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ORIGINAL ARTICLE

Nabiximols and botulinum toxin injections for patients with multiple sclerosis: efficacy on spasticity and spasms in a single-centre experience

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Abstract

Background Spasticity is a common and disabling symptom in patients with multiple sclerosis (PwMS): as highlighted by many epidemiological studies, it is often a severe and not well treated. Despite the availability of evidence-based spasticity management guidelines, there is still great variability in everyday therapeutic approach, especially for the most complex cases.

Methods In our single-centre study, we retrospectively evaluated PwMS-treated nabiximols and botulinum toxin injections (BTI) from July 2015 to April 2019. Clinical and demographic data were collected. The severity of spasticity and spasms was recorded by modified Ashworth Scale (mAS) and Penn Spasm Frequency Scale (PSFS) at baseline and after 1 month of treatment.

Results We evaluated 64 treatments for MS-related spasticity: 28 patients were treated with BTI and 36 patients with nabiximols. We found that both BTI and nabiximols are effective in reducing mAS (nabiximols, BTI: $p < 0.001$), PSFS frequency (nabiximols: $p = 0.001$, BTI: $p = 0.008$) and intensity (nabiximols: $p = 0.001$, BTI $p = 0.016$). No differences were found when directly comparing the efficacy of the two treatments, except for a statistical trend favouring BTI on spasms intensity ($p = 0.091$). Eleven patients were treated with both BTI and nabiximols, and only four patients continued both treatments. All dropouts were due to inefficacy of at least one of the two therapies.

Conclusions Our single-centre experience highlights that both BTI and nabiximols are effective in treating multiple sclerosis-related spasticity; however, BTI treatment may be more effective on spasms intensity. Combined nabiximols and BTI treatment could represent a therapeutic option for severe spasticity.

Keywords Multiple sclerosis · Spasticity · Spasms · Nabiximols · Botulinum toxin

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that affects more than 2 million people worldwide, and it represents a major cause of nontraumatic neurological disability in young adults [1]. Spasticity has been defined as 'involuntary muscle hyperactivity in the presence of central paresis.' Muscle hyperactivity includes different phenomena such as spasticity *sensu strictu*, dystonia, rigidity and spasms. Patients with spasticity may develop unpleasant complications such as chronic pain and contractures [2].

Spasticity is a common condition in patients with Multiple Sclerosis (PwMS): in a Spanish survey, 65.7% of interviewed PwMS reported spasticity, and 40% of them rated their

Highlights
- BTI and nabiximols are both effective in treating MS spasticity.
- BTI may be more effective in reducing spasms intensity.
- Nabiximols and BTI may be safely combined in patients with severe spasticity.

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symptoms as moderate or severe. Patient with Relapsing-Remitting Multiple Sclerosis (RRMS) were more frequently affected by spasticity, whereas the patients reporting more severe symptoms were predominantly patients with Progressive Multiple Sclerosis (PMS) [3]. MS-related spasticity has a great impact on Quality of Life (QoL), as demonstrated in the cross-sectional burden of disease German study MOVE-12, which found that patients with severe spasticity had a greater impairment in both QoL and activity of daily life (ADL) scales in comparison with patients with mild spasticity [4]. The degree of spasticity has also been strongly related to reduced quality-adjusted life years (QALY) and higher direct nonmedical costs [5]. The multicentre Spanish epidemiological study CANDLE [6] confirmed the significant impact of spasticity on QoL, in particular on physical and general health scores on the SF-12 QoL questionnaire, and highlighted the difference in the rating of spasticity between patients' self-reported NRS spasticity scale and physician-reported modified Ashworth Scale (mAS). In the CANDLE study, more than 70% of patients complained moderate or severe spasticity, despite being treated with first- or second-line therapies. Taken together, those data show that the burden of spasticity is a relevant issue in PwMS: spasticity is a major contributor to the reduction in QoL, and it often represents a severe and not well-treated symptom.

A recent consensus paper has been proposed in order to achieve an evidence-based therapeutic management of spasticity in PwMS [7], and the authors provided a treatment algorithm based on the severity and on type of spasticity, focal or generalized. Those guidelines represent an update to the previous ones proposed in Spain and Germany (as reviewed in [8]). Generalized spasticity should be initially treated with oral antispastic agents [9] (such as baclofen, gabapentin, tizanidine as first choice, diazepam and dantrolene as a second choice). Nabiximols [10], a THC-CBD-based oral spray, is suggested as an add-on treatment in case of failure of first line oral therapies. Selected cases of unresponsive patients may be screened with an intrathecal baclofen test to evaluate the possible efficacy of intrathecal baclofen pump implant [11, 12]. In focal spasticity of lower limbs, treatment with botulinum toxin injection (BTI), associated with physical therapy, is recommended [13–15]. Otero-Romero and colleagues, besides providing a practical therapeutic algorithm, raised concern about the methodological issues that affect most of the evidences provided in literature: many studies have a small sample size, short follow-up duration and a marked heterogeneity in patients. Spasticity and its burden are also difficult to quantify and to define: patients' reported symptoms and their severity often do not correspond to the objective neurological assessment. Overall, the methodological quality of those studies is poor, and there is a great discrepancy between published evidence and everyday clinical practice in MS centres.

In order to evaluate efficacy and tolerability of spasticity management in a real-life setting, we conducted a single-centre retrospective study considering treatments with nabiximols, BTI or both in PwMS.

Materials and methods

In our retrospective single-centre study, we reviewed the medical records of PwMS of our MS centre (Neurology Unit, University of Trieste), treated with BTI (onabotulinum toxin-A ONA, Botox® or incobotulinum toxin A INCO, Xeomin®) and/or nabiximols, from July 2015 to July 2019. The aim of our study was to evaluate the clinical characteristics of the treated patients, tolerability and efficacy of treatments on spasticity and spasms.

We collected the following clinical and demographic data: (1) gender, (2) age, (3) disease duration, (4) expanded disability status scale (EDSS), (5) disease course, (6) type of spasticity, (7) concomitant symptomatic treatment for spasticity and concomitant disease-modifying drugs (DMDs).

Modified Ashworth Scale (mAS) and Penn Spasm Frequency Scale (PSFS) were used, at baseline and 1 month after the beginning of treatment, in order to evaluate the severity of spasticity and spasms, respectively. We recorded the dose of BTI, expressed in Units (U) and the dose of nabiximols, expressed in number of puffs per day.

Patients who dropped out from treatment were categorized according to inefficacy of treatment, side effects or both.

To evaluate the efficacy of each treatment (BTI, nabiximols), we compared baseline and follow-up scores (mAS, PSFS) within each treatment group. In order to compare the two treatments, we compared *delta* mAS and PSFS, defined as the difference between follow-up and baseline values of mAS and PSFS scores, between the two treatment groups.

We collected clinical and demographic data of patients treated with both BTI and nabiximols. Patients were categorized according to the first treatment received (BTI or nabiximols).

Statistical analysis was performed with IBM SPSS 24.0.

Variables were presented as median and range or mean and standard deviation according to their distribution. Shapiro–Wilk test was used to verify the normal distribution of the variables. Wilcoxon signed rank test was used for the comparison within each group. Mann–Whitney U test and Pearson's chi-squared were used for the comparison of the variables between groups, as appropriate. Statistical significance was assumed at p value < 0.05.

Results

Sixty-four treatments for MS-related spasticity were performed: 28 patients were treated with BTI, 36 patients with nabiximols and 11 patients with both therapies.

Clinical and demographical data are summarized in Table 1: no differences in gender, age, EDSS, disease duration and course, type of spasticity, concomitant treatments and DMDs were found between the two groups.

Median mAS score at baseline was 3 (range 1–4) in patients who received BTI and 2 (range 0–4) in those who received nabiximols. Median PSFS frequency was, respectively, 1 (0–4) and 2 (0–3), while median PSFS intensity was, respectively, 1 (0–4) and 2 (0–3). No significant differences were found between the two groups (Table 2). Dropout rates for side effects (12.5% in BTI groups and 25% in nabiximols group), lack of efficacy (87.5% and 57.3%, respectively) or both (12.5% and 25%, respectively) were similar in the two groups (Table 1).

We compared mAS, PSFS intensity and PSFS frequency at baseline and after 1 month of treatment within the two groups of treated patients, and we found that both BTI and nabiximols significantly reduced mAS, PSFS intensity and frequency scores at follow-up (Table 3).

Table 1 Clinical and demographic data

Patients' characteristics	BTI (n = 28)	Nabiximols (n = 36)	p
Gender n (%)			
Male	15 (53.6%)	18 (50%)	0.780[a]
Female	13 (46.4%)	18 (50%)	
Age, mean ± SD	52.8 ± 10.3	53.9 ± 8.7	0.644[b]
Disease duration (months), median (range)	187.5 (56–470)	178 (8–447)	0.823[c]
EDSS, median (range)	7 (2–8)	6.75 (2.5–9)	0.786[c]
Disease form n (%)			0.890[a]
Relapsing remitting	8 (28.6%)	9 (25%)	
Secondary progressive	15 (53.6%)	19 (52.8%)	
Primary progressive	5 (17.9%)	8 (22.2%)	
Type of spasticity n (%)			0.438[a]
Focal	5 (17.9%)	2 (5.6%)	
Upper limbs	1 (3.6%)	2 (5.6%)	
Paraspasticity	16 (57.1)	25 (69.4%)	
Tetraspasticity	6 (21.4%)	7 (19.4%)	
Previous/concomitant symptomatic treatments n (%)			
Baclofen	18 (64.3%)	30 (83.3%)	0.081[a]
Benzodiazepines	7 (25%)	14 (38.9%)	0.240[a]
Concomitant disease modifying treatment n (%)	7 (25%)	11 (30.6%)	0.624[a]
Line of treatment n (%)			0.875[a]
First line	5 (71.4%)	7 (63.6%)	
Second line	1 (14.3%)	3 (27.3%)	
Other	1 (14.3%)	1 (9.1%)	
Botulinum toxin type			
Botox® n (%)	10 (35.7%)		na
Dose, median (range)	100 (50–300)		na
Xeomin® n (%)	18 (64.3%)		na
Dose, median (range)	62.5 (20–300)		na
Nabiximols sprays, median (range)		6 (3–11)	na
Dropout n (%)	8 (28.6%)	12 (33.3%)	0.683[d]
Lack of efficacy	7 (87.5%)	7 (58.3%)	
Side effects	1 (12.5%)	3 (25.0%)	
Lack of efficacy and side effects	0 (0%)	2 (16.7%)	

[a] Pearson's chi-square

[b] Independent samples t test

[c] Mann–Whitney U test

[d] Fisher's exact test

BTI, botulinum toxin injections; *SD*, standard deviation; *EDSS*, expanded disability status scale

Table 2 Pretreatment mAS and PSFS scores

	BTI (n = 28)	Nabiximols (n = 36)	p[a]
mAS	3 (1–4)	2 (0–4)	0.334
PSFS (frequency)	1 (0–4)	2 (0–3)	0.965
PSFS (intensity)	1 (0–4)	2 (0–3)	0.466

[a] Wilcoxon signed rank test

BTI, botulinum toxin injections; *mAS*, modified Ashworth Scale; *PSFS*, Penn Spasm Frequency Scale

We compared *delta* mAS, PSFS intensity and frequency between the two groups, in order to evaluate the efficacy of the two treatments. *delta* mAS was −0.75 (range –2 to 0) in those who were treated with BTI and 0 (–1 to 0) in those who received nabiximols. *delta* PSFS frequency was 0 (–3 to 0) and 0 (–2 to 0), *delta* PSFS intensity was 0 (–3 to 0) and 0 (–2 to 0), respectively. No significant differences were found (Table 4); however, a trend towards a greater reduction of PSFS intensity was noted in patients treated with BTI (p value 0.091).

Eleven patients (five females, six males) were treated with both BTI and nabiximols. Mean age was 54.2 years (SD 8.5 years), with median disease duration of 183 months (range 120–447). Median EDSS was 7 (range 5–8). Six patients (54.5%) had an SP disease course and two (18.2%) a PP form. Eight (72.7%) had a paraspasticity, one patient a tetraspasticity while only two patients presented a focal spasticity. All patients were previously treated with a first line oral treatment (81.8% baclofen, 36.4% benzodiazepines). Four patients received a concomitant DMD (two first line, one second line, one other).

Three patients were treated with BTI before nabiximols, while eight patients received nabiximols before BTI. Demographic and clinical characteristics were similar in the two groups (Supplementary Tables 5 and 6).

Table 3 Pretreatment and posttreatment mAS and PSFS scores

	Pre-treatment scores	Post-treatment scores	p[a]
Nabiximols (n = 36)			
mAS	2 (0–4)	2 (0–4)	<0.001
PSFS (frequency)	2 (0–3)	0 (0–3)	0.001
PSFS (intensity)	2 (0–3)	0 (0–3)	0.001
BTI (n = 28)			
mAS	3 (1–4)	2 (1–4)	<0.001
PSFS (frequency)	1 (0–4)	0 (0–3)	0.008
PSFS (intensity)	1 (0–4)	0 (0–2)	0.016

Expressed as median (range)

[a] Wilcoxon signed rank test

BTI, botulinum toxin injections; *mAS*, modified Ashworth Scale; *PSFS*, Penn Spasm Frequency Scale

Table 4 Comparison of BTI and nabiximols efficacy on mAS and PSFS

	BTI (n = 28)	Nabiximols (n = 36)	p[a]
mAS	−0.75 (−2 to 0)	0 (−1 to 0)	0.545
PSFS (frequency)	0 (−3 to 0)	0 (−2 to 0)	0.352
PSFS (intensity)	0 (−3 to 0)	0 (−2 to 0)	0.091

[a] Mann-Whitney U test

BTI, botulinum toxin injections; *mAS*, modified Ashworth Scale; *PSFS*, Penn Spasm Frequency Scale

Three of those patients dropped out from BTI, three from nabiximols and one from both therapies. No patients initially treated with BTI discontinued the first received treatment, while three patients initially treated with nabiximols dropped out (one case for inefficacy, one for side effects and one for both inefficacy and side effects). Second treatment discontinuation was observed in one patient who received BTI before nabiximols and in three patients who received nabiximols before BTI; in all those cases, dropouts were due to inefficacy. Only two patients for each group (according to the first treatment received) continued both BTI and nabiximols. Due to the low number of treated patients, it was not possible to perform a proper statistical analysis in order to evaluate a possible additional effect of the two treatments on spasticity and spasm scales.

Discussion

Our single-centre experience shows that the need for a further treatment beside first-line oral medications is particularly evident in a population with relatively high age (>50 years), long disease duration (≈15 years) and a progressive disease course (>75%). Baclofen was the most used first line medication in both groups, followed by benzodiazepines. Patients treated with nabiximols and BTI had similar baseline characteristics and did not differ in the type of spasticity, the large majority of PwMS presenting with paraspasticity.

We found no differences in the dropout rates both due to inefficacy or side effects in the two treatment groups: in a recent meta-analysis, Fu and colleagues [16] found that BTI and nabiximols were both effective in treating spasticity; however, the safety profile of the latter remained to be verified. In our experience, nabiximols and BTI have similar safety profiles since there is no difference in dropout rates for side effects in the two groups. No major side effects were detected in both groups.

The MOVE-2 interim analysis in Italian PwMS treated with nabiximols [17] found that 24 patients (8.7%) discontinued treatment after 1 month, half of them for inefficacy and half for side effects. Similar results were found by Paolicelli and colleagues

[18], who reported that 15 patients dropped out after the first month of treatment, eight for adverse effects and seven for lack of efficacy. Patti and colleagues [19] reported a discontinuation rate of 18.7% due to adverse events after the first month of therapy. Two large Italian cohort studies, based on the national e-registry, seem to suggest higher rates. In the SA.FE. study, 20.8% and 26.4% of patients discontinued the treatment at 4 and 6 weeks, respectively [20]. More recently, an almost constant rate of treatment discontinuation was reported throughout weeks, with 48.3% of discontinuation at 72 weeks after treatment onset [21]. In our patients, a higher discontinuation rate (33.3%) was seen, compared to previous literature, due to side effects and/or lack of efficacy. This difference may be hypothesized to be due to the retrospective nature of our investigation. The only study that analysed discontinuation of BTI in PwMS [22] found that the two predictors of this phenomenon were the lack of caregivers and rehabilitation. We did not take in account those factors; however, our data would not be comparable to the ones of Latino and colleagues due to differences in follow-up duration (1 month vs. 1 or more years). Nevertheless, the importance of physiotherapy programme seems to be crucial also in nabiximols-treated patients, since it increases treatment efficacy and also treatment persistence [23].

Nabiximols significantly reduced mAS, PSFS intensity and PSFS frequency scores. The efficacy of nabiximols on spasticity and spasms has been highlighted in the phase 3 placebo-controlled study [10], where it has been demonstrated to significantly reduce the self-reported Numeric Rating Scale for spasticity and improve many secondary outcome measures such as sleep quality, spasms, functional measures and the impressions of caregiver and physician. Although mAS score was not evaluated in the phase 3 study, subsequent real-life studies (German and Italian MOVE-2) found a significant reduction in mAS scores after treatment with nabiximols [17, 24]. Nabiximols efficacy has been proven in many randomized controlled trials (RCTs) as well as real-life studies, and it has been reported to improve spasticity in 41.7% up to 72% of treated patients [25]. Our data, consistently with previous literature, showed that about 67% of patients continued nabiximols with relief on spasticity after 1 month of treatment.

The role of BTI in treating MS-related spasticity has recently been underlined by the IAB-Interdisciplinary Working Group for Movement Disorders task force. BTI has proven to be reduce both spasticity and spasms in PwMS; however, due to methodological limitations of previous studies, its role has been long underestimated. Indeed, only few RCTs have been published, and the great majority of the available observational and interventional studies include spasticity due not only to MS but also to other conditions such as stroke or spinal lesions [15].

In our experience, 71.4% of patients continued treatment with BTI after 1 month, and an improvement of mAS, PSFS intensity and frequency was found. Despite the short follow-up duration, our data show that BTI can cause a relief on spasticity even after 1 month after treatment, starting with a low injected dosage of toxin. BTI has a prominent role in treating focal spasticity, but, in our population, the percentage of patients with focal spasticity did not differ between BTI and nabiximols groups. This result highlights that BTI could even have a role in treating patient with para- or tetraspasticity, beside their role in focal hypertonia.

Given those observations, we compared BTI and nabiximols effects on mAS, PSFS intensity and frequency. We found no significant differences when comparing *delta* mAS and PSFS in the two groups, with the exception of a statistical trend ($p = 0.091$) in the reduction of PSFS intensity. This finding confirms a previously described reduction of spasms after BTI treatment [26], although another study was not able to show a significant difference from placebo in terms of efficacy [14].

Eleven of our patients were treated with both nabiximols and BTI; however, only four patients continued both treatments. All the dropout patients stopped at least one of the treatments for inefficacy. Even though a proper statistical analysis could not be performed due to a small sample size, our results show that only 4/11 (36%) patients had an improvement after both treatments. Intrathecal baclofen pump may represent a suitable alternative for those patients with treatment-resistant spasticity, and, indeed, one of our patients was implanted an intrathecal pump with relief (data not shown). As far as we know, no previous data regarding combined BTI and nabiximols treatment have been reported: combining the systemic effect of nabiximols with the focal efficacy of BTI could be worth of further multicentre studies, in order to elucidate any cumulative effect on unresponsive spasticity.

Conclusion

Our single-centre retrospective study showed that both nabiximols and BTI are effective in treating spasticity and have a similar safety profile. Improvement in spasticity scores was similar in the two treatment groups on mAS, PSFS intensity and frequency, although a statistical trend favouring BTX in reducing PSFS intensity was detected. Finally, we reported data of patients treated with both nabiximols and BTI, which may represent a combined treatment opportunity in those patients with severe and unresponsive spasticity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10072-021-05182-6.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval The protocol and procedures employed in this study were approved by the Local Ethical Committee. An informed consent was signed by all participants prior to assessment, according to the Declaration of Helsinski (October 2013 version).

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