neuronal or neuromuscular blockade, but that controlled comparative studies (e.g. with BTX-A) are urgently needed. Particular attention should be paid to comparing side effects and cost-effectiveness. This conclusion seems to be supported by the literature on the treatment of post stroke spasticity with phenol or alcohol in general (24–40, 70–73).

Botulinum toxin

The efficacy of BTX-A treatment on tone and PROM was demonstrated by the RCT performed by Simpson et al. (57) and supported by other studies (58, 59, 61–66). In addition, Hesse et al. (60) found evidence of a synergistic effect of ES combined with BTX-A treatment. In particular, the combined treatment of BTX-A and ES seemed superior with regard to the facilitation of hand hygiene and spasticity reduction. This synergism might be explained by a stimulating effect of ES on the uptake of BTX-A in the terminal nerve branches. Therefore, the degree of motor activity may be an important factor for the potency of BTX-A. Although Hesse et al. did not find a statistically significant reduction in spasticity in the BTX-A only group compared with the placebo group, an average reduction of 0.5 Ashworth score at 6 weeks was still seen, which may not have been reached statistical significance due to the small group size ($n = 6$) (see Results).

Dosage and duration of effects. Although a clear dose–response relationship could not be demonstrated, a tendency for a dose-related improvement of the Ashworth score and PROM was seen in the studies of Simpson et al. (57), Smith et al. (59) and Bakheit et al. (58). Their results suggest a critical dosage of BTX-A to achieve a clinically significant tone reduction. The reported doses were globally 200 MU Botox® (600–1000 MU Dysport®) for the biceps, 100 MU Botox® (400–500 MU Dysport®) in total for the wrist flexors, and 100 MU Botox® (300 MU Dysport®) in total for the finger flexors. These dosages seem to correspond with the suggested maximal dose of the dosing guidelines for adult onset spasticity by the Spasticity Study Group (69).

The duration of the reported effects varied between 10 weeks and 4 months (57–66). The first effects of treatment became apparent not earlier than 2–3 days after injection (63), and the peak effects were reported between 2–6 weeks post injection (62, 65). The efficacy of *repeated* BTX-A injections was specifically studied by Lagalla et al. (61). All patients exhibited a tone reduction (mean reduction in MAS 1 point) and PROM increase (mean increase at the elbow 5°, at the wrist 19°) after the first injection, which effects remained constant across repeated injections. Although the dose injected over time did not change, the intervals between injections became significantly longer, which may possibly be related to a decreasing capacity for terminal neuronal sprouting.

It is not possible to further specify the optimal dose of BTX-A for the treatment of post stroke upper limb spasticity from the studies included in this review, because the magnitude and duration of the spasmolytic effects are theoretically influenced by the presence of other forms of hypertonia or muscle stiffness as well as by loss of muscle length (and thus by concomitant therapy directed at these muscle characteristics), for which influences no study adequately controlled. In addition, the products and dosages of BTX-A differed considerably between studies (Table III).

Safety. In all selected studies, only minor side effects were

seen, such as transient skin rash (58), soreness, and pain at the injection sides (57, 61, 62, 66). Incidentally, flu-like symptoms were reported (58, 59 65) and in one study bladder instability was observed in one patient after BTX-A treatment (57). The most serious reported side effect seems to be an excessive muscle weakness due to an overdose of BTX-A. This seems of particular functional importance for the finger flexors. Bakheit et al. (58) found a critical dosage for preserving active movement of the finger flexors at 300 MU Dysport®. This finding was supported by Rodriquez et al. (64), who reported a critical dosage of 100 MU Botox® for preserving active finger flexion. Hence BTX-A treatment seems to be a safe treatment for upper extremity spasticity as long as these critical dosages are appreciated.

Functional abilities. Despite the reported improvements in tone and PROM of BTX-A treatment a clear impact on functional abilities could not be convincingly demonstrated. Also, the overall reported effect on global disability scores was minimal. Nevertheless, patients in the study of Smith et al. (59) reported that the arm felt looser and appeared more relaxed particularly during walking after BTX-A injection into the biceps brachii and brachialis muscles. Subjectively, beneficial findings in gait quality and balance were reported by some ambulatory patients. Sampaio et al. (65) reported improvement in functional ability of the affected arm as assessed by the Frenchay Arm Test (FAT benefit of 1 point) in patients who were able to perform only minimal voluntary movements of the upper limb before treatment due to spasticity. Lagalla et al. (61) reported a FAT benefit of 2 points in a similar subgroup of 8 patients (29%). Although Reiter et al. (62) did not find a beneficial effect on the median FAT in the total treatment group, subgroup analysis gave a more discriminative picture. One subgroup (4/17) with relatively mild spasticity and voluntary motor activity of the extensor muscles showed an increase (5%) in median FAT score after BTX-A treatment. No changes in a global disability measure (FIM) were seen which can be explained by a ceiling effect and lack of responsiveness of this measure to functional improvement of a single arm. A second subgroup (4/17) consisted of paralytic patients with relatively severe spasticity, in which BTX-A treatment resulted in PROM increase, better passive positioning of and care for the affected limb (e.g. easier fitting of splints).

CONCLUSION

This review emphasizes the importance of adequate patient and goal selection when treating upper extremity spasticity in chronic stroke patients. Since most authors used a standardised treatment protocol, the muscles selected for treatment may not have been the most optimal targets adapted to the needs of individual patients. A more individualised approach based on the distribution of spasticity as well as on a patient's personal needs might give a better indication of the potential functional benefits of BTX-A in treating upper extremity spasticity following stroke. Indeed, the results of Hesse et al. (60) suggest that individualised goal attainment scales may be essential to identify relevant functional changes. To identify relevant functional changes, it is of utmost importance that adequate measures to quantify functional outcome in all stages of recovery will be developed. Moreover, larger controlled studies are needed to compare the effectiveness of different and/or combined treatment approaches to reducing focal spasticity in stroke patients. In particular, adequate clinical trials are needed to compare the efficacy of BTX-A neuromuscular blockade versus phenol nerve blockade in upper limb spasticity. The application of neurolytic techniques (chemical or thermal) to some of the (predominantly) motor branches of the upper arm seems to be a promising area of further research. Special attention should be paid to comparisons of the (duration of) functional benefits, essential co-treatment and aftercare, the (duration and severity of) side-effects as well as cost-effectiveness. Another important issue for further research is the identification of prognostic factors in patients at risk of deterioration of arm–hand function by developing upper limb spasticity and the early institution of anti-spastic treatments before secondary complications have developed to optimise functional recovery.

REFERENCES

1. Lance JW. Symposium synopsis. In: Feldman RG, Young RR, Koella WP, editors. Spasticity: disordered motor control. Chicago: Yearbook Medical Publishers; 1980. p. 485–494.
2. Becher JG. Measurement of impaired muscle function in upper motor neuron syndromes: method and clinical application. PhD Thesis. Enschede: drukkerij PrintPartners Ipskamp BV, 2000.
3. Mayer NH. Clinicophysiologic concepts of spasticity and motor dysfunction in adults with upper motoneuron lesion. Muscle Nerve 1997; 20 (suppl 6): S1–S13.
4. Caldwell CB, Wilson DJ, Braun RM. Evaluation and treatment of the upper extremity in the hemiplegic stroke patient. Clin Orthop 1969; 63: 69–93.
5. Caldwell CB, Braun RM. Spasticity in the upper extremity. Clin Orthop 1974; 104: 80–91.
6. Katz RT. Management of spasticity. Am J Phys Med Rehabil 1988; 67: 108–116.
7. Glenn MB, Elovic E. Chemical denervation for the treatment of hypertonia and related motor disorders: phenol and Botulinum toxin. J Head Trauma Rehabil 1997; 12: 40–62.
8. Keenan MA. Management of the spastic upper extremity in the neurologically impaired adult. Clin Orthop 1988; 233: 116–125.
9. Skeil DA, Barnes MP. The local treatment of spasticity. Clin Rehabil 1994; 8: 240–246.
10. Gracies JM, Elovic E, McGuire J, Simpson DM. Traditional pharmacological treatments for spasticity. Part I: Local treatments. Muscle Nerve 1997; 20 (suppl 6): S61–S91.
11. Chambers HG. The surgical treatment of spasticity. Muscle Nerve 1997; 20 (suppl 6): S121–S128.
12. Fève A, Decq Ph, Filipetti P, Kéravel Y. Traitement de la spasticité par injections de toxine botulique. Revue de la litérature. Neurochirurgie 1998; 44: 192–196.
13. Braun RM, Botte MJ. Treatment of shoulder deformity in acquired spasticity. Clin Orthop 1999; 368: 54–65.
14. Khalili AA, Betts HB. Peripheral nerve block with phenol in the management of spasticity. Indications and complications. JAMA 1967; 200: 1155–1157.
15. Nathan PW, Sears TA. Effects of phenol on nervous conduction. J Physiol 1960; 150: 565–580.

16. Brattström M, Moritz U, Svantesson G. Electromyographic studies of peripheral nerve block with phenol. Scand J Rehabil Med 1970; 2: 17–22.
17. Fusfeld RD. Electromyographic findings after phenol block. Arch Phys Med Rehabil 1968; 49: 217–220.
18. Mooney V, Frykman G, McLamb J. Current status of intraneural phenol injections. Clin Orthop 1969; 63: 122–131.
19. Fischer E, Cress RH, Haines G, Panin N, Paul BJ. Evoked nerve conduction after nerve block by chemical means. Am J Phys Med 1970; 49: 333–347.
20. Felsenthal G. Pharmacology of phenol in peripheral nerve blocks: a review. Arch Phys Med Rehabil 1974; 55: 13–16.
21. Wood KM. The use of phenol as a neurolytic agent: a review. Pain 1978; 5: 205–229.
22. Halpern D. Histologic studies in animals after intramuscular neurolysis with phenol. Arch Phys Med Rehabil 1977; 58: 438–443.
23. Bodine Fowler SC, Allsing S, Botte MJ. Time course of muscle atrophy and recovery following a phenol induced nerve block. Muscle Nerve 1996; 19: 497–504.
24. Khalili AA, Harmel MH, Forster S, Benton JG. Management of spasticity by selective peripheral nerve block with dilute phenol solutions in clinical rehabilitation. Arch Phys Med Rehabil 1964; 45: 513–519.
25. Halpern D, Meelhuysen FE. Phenol motor point block in the management of muscular hypertonia. Arch Phys Med Rehabil 1966; 47: 659–664.
26. Halpern D, Meelhuysen FE. Duration of relaxation after intramuscular neurolysis with phenol. JAMA 1967; 200: 1152–1154.
27. Khalili AA, Benton JG. A physiologic approach to the evaluation and the management of spasticity with procaine and phenol nerve block: including a review of the physiology of the stretch reflex. Clin Orthop 1966; 47: 97–104.
28. Katz J, Knott LK, Feldman DJ. Brachial plexus infiltration with dilute phenol solution in the management of upper extremity spasticity. Anesthesiology 1966; 27: 87–88.
29. Katz J, Knott LW, Feldman DJ. Peripheral nerve injections with phenol in the management of spastic patients. Arch Phys Med Rehabil 1967; 48: 97–99.
30. Rozin R, Magora F, Robin GC, Magora A. Treatment of spasticity by phenol block. Isr J Med Sci 1970; 6: 555–560.
31. Copp EP, Keenan J. Phenol nerve and motor point block in spasticity. Rheumatol Phys Med 1972; 11: 287–292.
32. Braun RM, Hoffer MM, Mooney V, McKeever J, Roper B. Phenol nerve block in the treatment of acquired spastic hemiplegia in the upper limb. J Bone Joint Surg 1973; 55(A): 580–585.
33. Garland DE, Lucie RS, Waters RL. Current uses of open phenol nerve block for adult acquired spasticity. Clin Orthop 1982; 165: 217–222.
34. Garland DE, Lilling M, Keenan MA. Percutaneous phenol blocks to motor points of spastic forearm muscles in head injured adults. Arch Phys Med Rehabil 1984; 65: 243–245.
35. Keenan MA, Todderud EP, Henderson R, Botte M. Management of intrinsic spasticity in the hand with phenol injection or neurectomy of the motor branch of the ulnar nerve. J Hand Surg Am 1987; 12: 734–739.
36. Meals RA. Denervation for the treatment of acquired spasticity of the brachioradialis. Arch Phys Med Rehabil 1988; 70(A): 1081–1084.
37. Chironna RL, Hecht JS. Subscapularis motor point block for the painful hemiplegic shoulder. Arch Phys Med Rehabil 1990; 71: 428–429.
38. Herz DA, Looman JE, Tiberio A, Ketterling K, Kreitsch RK, Colwill JC, Grin OD Jr. The management of paralytic spasticity. Neurosurg 1990; 26: 300–306.
39. Keenan MA, Tomas ES, Stone L, Gersten LM. Percutaneous phenol block of the musculocutaneous nerve to control elbow flexor spasticity. J Hand Surg Am 1990; 15: 340–346.
40. Beckerman H, Lankhorst GJ, Verbeek ALM, Becher J. The effects of phenol nerve and muscle blocks in treating spasticity: review of the literature. Crit Rev Phys Rehab Med 1996; 8: 111–124.
41. Das TK, Park DM. Effect of treatment with Botulinum toxin on spasticity. Postgrad Med J 1989; 65: 208–210.
42. Das TK, Park DM. Botulinum toxin in treating spasticity. Br J Clin Practice 1989; 43: 410–403.
43. Snow BJ, Tsui JKC, Bhatt MH, Varelas M, Hashimoto SA, Calne DB. Treatment of spasticity with Botulinum toxin: a double-blind study. Ann Neurol 1990; 28: 512–515.
44. Memin B, Pollak P, Hommel M, Perret J. Traitement de la spasticité par la toxine botulique. Rev Neurol 1992; 148: 212–214.
45. Konstanzer A, Ceballos-Baumann AO, Dressnandt J, Conrad B. Lokale Injektionsbehandlun g mit Botulinum-Toxin A bei schwerer Arm- und Beinspastik. Nervenarzt 1993; 64: 517–523.
46. Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. Neurology 1995; 45: 712–717.
47. Pullman SL, Greene P, Fahn S, Pedersen SF. Approach to the treatment of limb disorders with Botulinum toxin A. Experience with 187 patients. Arch Neurol 1996; 53: 617–624.
48. Girlanda P, Quartarone A, Sinicropi S, Nicolosi C, Roberto ML, Picciolo G, Macaione V, Battaglia F, Ruggeri M, Messina C. Botulinum toxin in upper limb spasticity: study of reciprocal inhibition between forearm muscles. Neuroreport 1997; 8: 3039–3044.
49. Watanabe Y, Bakheit AM, McLellan DL. A study of the effectiveness of Botulinum toxin type A in the management of muscle spasticity. Disabil Rehabil 1998; 20; 62–65.
50. Chalmers TC, Smith H, Blackburn B, Silverman B, Schroeder B, Rietman D, Ambroz A. A method for assessing the quality of a randomised controlled trial. Control Clin Trials 1981; 2: 31–49.
51. Skilbeck CE, Wade DT, Langton Hewer R, Wood VA. Recovery after stroke. J Neurol Neurosurg Psychiatry 1983; 46: 5–8.
52. Langton Hewer RL. Rehabilitation after stroke. Q J Med 1990; 76: 659–674.
53. O'Brien CF. Injection techniques for Botulinum toxin using electromyography and electrical stimulation. Eur J Neurol 1997; 4 (suppl 2): S47–S50.
54. O'Brien CF. Injection techniques for Botulinum toxin using electromyography and electrical stimulation. Muscle Nerve 1997; 20 (suppl 6): S176–S180.
55. Shaari CM, Sanders I. Quantifying how location and dose of Botulinum toxin injections affect muscle paralysis. Muscle Nerve 1993; 16: 964–969.
56. Pierson SH. Outcome measures in spasticity management. Muscle Nerve 1997; 20 (suppl 6): S36–S60.
57. Simpson DM, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM, et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomised, double blind, placebo-controlled trial. Neurology 1996; 46: 1306–1310.
58. Bakheit AMO, Thilmann AF, Ward AB, Poewe W, Wissel J, Muller J, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of Botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke 2000; 31: 2402–2406.
59. Smith SJ, Ellis E, White S, Moore AP. A double-blind placebo-controlled study of Botulinum toxin in upper limb spasticity after stroke or head injury. Clin Rehabil 2000; 14: 5–13.
60. Hesse S, Reiter F, Konrad M, Jahnke MT. Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial. Clin Rehabil 1998; 12: 381–388.
61. Lagalla G, Danni M, Reiter F, Ceravolo MG, Provinciali L. Post-stroke spasticity management with repeated Botulinum toxin injections in the upper limb. Am J Phys Med Rehabil 2000; 79: 377–384.
62. Reiter F, Danni M, Ceravolo MG, Provinciali L. Disability changes after treatment of upper limb spasticity with Botulinum toxin. J Neurol Rehab 1996; 10: 47–52.
63. Bhakta BB, Cozens JA, Bamford JM, Chamberlain MA. Use of Botulinum toxin in stroke patients with severe upper limb spasticity. J Neurol Neurosurg Psychiatry 1996; 61: 30–35.
64. Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. Am J Phys Med Rehabil 2000; 79: 44–47.
65. Sampaio C, Ferreira JJ, Pinto AA, Crespo M, Ferro JM, Castro-Caldas A. Botulinum toxin type A for the treatment of arm and hand spasticity in stroke patients. Clin Rehabil 1997; 11: 3–7.

66. Pierson SH, Katz DI, Tarsy D. Botulinum toxin A in the treatment of spasticity: functional implications and patient selection. Arch Phys Med Rehabil 1996; 77: 717–721.
67. Kong KH, Chua KSG. Neurolysis of the musclocutaneous nerve with alcohol to treat poststroke elbow flexor spasticity. Arch Phys Med Rehabil 1999; 80: 1234–1236.
68. Hecht JS. Subscapular nerve block in the painful hemiplegic shoulder. Arch Phys Med Rehabil 1992; 73: 1036–1039.
69. Brin MF. Dosing, administration, and treatment algorithm for use of Botulinum toxin A for adult-onset spasticity. Muscle Nerve 1997; 20 (suppl 6): S208–S220.
70. Tardieu G, Tardieu C, Hariga J, Gagnard L. Treatment of spasticity by injection of dilute alcohol at the motor point or by the epidural route. Clinical extension of an experiment on the decerebrate cat. Dev Med Child Neurol 1968; 10: 555–568.
71. Tardieu G, Tardieu C, Hariga J. Selective partial denervation by alcohol injections and their results in spasticity. Reconstr Surg Traumatol 1972; 13: 13–86.
72. Cockin J, Hamilton EA, Nichols PJR, Price DA. Preliminary report on the treatment of spasticity with 45% Ethyl alcohol injections into the muscles. Br J Clin Practice 1971; 25: 73–75.
73. Pelissier J, Viel E, Enjalbert M, Kotzki N, Eledjam JJ. Neurolyse chimique a l'alcool dans le traitement de la spasticité chez l'hemiplegique. Cah Anesthiol 1993; 41: 139–143.