Original Article

Audit of Safety of Intramuscular Botulinum Toxin Injections among Patients Receiving Warfarin Anticoagulation Therapy

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Abstract

Background: Botulinum toxin (BTX) intramuscular injections are an effective treatment for spasticity in acquired brain injury. Despite use since the 1980s, issues concerning technique, dose and long-term side-effects remain unresolved. For example, the safety of BTX in warfarinised patients is unclear. There are two studies reporting the risk of intramuscular injections in patients receiving anticoagulant therapy with regard to possible local haematoma formation. There is no advice on this subject in the manufacturers' summary of product characteristics for the original brand of warfarin, Dysport, BOTOX, Xeomin or in the British National Formulary.
Aim: To assess the safety of BTX injections in patients receiving oral anticoagulation.
Design: Prospective audit of safe practice.
Setting: Outpatient setting in a rehabilitation centre.
Population: Adult population affected with spasticity with acquired brain injury and receiving concurrent warfarin anticoagulant therapy.
Methods: Fourteen patients who were receiving anticoagulant therapy were given regular BTX (number of injection cycles or total mean no of injections each). Patients gave written informed consent before the injections. Injection technique did not differ from that used for un-anticoagulated patients. Patients were assessed by the injector for obvious haemorrhage in the first 15 minutes after the injection resulting in swelling, bruising, tenderness or haematoma. Patients were asked to watch for appearance of local reactions like swelling, bruising or haematoma and pain in the first week.
Results: There were no clinically detectable local complications after intramuscular injections and no major or minor bleeding episodes after BTX injections.
Conclusion: In our group, BTX injections were administered intramuscularly to patients who were receiving anticoagulant therapy without significant risk of local bleeding. However, injections must be used with caution in patients with an INR above the therapeutic range.
Clinical rehabilitation impact: BTX can be safely given in patients on anticoagulation therapy with safety checks in place.

Key words: **Botulinum toxin, spasticity, warfarin, anticoagulation, acquired brain injury, intramuscular injection.**

Introduction:

Traditional teaching warns against giving intramuscular injections to patients who are anticoagulated because of an increase in the risk of developing muscle haematomas. If an intramuscular injection is essential for such a patient, it is recommended that it be administered in the upper extremity to permit easy access for manual compression, inspection for bleeding and/or the use of a pressure bandage[1]. Intramuscular injection into the desired muscle is the only route recommended for BTX injection and hence the need of multiple injections into deep seated muscles increases the risk in these patients. A recent caution from a pharmacy[2] prompted us to produce safety guidelines to inject BTX in our patients.

Warfarin is a narrow therapeutic range (index) drug, and additional caution should be taken when warfarin sodium is administered to certain patients. Reported risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable

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INRs, history of gastro-intestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs and long duration of warfarin therapy. Bleeding is more likely to occur during the starting period and with a higher dose of warfarin (resulting in a higher INR). Intramuscular (IM) injections of concomitant medications should be confined to the upper extremity which permits easy access for manual compression, inspections for bleeding and use of pressure bandages[3].

The number of people receiving an oral anticoagulation therapy has increased over the past years as a result of greater number of its indications in patients with long term neurological conditions. More people in this group are therefore likely to need botulinum injections.

The aim is to assess the safety of BTX injections in patients receiving oral anticoagulation.

Material and Methods:

Prospective audit of adult patients was carried out after implementing the protocol of using checklist in our spasticity outpatient clinic. The selected group of patients were receiving long-term warfarin therapies, who were followed up in their anticoagulation clinic and who were candidates for regular BTX injections, due to their spasticity, from February 2007 to February 2008 were considered for this audit. To be eligible (Table 1), patients were to be on warfarin and receiving BTX injection for spasticity. They were required to have an INR in the therapeutic range (2 to 3.5) within the last week of injection and must not have had any change in their warfarin dose for a minimum of two weeks before the study. The reason to choose this range of INR is because most of the patients are maintained in this therapeutic range. Patients were excluded (Table 2) if they had INR (>3.5) more than the therapeutic range, required frequent warfarin dose adjustments, or were not able to consent to injection. Informed consent as a usual standard protocol was taken before each injection episode. As it was audit of the checklist and these patients were consented prior to each injection, there is no need to separate ethical approval from the hospital. This treatment is well proven and is used in the hospital for many years. Age, indication for anticoagulation, baseline INR within last week and site of injections were recorded. Study patients were given regular therapeutic BTX injections into the various indicated group of muscles in the upper and lower limbs by a 27 gauge needle. No extra measures, except a cotton wool pressure on the skin, were taken to avoid complications. Patients were observed for 15 minutes in the outpatient clinic for obvious haemorrhage, local swelling, bruising, tenderness or even haematoma (Table 3). Patients continued to receive the same dosages of medications after the injections and were asked to report any adverse effect within the first week and report it and also asked specifically at the next visit. The study was not to evaluate spasticity and effect of toxin so we did not include any outcome measures for this particular group of patient. Although the patients did have goals and outcome measures for their clinical evaluation which was separate to this study.

Table 1: *Inclusion Criteria*

1. Patients on warfarin and receiving BTX injection for spasticity.
2. INR should be in the therapeutic range (2 to 3.5) within the week of injection.
3. The dosage of warfarin should be stable in the last two weeks of injection.

Table 2: *Exclusion Criteria*

1. INR > 3.5
2. Required frequent warfarin dose adjustments.
3. Patients unable to consent to injection treatment.

Table 3: *Checklist for Patients on Warfarin in Spasticity Clinic*

1. Clear documentation of patient taking Warafarin.
2. Check the latest INR (within last week) before giving Botulinum toxin
3. INR should be in the therapeutic range (<3.5)
4. Avoid BTX injections if INR >3.5
5. Use of thinnest possible (27G) needle for injection.
6. Pressure with cotton wool after injection
7. Observe the patient for 15 minutes for bleeding, swelling, local haematoma.
8. Ask patient look for swelling, local haematoma within 1 week and report it.

Results:

Fourteen patients (mean age, 62 years; age range, 40 to 82 years) were suitable for the audit. All patients were enrolled from June 2007 to February 2008. Only one patient was excluded because he had high INR at the time and didn't receive BTX injections as per the checklist. On an average each patient received about 8 injections, with total injection sites of 103 in these 14 patients, all patients had complete follow-up for 3 months until when they were seen for next set of repeat injections.

The patients were screened for local haematoma, pain, swelling and tenderness. No patient had significant pain, tenderness or swelling at the injection site (Table 4). There were no reported local or systemic adverse effects in all these patients on follow up. here were no major or minor bleeding episodes after the injection or during follow-up.

As previously stated this study was not for evaluation for spasticity or evaluation of effect of BTX.

Discussion:

In this study of fourteen patients receiving stable long-term anticoagulation with warfarin, intramuscular BTX did not have any significant adverse effects or systemic effects.

Because patients taking oral anticoagulant can develop large haematomas after intramuscular injections, the policy we made at our institution is to administer BTX by twenty-seven gauge needles, which minimises tissue damage due to intramuscular injection and it is fair to presume that it should not infer a substantial risk of haemorrhage. We are unaware of data indicating the safety of BTX injection in this group of patients. We therefore undertook this study to evaluate the issue more fully.

A review of the literature revealed few direct references to this issue. Wintrobe's Clinical Hematology (1992) makes a general statement about the wisdom of avoiding interventions such as intramuscular injections in the anticoagulated state[4]. Marder (1979) makes similar general statements[5]. The data sheets for the common brands of BTX (Dysport®, BOTOX®) give no specific precautionary advice in patients taking warfarin.

Two small studies have investigated IM influenza vaccine administration in elderly patients taking warfarin. In first of these 41 patients taking warfarin received 0.5 ml vaccine as a single IM injection in the deltoid region, followed by application of firm pressure for five minutes[6]. All patients were followed up for 14 days and there were no cases of localised bleeding or any change in arm girth after injections. In a second study, 13 patients received 0.5 ml vaccine IM and these were compared with 13 patients receiving the same

Table 4: *Patient Demographics, INR at the Time of Injection and the Muscles Injection Sites*

Patient	Age	Sex	INR	Injection sites	No. of injections	Local complications
1.	40	M	2.5	GM, TP	3	None
2.	74	F	2.8	GM, SL, TP,FDL, EHL	7	None
3.	66	F	2.6	PM, BC, BR, FDS	6	None
4.	49	M	1.2	GM, SL, FHL, FHB, TP, BC, BR	10	None
5.	63	F	2.4	BC, BR, FDS, FCR, FDP	7	None
6.	82	M	3.1	PM, LD, BC, BR, ADD	8	None
7.	61	M	2.9	BC, BR, FDS, FCR, FCU, GM, SL, TP	11	None
8.	82	M	3.1	PM, BC, BR, ADD, HS, EHL	10	None
9.	62	M	2.5	GM	2	None
10.	49	F	2.9	BC, BR, FCR, FDS, FDP, FPL, FPB, GM, TP	12	None
11.	62	M	2.5	BC, BR, FCR, FDP, FDS, FPL	7	None
12.	49	F	3.5	BC, BR, FDS, FCR, FDP	7	None
13.	78	M	2.6	BC, FDS, FDP	5	None
14.	51	F	2.8	ADD, BilTP, BilGM	8	None

vaccine subcutaneously[7]. Three patients in each group had discomfort or pain at the injection site, but no local bleeding was recorded. It has been advised that when intramuscular injections are necessary in warfarinised patients, the injections be administered into an upper extremity as a precaution to permit easy access for manual compression, inspection of bleeding, and/or application of pressure bandages if necessary[1]. However with BTX we have to give multiple deep injections into individual muscles where access for manual compression or inspection is difficult.

Recently, a single blinded, randomised, controlled trial with 229 patients by Casajuana *et al*[8] also observed no major side effects or major haemorrhage during the intramuscular injections. In this study 129 patients were randomised to receive intramuscular influenza vaccines compared to 100 patients received subcutaneous vaccination in the control group. The appearance of local adverse reactions was more frequent in the subcutaneous administration group.

Theoretically intramuscular injections may cause some local bleeding within muscle due to the needle rupturing small blood vessels, it appears to us from our current practice that the rationale for the contra-indication of intramuscular injections in the anticoagulated state is far from clear. It seems to be one of presumed common sense. With increasing numbers of this group of patients being warfarinised for conditions such as DVT, ischaemic stroke and pulmonary embolism, and the wider use of BTX injections in the long term management of spasticity, we need to have safety guidelines and checks.

Conclusion:

It is unclear if there is a 'safe' INR level but our experience seems to suggest that it may be safe up to an INR level of 3.5. Our practice to administer BTX by 27 gauge needles also appears to be a safe approach but requires more studies to evaluate. It remains unclear the risk of gauge of needle to use, but our practice of using 27 guage has been avoiding bleeding complicatons.

Given the number of patients with spasticity on anticoagulants, more large scale studies on this issue are required to establish safe practice parameters.

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