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Botulinum toxin therapy in patients with oral anticoagulation: is it safe?

Christoph Schrader[1] · Markus Ebke[2] · Fereshte Adib Saberi[3] · Dirk Dressler[1]

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Abstract When used therapeutically, botulinum toxin (BT) has to be injected into its target tissues. All manufacturers warn not to do so in patients with oral anticoagulation to avoid haematoma. We wanted to study the haematoma frequency (HF) in patients with anticoagulation receiving BT therapy. 32 patients (16 females, 16 males, age 69.3 ± 10.0 years) with blepharospasm ($n = 6$), hemifacial spasm ($n = 8$), post-stroke spasticity ($n = 16$), and cervical dystonia ($n = 2$) received BT therapy (needle size 27G, post-injection tissue compression) whilst on anticoagulation (anticoagulation group, AG). 32 patients matched for disease, target muscles, age, and gender received identical BT therapy without anticoagulation (control group, CG). Anticoagulation was performed with phenprocoumon. International normalised ratio (INR) at the time of BT injection was in all patients within the recommended margins of 2.0 and 3.0 (mean 2.6 ± 0.27). Overall HF was 3.0% in AG and 1.8% in CG (not significant). All hematomas occurred in blepharospasm patients (AG 5.2%, CG 2.6%, not significant) and hemifacial spasm patients (AG 3.9%, CG 2.9%, not significant). In cervical dystonia and spasticity there were no haematomas. Throughout an observation period of 4 years, none of the haematomas was surgically relevant. Haematomas are a rare complication of BT therapy, mainly occurring in periocular injections. Anticoagulation only marginally increases HF, provided INR is controlled and appropriate injection techniques are used. Surgically relevant haematomas do not occur. Interruption of oral anticoagulation to perform BT therapy is not justified.

Keywords Anticoagulation · Haematoma · Botulinum toxin · Adverse effects · Drug safety

Introduction

Therapeutic use of botulinum toxin (BT) requires injections into its target tissues including muscles and exocrine glands. All BT manufacturers warn not to do so in patients with oral anticoagulation to avoid haematoma. Scientific evidence for this warning, however, is scarce and actual practice seems inconsistent (Jang et al. 2016; Kassam et al. 2016). On the other hand, patients with blepharospasm, hemifacial spasm and spasticity often are elderly, and concomitant cardiovascular diseases frequently require oral anticoagulation. Repeated periprocedural discontinuation of anticoagulation with heparin bridging is not only cumbersome, but also bears substantial thromboembolic risks. We wanted to study the haematoma frequency (HF) in patients with oral anticoagulation receiving BT therapy.

Methods

Design

The study followed a retrospective chart review design. All patients of our computerised BT therapy database fulfilling the inclusion and exclusion criteria were identified

✉ Christoph Schrader
schrader.christoph@mh-hannover.de

[1] Movement Disorders Section, Department of Neurology, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany

[2] Neurologisches Rehabilitationszentrum, Bad Salzuflen, Germany

[3] IAB-Interdisziplinärer Arbeitskreis Bewegungsstörungen, Hamburg, Germany

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(anticoagulation group, AG). Inclusion criteria were BT therapy for either cervical dystonia, blepharospasm, hemifacial spasm, or post-stroke spasticity, and the use of oral anticoagulation with International Normalised Ratio (INR) values between 2.0 and 3.0. INR assessment had to be as current as not more than 4 days before BT injection. Exclusion criteria were INR > 3.0, intermittent cessation of oral anticoagulation during the treatment, and incomplete data during treatment cycles. A control group (CG) consisted of patients receiving identical BT therapy without oral anticoagulation. CG was matched with AG for age, indication, BT type used, BT therapy details, and numbers of consecutive injection series. Injection series comprises the entirety of all consecutive treatment sessions in an individual patient, and not only single injections per session. All patients had given written informed consent prior to BT therapy initiation. As part of the routine BT therapy follow-up, all patients and caregivers were instructed to report any local or systemic adverse events including prolonged post-injection bleeding, haematoma, pain, sensory impairment, swelling, weakness, and infection. If necessary, patients were re-evaluated at any time in between BT injection series.

Oral anticoagulation

Oral anticoagulation was performed with phenprocoumon. Its efficacy and safety was monitored by INR. INR was kept within recommended margins of 2.0 and 3.0. INR measurements had to be no older than 4 days at the time of BT injections.

Safety monitoring

To determine HF, all minor and major haematomas were recorded. Minor haematoma was defined as haematoma not requiring additional intervention, major haematoma as haematoma requiring surgical intervention, hospitalisation, or discontinuation of the anticoagulant and/or transfusion of blood products. All adverse effects other than haematoma were assessed using a standardised interview.

BT therapy

BT therapy was performed with 27G needles of different lengths. After BT application the injection sites were compressed for several seconds. BT drugs used were onabotulinumtoxinA (100 MU/2.5 ml normal saline), abobotulinumtoxinA (100 MU/0.5 ml normal saline) and incobotulinumtoxinA (100 MU/2.5 ml normal saline). Only data of consecutive treatment cycles for which INR data at the time of injection were available were included in the analysis.

Statistics

To compare data from AG and CG, logistic regression as a widely established multivariable method for modelling dichotomous outcomes was used. Significance was defined as $p < 0.05$.

Results

The results of the study are summarised in Table 1. Of 38 patients with BT therapy and oral anticoagulation, 6 had to be excluded due to incomplete data or intermittent cessation of oral anticoagulation. Thus, 32 patients (16 females, 16 males, age 69.3 ± 10.0 years) were included in AG. 16 of them were treated for post-stroke spasticity, 6 for blepharospasm, 8 for hemifacial spasm, and 2 for cervical dystonia. INR values ranged from 2.0 to 3.0 (mean 2.6 ± 0.27). 26 patients received oral anticoagulation for atrial fibrillation, 3 for cardiac valve replacement, 2 for recurrent thromboses, and 1 for persistent foramen ovale. CG consisted of 32 patients (20 females, 12 males, age 69.4 ± 9.3 years).

A total of 328 treatment cycles with more than a total of 20,900 single injections was evaluated in each group (AG: min 2, max 60, 10.6 ± 13.6. CG: 10.2 ± 12.3). Except for gender, all variables were matched between AG and CG.

Overall HF was 3.1% in AG and 1.8% in CG ($p = 0.997$, odds ratio 0.997, 95% Cl +0.202 to +4.889). Frequency of other adverse effects was 5.5% in AG and 9.8% in CG ($p = 0.995$, odds ratio 0.968, 95% Cl +0.23 to +4.107).

In blepharospasm, HF was 5.2% in AG and 2.6% in CG ($p = 0.73$, odds ratio 1.33, 95% Cl +0.261 to +6.760). Other adverse effects in blepharospasm were more common (9.5%; 11/116) and comprised ptosis (8/116 injection series), mydriasis (1/116 injection series), xerophthalmia (1/116 injection series), and diplopia (1/116 injection series). Controls had a higher frequency of adverse effects (19.1%; 22/115 injections series). Adverse effects were ptosis (15/115 injection series) and xerophthalmia (7/115 injections series).

In hemifacial spasm, HF was 3.9% in AG and 2.9% in CG. The frequency of other adverse effects was the same in AG and CG (each 6.8%; 7/103 injection series) and encompassed ptosis (AG 5/103 and CG 4/103 injection series), xerophthalmia (AG 1/103 and CG 3/103 injection series), and diplopia (AG 1/103 injection series).

In cervical dystonia and post-stroke spasticity, neither in AG nor in CG any haematoma was reported nor were any chronic organised haematomas noticed on clinical examination. Other adverse effects were also not recorded.

When haemorrhage occurred shortly after injection it could readily be stopped by gentle tissue compression.

Table 1 Haematoma frequency in patients treated with botulinum toxin with oral coagulation (anticoagulation group) and without oral anticoagulation (control group)

	Total	BS	HFS	CD	SP
Anticoagulation group					
Number of patients (*n*)	32[ns]	6[ns]	8[ns]	2[ns]	16[ns]
Age (M ± SD) (years)	69.3 ± 10.0	74.5 ± 7.3	72.3 ± 7.1	69.0 ± 14.1	65.8 ± 11.2
Gender (males:females) (*n*)	16:16[ns]	5:1[ns]	4:4	2:0	5:11
Injection series (*n*)	328	116[ns]	103[ns]	8[ns]	101[ns]
Haematoma frequency (%)	3.0[ns]	5.2[ns]	3.9	0	0
Frequency of other adverse effects (%)	5.5[ns]	9.5[a]	6.8[b]	0	0
Control group					
Number of patients (*n*)	32[ns]	6[ns]	8[na]	2	16
Age (M ± SD) (years)	69.4 ± 9.3	74.0 ± 5.5	72.9 ± 6.7	71.2 ± 9.2	65.8 ± 10.6
Gender (males:females)	12:20	2:4	2:6	1:1	7:9
Injection series (*n*)	328	115[ns]	103[ns]	8[ns]	102[ns]
Haematoma frequency (%)	1.8[ns]	2.6[ns]	2.9	0	0
Frequency of other adverse effects (%)	9.8[ns]	19.1[c]	6.8[d]	0	0

BS patients with blepharospasm, *HFS* patients with hemifacial spasm, *CD* patients with cervical dystonia, *SP* patients with post-stroke spasticity, *M* ± *SD* mean ± standard deviation, *n* number, *ns* difference between anticoagulation group and control group not statistically different

* Difference between anticoagulation group and control group statistically significant ($p < 0.05$)

[a]8× ptosis, 1× mydriasis, 1× xerophthalmia, 1× diplopia

[b]5× ptosis, 1× xerophthalmia, 1× diplopia

[c]15× ptosis, 7× xerophthalmia

[d]4× ptosis, 3× xerophthalmia

Discussion

BT injections are accepted as first-line treatment of focal dystonia and spasticity (Borg et al. 2011; Simpson et al. 2008). A meta-analysis of 36 randomised controlled studies reporting 1425 patients treated with onabotulinumtoxinA reveals adverse effects in 25% of the patients and in 15% of controls (Naumann and Jankovic 2004). Adverse effects depended on the target tissue injected and included dysphagia, neck muscle weakness, injection side pain, and 'flu-like' symptoms. Hematoma was not reported, but neither was the patients' oral anticoagulation status.

Our study was based on using 27G injection needles. These needles come in different lengths and allow injection of all relevant target muscles for the indications analysed. HF was not studied for the use of larger diameter injection needles necessary for EMG-based BT application. It was also based on brief compression of the injection site after BT application which is common practice to facilitate tissue diffusion. Recently obtained INR values had to be within recommended margins to exclude patients with unrecognised insufficient (especially reduced) anticoagulation.

Under these conditions HF showed a trend to be higher in all AG patients than in all CG patients, as well as in all patients treated for blepharospasm and hemifacial spasm. However, none of these trends was statistically significant. If haematomas occurred, they were mild, could easily be stopped, and their occurrence was limited to the treatment of cranial conditions.

Our HF was similar to a previously reported statistically insignificant HF of 2.1% in spasticity patients (Barnes et al. 2010) and the complete absence of haematomas in spasticity patients (Jagatsinh and George 2012). Lack of haematoma in patients undergoing paraspinal and calf EMG under anticoagulation indicates principle safety of needle insertions in anticoagulated patients (Roesler 2015).

Marginally increased HF and lack of serious adverse effects on one side and the potentially serious risk of thromboembolic complications seem to favour continuation of oral anticoagulation during BT therapy. This recommendation is in line with several recommendations in similar situations. The American Academy of Neurology recommends continuation of aspirin intake and anticoagulation in stroke patients during minimal invasive surgery (Armstrong et al. 2013), and the US Centers for Disease Control and Prevention recommend intramuscular influenza immunisation in patients receiving oral anticoagulation (Raj et al. 1995).

In summary, the risk of minor hematoma after BT injections in anticoagulated patients is slightly, but not significantly increased and occurs only when injecting facial muscles. No major hematomas occur. When thin injection needles are used, when the injection site is compressed briefly, and when anticoagulation is properly controlled, BT therapy can be performed safely in patients with oral

anticoagulation. Changing oral anticoagulation to heparin with its potentially serious risks and inconveniences is not justified to perform BT therapy. Use of thinner injection needles, which we recently started for treatment of facial conditions, will probably further reduce HF. The risk of hematoma following BT injections in patients using new oral anticoagulants needs to be studied; however, we cannot see any reason why the risk of bleeding should be higher than in patients on phenprocoumon.

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