EUR J PHYS REHABIL MED 2010;46:11-8

Botulinum toxin type A *versus* phenol. A clinical and neurophysiological study in the treatment of ankle clonus

M. MANCA [1], A. MERLO [2], G. FERRARESI [1], S. CAVAZZA [1], P. MARCHI [1]

[1]*Movement Analysis Lab, Rehabilitation Medicine Unit University Hospital of Ferrara, Ferrara, Italy*
[2]*Movement Analysis Lab, Rehabilitation Department Reggio Emilia Local Health Unit Correggio, Reggio Emilia, Italy*

Aim. **To reduce ankle clonus in patients with spastic paresis either phenol nerve block of the tibialis posterior nerve or botulinum toxin type A (BTA) injection in triceps surae muscles can be used. This study aims to compare the efficacy over time of phenol nerve block and BTA injection in the inhibition of ankle clonus.**
Methods. **Twenty-two patients with spastic paresis presenting with ankle clonus were randomly treated with phenol nerve block of the tibialis posterior nerve or BTA injection in triceps surae muscles. Ankle passive dorsiflexion, clonus, M and H responses and H/M ratio were measured in all patients prior to treatment and 15 days afterwards, as well as one, three and six months later in 12 patients. Patient satisfaction was also recorded.**
Results. **Both patient groups showed significant clonus reduction over time with the effect of phenol being greater than that of BTA. In one month, the degree of passive dorsiflexion significantly increased in both groups without any significant difference between them. H/M ratio reduced after phenol treatment and remained almost constant during the following six months, whereas it remained at baseline level after BTA treatment.**
Conclusion. **While both treatments led to reduction in ankle clonus, phenol showed greater clinical efficacy. The difference in the neurophysiological results suggests that the two drugs have different action mechanisms with a more prevalent reduction of alpha motoneuron excitability in phenol-treated patients.**

KEY WORDS: Ankle clonus - Botulinum Toxins - Nerve block - H-Reflex.

Received on June 11, 2009.
Accepted for publication on January 17, 2010.
Epub ahead of print on February 18, 2010.

Corresponding author: M. Manca, MD, Movement Analysis Lab, Rehabilitation Medicine Unit, University Hospital of Ferrara, via della Fiera, 44100 Ferrara, Italy. E-mail m.manca@ospfe.it

The efficacy of phenol block and BTA injection in the focal treatment of spasticity is well described [1-4]. Both drugs are used for the same purpose but with different modalities of administration due to their different mechanisms of action.

Phenol, which produces an immediate conduction block of peripheral nerves causing relaxation of the muscles involved, must be administered as close as possible to the nerve trunk due to its limited diffusion. BTA, which produces a block in neuromuscular transmission seven to ten days later, is administered by intramuscular injection. The effect of both treatments lasts for several months. The increased cost of BTA is offset by its ease of administration and reduced incidence of complications when compared to phenol.

As both drugs have a similar therapeutic effect but achieve it through different action mechanisms, it would be useful to carry out a comparative study on their efficacy.

In his review of the literature from 1966 to 2003, Cormack [5] found only three papers that compared the efficacy of BTA *versus* phenol. Kirazli *et al.*[6] studied the efficacy of BTA *versus* phenol in the treatment of equinovarus in a group of hemiplegic patients after stroke by means of a clinical evaluation of the impair-

TABLE I.—*Characteristics of study groups. For both groups, patients 1 to 6 were assessed at T0, T1, T2, T3 and T4; patients 7 to 11 where assessed at T0, T1. See text for details about drug injection and dose selection.*

Drug	Subj.	Sex	Age	Months since lesion	Etiology	Clonus	Dosage
PHEN	1	M	53	9	Stroke	4	4.5
	2	M	59	7	Myelopathy	3	5.0
	3	F	62	24	Stroke	3	5.5
	4	M	55	9	Stroke	4	8.0
	5	M	69	16	Stroke	3	7.0
	6	F	34	9	TBI	4	7.5
	7	M	67	21	Stroke	2	4.5
	8	M	78	4	Stroke	3	6.0
	9	M	47	4	Stroke	3	7.0
	10	M	25	12	Myelopathy	4	7.0
	11	M	69	18	Stroke	3	5.0
BTA	1	M	36	16	Stroke	4	300
	2	F	57	21	Stroke	3	300
	3	M	49	12	Myelopathy	3	300
	4	F	62	4	Stroke	4	300
	5	M	78	4	Stroke	3	300
	6	F	52	4	Stroke	3	300
	7	M	41	10	Stroke	4	300
	8	M	69	36	Stroke	3	300
	9	M	54	9	Stroke	3	300
	10	M	17	96	Stroke	4	300
	11	M	39	6	Myelopathy	4	300

Dosages are expressed in ml for phenol (6% concentration) and in units for BTA (Botulinum toxin type A - Botox). TBI: traumatic brain injury.

ment. The authors found BTA to be more efficacious than phenol during the first four weeks following treatment, whereas at the three-month follow-up the effects of the two drugs were essentially the same. In a later electrophysiological study in 1999,[7] the authors hypothesized that phenol acted directly on the alpha motoneuron, whereas BTA acted prevalently on the fusal muscle fire system and consequently on the Ia afferents and the alpha motoneuron. No significant differences between the two drugs were seen with respect to the excitability responses of the monosynaptic reflex. In a review of the literature on treatment of upper limb spasticity, Van Kuijk *et al.*[8] noted that evidence to support the choice of either BTA or phenol was lacking and highlighted the need for evidence from clinical trials.

In a study on children with spastic diplegia due to cerebral palsy, Wong *et al.* compared the efficacy on gait of BTA injections *versus* phenol blocks [9] and reported a greater improvement in gait-related variables after BTA injections. However, unlike previous studies, different target muscles were selected for both groups and the phenol blocks were carried out on motor points.

Comparative studies on the use of different techniques and their therapeutic outcome are subject to bias such as: disability variations in the population examined; changes in muscle viscosity and elasticity in stabilised patients; methods of administration and dosage amounts.

In this study, based on clinical and neurophysiological parameters, the suppression of ankle clonus was selected as clinically significant outcome. Ankle clonus may impair several motor functions, as it limits or prevent ankle dorsiflexion. During gait, for example, it may alter both the foot prepositioning before foot contact and the leg progression over the stance foot. Consequently, both loading and progression ability are compromised. Ankle clonus, typically triggered by a lengthening of the triceps muscle, is a stretch-sensitive form of overactivity, thus being a natural target of focal treatments, as in this study.

The following aspects were investigated:
— efficacy of the two treatment modalities in the inhibition of clonus;
— action of the two drugs on the spinal reflex;
— efficacy at a six-month follow-up.

Materials and methods

Subjects analyzed in the study were both outpatients and inpatients referred to the Rehabilitation Unit of our hospital.

Inclusion criteria

Patients were selected based on the following criteria: spastic paresis of various origins; persistent ankle clonus evoked by passive sharp dorsiflexion of the ankle; spontaneous onset of clonus interfering with gait, posture or with wheelchair transfers in non-ambulant patients.

Exclusion criteria

Patients with the following criteria were excluded: presence of peripheral nerve lesion; structural ankle joint deformity; recent or ongoing systemic anti-spastic therapy; previous focal therapy in the calf muscle; other neuromuscular disorders.

Sample

The study included 22 patients, 18 males and four females with ages ranging from 17 to 78 years, affected by spastic paresis for over four months and presenting ankle clonus. Paresis was due to ischemic stroke (11 cases), hemorrhagic stroke (6), traumatic brain injury (1), ischemic or post-trauma degenerative myelopathy (4). Table I describes the patient sample in more detail.

All patients underwent a focal treatment to inhibit the ankle clonus. The selection of treatment between BTX and PHEN was based on:
— patient interviews to identify individual needs;
— evaluation of impairment signs as measured by ankle joint range and tendon reflex;
— observational and/or instrumental analysis of gait and posture.

Clonus affected transfer to/from or positioning in wheelchairs in three non-ambulant patients. Clonus interference on gait was evident at observational gait analysis for 7 of the 19 ambulant patients and was verified by electromyographic assessment in the remaining 12.

Following this assessment, the 22 candidates were randomized into two equal numbered groups using a permuted block design with a treatment allocation ratio of 1:1. One group of 11 patients, referred to as group A, received phenol blockage; the other group, referred to as group B, received BTA injection. All patients were evaluated prior to treatment (T0) and 15 days afterwards (T1). Six patients in each group were also evaluated at one (T2), three (T3) and six (T4) months following treatment. The flow of participants through the study is presented in Figure 1. This study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion.

Evaluation

Evaluation of the maximum passive dorsiflexion of the ankle joint was carried out using a universal hand goniometer in accordance with Clarkson and Gilewich [10]. Measurement was achieved by placing the fulcrum of the goniometer about 1.5 cm below the lateral malleolus with one arm placed laterally to the longitudinal axis of the fibula and the other arm parallel to the longitudinal axis of the fifth metatarsal bone.

With the patient supine, clonus was evoked manually by a rapid stretching of the sural triceps. To evaluate the response level and any possible changes following treatment, a five-point scale was used:[11] 0-no response; 1-jerking response; 2-exhaustible clonus; 3-inexhaustible clonus; 4-inexhaustible clonus triggered by a slow stretch.

Patient satisfaction of treatment was assessed by a three level scale (“less than you expected”, “what you expected”, “better than you expected”).

Recording of M and H reflex responses of the soleus muscle was based on the standard method recommended in literature.[12] With the patient in a prone position, the tibialis posterior nerve was stimulated at the popliteal fossa by a bipolar stimulator. Measurement was taken with the recording electrode on the surface of the soleus muscle and the reference electrode on the Achilles tendon. Rectangular stimuli lasting one millisecond at a frequency of 0.1 Hz were delivered. Stimulus intensity was gradually increased

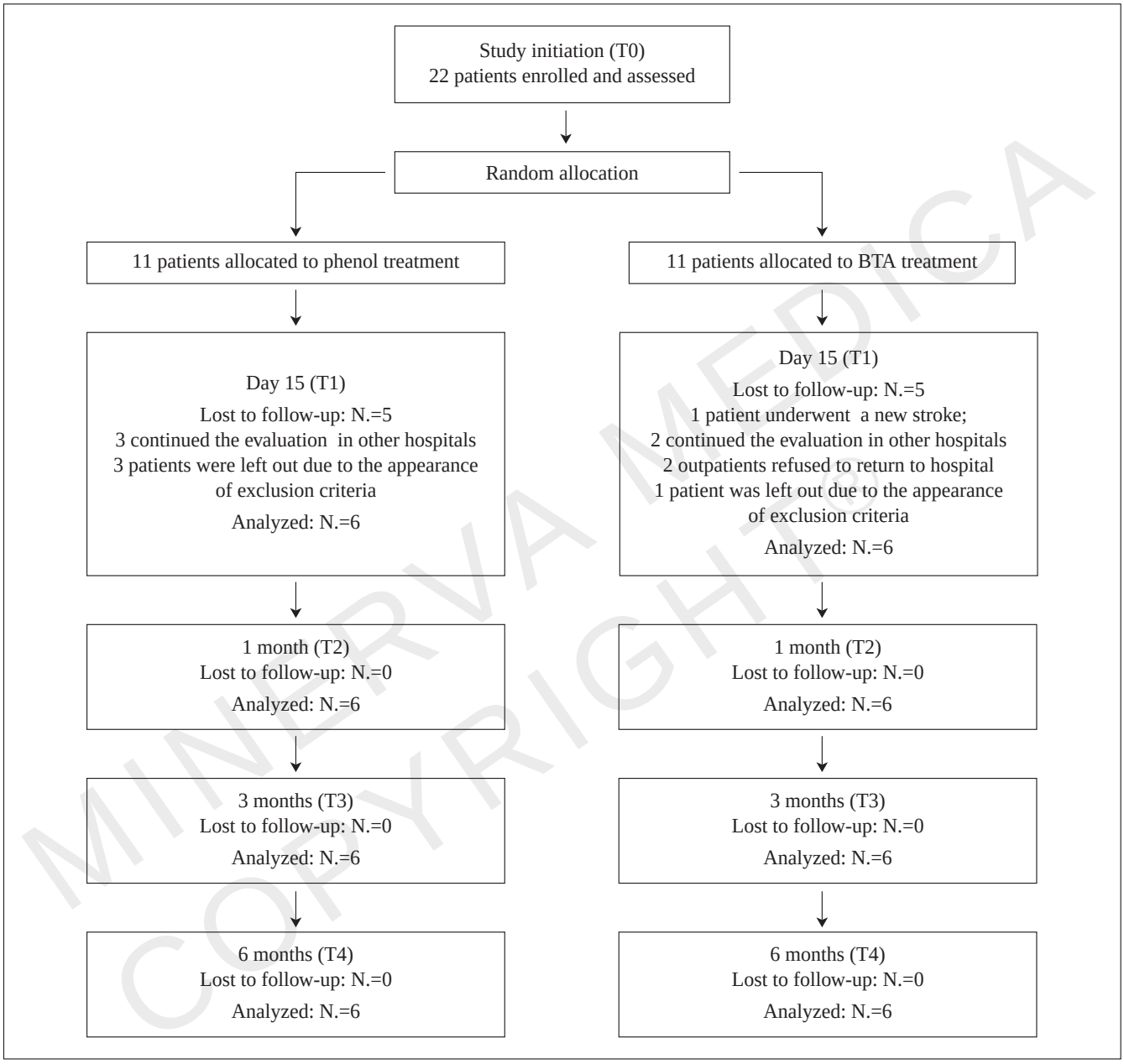

Figure 1.—Flow of participants through the study.

to achieve a maximum H response and then, with maximum stimulation, a maximum M response was acquired. The responses were recorded using an electromyograph (Multibasis OTE Biomedical, Milan, Italy) with a 20-5000 Hz band-pass filter. The peak-to-peak amplitude of the H and M responses and the H-max/M-max ratio were calculated and used for further analysis.

Both clinical and neurophysiological evaluations were carried out by the same operator (a medical

TABLE II.—*Median values and ranges (in brackets) of parameters evaluated prior to treatment (T0, N.=11 per group), 15 days afterwards (T1, N.=11 per group), after one month (T2, N.=6 per group), after three months (T3, N.=6 per group) and after six months (T4, N.=6 per group).*

	Experimental session				
	T0	T1	T2	T3	T4
Phenol					1 (0-3) *
Clonus	3 (2-4)	0 (0-1) * +	0 (0-1) * +	0 (0-2) *	10 (0-15)
Dorsiflexion	0 (0-20)	15 (5-25) *	10 (5-15) *	10 (5-15) *	0.3 (0.1-0.7) * +
H/M	0.7 (0.4-1.0)	0.4 (0.1-0.8) * +	0.2 (0.1-0.7) *	0.3 (0.1-0.8)	
					2 (0-3) *
BTA					10 (10-20) *
Clonus	3 (3-4)	2 (0-3) * +	1 (0-2) * +	1 (0-3) *	0.6 (0.5-1.0) +
Dorsiflexion	5 (-5-15)	10 (0-20) *	13 (10-20) *	10 (10-20) *	
H/M	0.6 (0.3-0.9)	0.6 (0.4-1.0) +	0.5 (0.4-0.9)	0.6 (0.3-0.8)	

Comparisons of the median values in time, with respect to T0, were carried out using the Wilcoxon test with significance set at 5%. The asterisk (*) indicates the presence of a significant difference.
Comparison between the median values of the two groups at each session was carried out using the Mann-Whitney U test with significance set at 5%. The plus sign (+) indicates a significant difference.

doctor), who was not blind to the randomization process.

Treatment

PHENOL BLOCK

After pinpointing the injection site of the tibialis posterior nerve in the popliteal fossa by percutaneous stimulation, (Neuroton 726 Siemens) phenol block was performed on the motor branch of the tibialis posterior nerve. A Teflon needle electrode was used to deliver the stimuli and inject the phenol. Once a motor response was obtained on the calf muscle with a stimulus intensity of 1 mA (rectangular stimuli, lasting 0.1 ms at a frequency of 1 Hz), phenol in a 6% aqueous solution was injected. During the treatment, each patient received phenol until the manual rapid stretching of triceps surae ceased to trigger clonus. In some cases, this approach led to the use of higher dosages as compared to literature.[1]

BOTULINUM TOXIN

The medial and lateral gastrocnemius and the soleus muscles were treated. In accordance with literature,[13] a total dosage of 300 units of BTA was injected. Each muscle (Gastrocnemius medialis, Gastrocnemius lateralis and Soleus) received 100 mouse units (Botox-Allergan) in a concentration of 50 U/mL of saline solution divided at two sites for muscle.

Statistical analysis

The effect over time of each pharmaceutical was assessed by the Wilcoxon test for paired measures. Comparison between the two groups at T0, T1, T2, T3 and T4 was carried out by the Mann Whitney U test. In both tests, significance was set at 5%.

Results

Randomization produced groups A and B, which were similar in terms of gender distribution (9 M, 2 F and 8 M, 3F, respectively), median age (59 and 52 years, respectively) and median time since lesion (9 and 10 months, respectively).

All treatment results are illustrated in Table II. Given the small number of patients in the two groups, median values and ranges are reported for each variable.

Clonus

Both patient groups had similar median scores at T0. At T1, scores had decreased from 3 to 0 ($P<0.01$) in patients treated with phenol and from 3 to 2 ($P<0.01$) in those treated with BTA. At T1, clonus of the BTA-treated group was greater than that of the phenol-treated group ($P=0.01$). In both patient groups, clonus showed significant reduction over time, the effect from phenol being greater than that from BTA (Table II) with a statistically significant difference at both T1

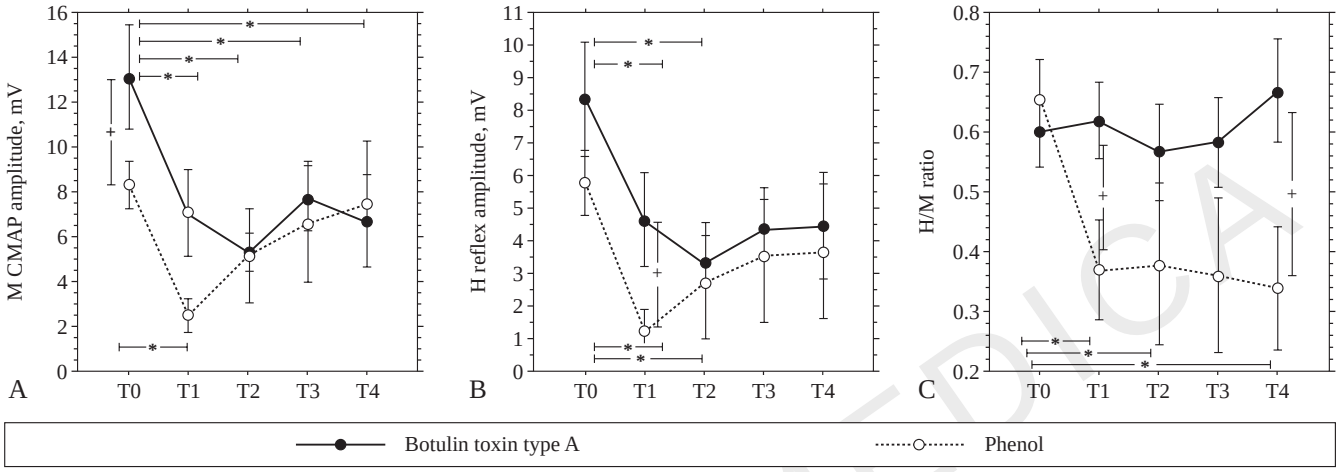

Figure 2.—Evolution over time of the different parameters analysed.

(P<0.01) and T2 (P<0.05). The median value of clonus scores remained lower for the phenol-treated group also at T3 and T4.

Passive ankle dorsiflexion

Both patient groups had similar median scores at T0. At T1 and T2, degree of dorsiflexion significantly increased in both groups with no significant differences between them. This increase tended to taper-off at T3 and T4 (Table II).

Perceived results

Eight patients treated with phenol and eight with BTA reported that the outcome of treatment met their expectations. According with the treatment target, function was improved. In walking patients gait was not destabilized by clonus during the stance period. In non-walking subjects clonus reduction permitted a better comfort in both sitting and supine postures, without the frequent disturbing shakes at rest. In the phenol-treated group, one patient reported that their results did not reach the expectations and, conversely, two patients reported that results exceeded their expectations. In the BTA-treated group, two patients reported that results did not reach their expectations and one that results exceeded expectations. Two phenol-treated patients reported symptoms which were typical side effects of the therapy, leg pain and tingling in the heel, respectively.

Neurophysiological evaluation

The evolution over time of the different parameters analyzed is shown in Figure 2.

At T0, there was a trend towards significance in the effect of intervention on the M-response with a higher median score in the BTA group (P=0.07). The M response in the phenol-treated group showed a statistically significant reduction only at T1, whereas in the BTA-treated group, the M response reduction was significant until T2.

The M response reduction, expressed as a percentage of the T0 value, was greater in the phenol-treated group (-70%) than in the BTA-treated group (57%).

The H reflex showed similar amplitudes at T0 and a statistically significant reduction until T2 in both groups. At T1, the reduction in median amplitudes was greater in the phenol-treated group.

The H/M ratio was similar between the two groups at T0. After treatment, it decreased over time and then remained constant in the phenol-treated group, while in the BTA-treated group it did not decrease and remained unchanged (Figure 2). Comparison between the two patient groups reached statistically significant differences at T1 (P<0.05), where median H/M was 0.4 for the phenol-treated group and 0.6 for the BTA-treated group. While differences in the H/M ratio were not statistically significant at T2 and T3 (P=0.26 and P=0.17, respectively), they became so again at T4 (P<0.05).

Discussion

The aim of the study was to verify the efficacy of two drugs, phenol and BTA, which are frequently used for in clinical practice in the focal treatment of spasticity.

Notwithstanding the small number of patients in the study sample, the six-month follow-up revealed new knowledge that can be added to the current literature on this topic.

Most patients and their relatives reported a significant benefit from both types of treatment. The two patients who presented phenol-related side effects reported relief from those symptoms at one and three weeks following treatment respectively. The rate of side effects we found is similar to data reported in literature [14] and did not seem to correlate with dosage amount. The risk for temporary side effects should be considered before selecting the treatment.

Relief from clonus was present in both patient groups after focal treatment. In the phenol-treated group, greater relief was observed at T1 with a statistically significant duration of effect until T4. In the BTA-treated group, there was less initial clonus relief. This discrepancy may be due to the modality of phenol treatment, which allows for immediate adjustment of dosage until clonus is completely eliminated. Throughout all the sessions, the median value of the clonus score was lower in the phenol group than in the BTA group, without statistical significance, even though the power of the statistical test in discriminating differences between groups is low when the sample size is limited. This result may appear to be in conflict with that of Kirazli,[6] who observed greater reduction in the Ashworth Score (tested for ankle dorsiflexion) in patients treated with BTA. In the present study, we investigated variations in clonus and did not measure degree of spasticity as assessed by the Ashworth Scale, because of the limited validity and reliability of this scale.[15, 16] Thus, a direct comparison between the results of the two studies is difficult. Furthermore, the very high Ashworth scores seen in Kirazli's sample may be less reliable than clonus for measuring spasticity due to the probable presence of muscle contracture.[17]

Passive ankle dorsiflexion significantly increased in both groups after treatment and reached a median of 10° until the end of study. This result may be related to both a reduction in active reflex stiffness due to the direct effect of the drugs on muscle hyperactivity and a reduction in passive calf muscle stiffness due to greater overall joint mobility after treatment.[18-20]

Both pharmaceuticals caused a reduction in the M-response amplitude, lowest for phenol at T1 and for BTA at T2, in line with the observed clonus reduction. A comparison of the absolute M-values between the two groups was not performed due to the differences at T0.

Comparison between the two groups at T1 showed greater efficacy of the phenol in reducing the H-wave amplitude. This difference was maintained over time although no significant difference was found when observing the follow-up group (N.=6 per group) as compared to the whole study sample at T1 (N.=11 per group). Similarly to results for the M-wave amplitude, the effect of BTA was seen to have stabilized as early as T1, whereas the phenol treatment stabilized at T2 with a reduction in efficacy compared to the evaluation at T1. The partial increase in the H-response amplitude after T1 could be explained by temporary damage to the deeper axons caused by phenol spreading to the inner nerve trunk in relation to the concentration gradient. The greater efficacy shown by phenol may be explained by its action mechanism and the administration method used, where the phenol dose was determined by the disappearance of symptoms which, in some patients, led to a complete and permanent elimination of the H-response.

The H/M ratio quantified the excitability of the alpha motoneuron. The difference in the effect over time of the two pharmaceuticals on the ratio is the most interesting result of this study from a neurophysiological point of view. Phenol causes a major reduction in the H/M ratio up to T4 with significant differences between the two groups at T1 and T4.

The lack of a significant difference in the H/M ratio in BTA-treated patients is in agreement with existing literature.[7, 21, 22] Some authors attribute this result to BTA not acting specifically on intrafusal fibres, an hypothesis that has been supported by other evidence emerging from animal experiments.[23, 24] The decrease in the H/M ratio in the phenol-treated patients may be consistent with the prevalent destroying action of phenol on the afferent limb of the H-reflex, prior to its synapse with the alpha motoneuron. Consequently, an Ia fibre-mediated influence on alpha motoneuron excitability can be supposed. BTA only affects the neuromuscular junction of the end-target muscle, thus it would not be expected to reduce the H response as much. Our findings are not entirely in agreement with

the study by On *et al.*,[7] in which no significant changes were observed in the H/M ratio after both types of treatments. This discrepancy could be accounted for by either the greater concentration (6% *vs.* 5%) or the higher dosage of phenol (range 4.5-8 cc), or both, used in the present study. This could be investigated by further studies.

Limitations of the study

The main limitation of the study is the reduced number of patients in the follow-up groups, which will lead to a reduced power of the statistical test in discriminating differences between groups. Based on our data, with N.=11 and N.=6 patients per group, the Wilcoxon test failed to reject the null hypothesis of no difference between groups when $\Delta ROM<6°$ and $\Delta ROM<8°$ for ankle dorsiflexion and when $\Delta H/M<0.3$ and $\Delta H/M<0.4$ for the H/M ratio.

Another limit is that the operator was not blind to the treatment received by patients, thus introducing the risk of bias in results. However, both clonus presence and, particularly, electrophysiological assessments are unlikely to be affected by subjective interpretation.

Conclusions

Phenol doses used in the present study were higher than any described in existing literature and led to a greater efficacy of phenol, compared to BTX, on clonus inhibition and on H/M ratio reduction in the first month after treatment, with a rate of temporary side effects similar to that previously reported. The patient-reported outcome was satisfactory for both BTA and phenol, with similar changes in maximum passive ankle dorsiflexion.

High doses of phenol are a suitable treatment for ankle clonus when the risk for temporary side effect can be managed.

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