DOI: 10.5152/tftrd.2015.97769 Turk | Phys Med Rehab 2015;61:253-60

Approaches of Physicians across Turkey to Administer Botulinum Toxin Injections in Anticoagulated Patients

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Abstract

Objective: In the absence of national or international quidelines, physician approaches to administer botulinum toxin (BTX) injections in patients on an anticoagulant therapy may be variable. We aimed to document the preferences and attitudes of physicians for controlling the bleeding risk of BTX injections in anticoagulated patients.

Material and Methods: An electronic survey of physicians across Turkey who practice BTX administration for spasticity management was conducted. Results: In total, 80 physicians participated in the survey. There was a wide variance regarding the type of guidance and needle they used for injecting BTX in their routine practice. Among the respondents, only 7% reported refusing to administer BTX injections in anticoagulated patients, whereas 4% reported performing the injections without controlling the International Normalized Ratio (INR) value. Of the remaining respondents, the safe INR value for BTX injections was reported as \leq 2.0 by 45%, \leq 2.5 by 38%, and \leq 3.0 by 17% respondents. Most of the physicians reported altering some portion of their routine injection technique in anticoagulated patients.

Conclusion: A majority of physicians remain cautious and restrict the administration of BTX in some way for anticoagulated patients. Future studies are required to establish a safe INR value and to develop a consensus statement for BTX injections in this patient population.

Keywords: Spasticity, anticoagulant, warfarin, botulinum toxin

Introduction

There is an inherent risk of minor bleeding with intramuscular injections because of the needle rupturing the small blood vessels. This risk is augmented in patients receiving anticoagulation therapy. Continued intramuscular bleeding can progress to large hematomas and even compartment syndrome after intramuscular injections in these patients (1). Intramuscular injection into spastic limb muscles is the only route recommended for botulinum toxin (BTX) administration in the management of focal spasticity. Although it appears to be a well-tolerated and safe procedure, little is known about the complications of BTX injections when performed in patients taking anticoagulant medications. Indirect references to this issue may be provided from the reports of bleeding complications after needle electromyography (EMG) examinations. Although earlier case reports reported that serious bleeding complications can occur after EMG examinations in patients on anticoagulants, recent studies (2,3) demonstrated no statistically significant increase in bleeding compared with control groups not taking anticoagulant medications. Nevertheless, electromyographers have been advised to remain cautious when examining patients who had an International Normalized Ratio (INR) value of ≥3.0 and to weigh individual risks on a case-by-case basis (4,5). Although

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the BTX injection technique is similar to the needle EMG examination technique, the need of multiple injections of toxin into deep muscles may pose an additional risk of bleeding and hematoma formation. However, the degree of that risk has not been well examined, and no evidence-based guidelines exist regarding BTX injection procedures in anticoagulated patients. A review of the literature revealed only one attempt to provide a safety guideline regarding BTX injections in patients receiving oral anticoagulation medications (6). This study showed that intramuscular BTX injections did not have any significant adverse effect in 14 patients receiving stable long-term anticoagulation treatment with warfarin. However, this study included only the patients with an INR value in the therapeutic range (2–3.5) within the last week of injection. Although the authors suggested that it is safe up to an INR level of 3.5, the "safe" INR level for BTX injections in patients receiving oral anticoagulation remains unclear.

In the absence of good data or clear guidelines, practitioners anecdotally suspect bleeding and hematoma after BTX injections when performed in anticoagulated patients and may use various strategies to avoid these complications. It has come to our attention that routine injection techniques and approaches to injecting patients on anticoagulant medications show variability among physicians across Turkey. To establish a baseline for future clinical studies and facilitate the development of evidence-based guidelines, we conducted a survey of Turkish physicians who treat spasticity with BTX injections. We aimed to document their routine injection practices and their preferences and attitudes when treating spasticity with BTX injections in patients who are anticoagulated. We also aimed to explore the complications they experienced previously, which were related to BTX injections in anticoagulated patients. This is part of a larger research project aiming to document and compare the special practices of physicians in three countries (Canada, Turkey, and South Korea) from distinct geographical regions of the world.

Material and Methods

An electronic survey of physicians across Turkey who practice BTX administration for spasticity management was conducted. The survey invitation was delivered through electronic mail (e-mail) over the internet within the online e-mail group of the Turkish Society of Physical Medicine and Rehabilitation (PM&R), which has more than 1850 members. To target the correct and interested population, only the physicians practicing BTX injections for adult spasticity were invited to participate in the survey. Additionally, personalized e-mail invitations were sent to the physicians specializing in PM&R and neurology and who are known to have the experience in administering BTX injections.

The survey was created using the survey software of Google Forms (available from Google Drive at: http://drive.google.com/). The survey consisted of multiple choice questions with the options of "other" and "prefer not to respond". A cover

letter including the goals of the survey and the value of the respondents' responses was provided in the primary survey invitation message. The average time it would take to complete the survey (below 10 min) was included in the cover letter. A confidentiality statement mentioning that the survey did not include personally identifiable information and their data would be kept confidential was also included. Ethics committee approval was received for this study from the ethics committee of Ege University Medical Faculty. Filling out the survey was considered as an implicit consent to participation in the study. The cover letter that was mailed to the participants and survey questions are found in the Appendix 1.

The respondents were able to access the survey directly through the e-mail or through a link embedded in the e-mail. Once the respondents began the survey, they were able to return to complete the survey if needed by clicking on the link provided in the e-mail. When the respondents completed and submitted the survey, they were not able to modify or change their answers.

Two reminder mails were sent at 14 days and 21 days after the first invitation mail. Because the survey responses were recorded anonymously, reminder mails were sent to all recipients. We expressed our appreciations to the physicians who had already completed the survey. We added the updated response rate to reminder mails and sent a request to improve the response rate.

Table 1. Professional experiences of the respondents		
	n	%
Branch of practice		
PM&R	68	85
Neurology	12	15
Working affiliation		
University hospital	50	63
Research and training hospital	21	26
State hospital	3	4
Private practice	6	7
Years of experience		
Less than 1 year	2	3
1–3 years	8	10
3–5 years	11	14
5–10 years	30	37
More than 10 years	28	35
No response	1	1
Number of spasticity patients in the	roster	
0–10	9	11
10–30	26	33
30–50	23	29
More than 50	21	26
No response	1	1

		Branch of practice		
		PM&R	Neurology	Total
What form of guidance do you use for	ES only	13 (19%)	0	13 (16%)
injecting BTX in your clinical practice?*	EMG only	5 (7%)	5 (42%)	10 (13%)
	US only	1 (2%)	0	1 (1%)
	ES+EMG	12 (18%)	4 (33%)	16 (20%)
	ES+US	7 (10%)	0	7 (9%)
	No guide	30 (44%)	3 (25%)	33 (41%)
What type of needle do you mostly use for	22G	40 (59%)	3 (25%)	43 (54%)
njecting BTX in your clinical practice?	25G	21 (31%)	7 (58%)	28 (35%)
	27G	7 (10%)	2 (17%)	9 (11%)
	Total	68	12	80

^{*:} statistically significant difference between PM&R and neurology (p=0.009)

ES: electrical stimulation; EMG: electromyography; US: ultrasound; G: gauge

		Branch of practice		
		PM&R	Neurology	Total
Do you inject anticoagulated patients?	Never	4 (6%)	2 (17%)	6 (7%)
	Yes	64 (94%)	10 (83%)	74 (93%)
	Total	68	12	80
Do you control INR values prior to injections?	No	3 (5%)	0 (0%)	3 (4%)
	Yes	61 (94%)	10 (83%)	71 (93%)
	Total	64	10	74
What is your comfort INR range for BoNTA injections?*	≤2	24 (39%)	8 (80%)	32 (45%)
	≤2.5	25 (41%)	2 (20%)	27 (38%)
	≤3.0	12 (20%)	0 (0%)	12 (17%)
How recent an INR result do you use for determining to inject?*	Same day	17 (28%)	6 (60)	23 (32%)
	The day before	30 (50%)	2 (20%)	32 (46%)
	Within 2-7 days	13 (21%)	2 (20)	15 (21%)
	Mean of the last 5 days	1 (2%)	0	1 (1%)
	Total	61	10	71

^{*:} statistically significant difference between PM&R and neurology (p=0.039)

Statistical Analyses

The survey is connected directly to the database of Google Forms where all completed survey data is stored. Each response is viewed in a single row of a spreadsheet, with each question shown in a column. Frequencies were calculated for all survey responses. Comparisons of the approaches of physicians specializing in the field of PM&R and neurology were analyzed using the Chi-square test.

Results

In total, 80 physicians participated in the survey. Table 1 summarizes the professional experiences of the respondents.

Sixty-eight (85%) of the respondents specialized in PM&R and 12 (15%) in neurology. A majority of the respondents (63%) were practicing at a university hospital. Fifty-eight (72%) respondents had more than 5 years of experience in administering BTX injections for adult spasticity, and 21 (26%) had more than 50 patients on their roster.

Routine BTX injection practices of the respondents are shown in Table 2. There was a wide variance in practice regarding the type of guidance and needle they used for injecting BTX. Thirty-three (41%) respondents were injecting without guidance; others were using EMG, electrical stimulation (ES), ultrasound

BTX: botulinum toxin; INR: international normalized ratio; BoNTA: botulinum neurotoxin A

		Branch of practice			
		PM&R	Neurology	Total	
Do you change the type of needle you use for injecting?	No	28 (44%)	5 (50%)	33 (45%)	
	Yes, prefer smaller size	36 (56%)	5 (50%)	41 (55%)	
Do you change the type of guide you use for injecting?	No	50 (78%)	10 (100%)	60 (81%)	
	Yes, prefer injecting without a guide	14 (22%)	0	14 (9%)	
Do you inject deep compartment muscles?	No	9 (14%)	0	9 (13%)	
	Yes	55 (86%)	10 (100%)	65 (87%)	
	Total	64	10	74	

(US), or a combination of two. Preferences of guidance were significantly different between physicians specializing in PM&R and those in neurology. Most of the neurologists preferred EMG, whereas PM&R physicians used ES and US more frequently (p=0.009). More than half of the respondents (54%) were using a 22G needle, whereas only 11% were using a 27G needle for injection. Most respondents (94%) were aware of bleeding complications, and 80% were aware of compartment syndrome related to BTX injections in anticoagulated patients.

The responses regarding the practice of BTX injections in patients on anticoagulant medications are seen in Table 3. Only six respondents (7%) reported refusal to administer BTX injections in anticoagulated patients. Among 74 respondents (93%) who were administering BTX injections in this patient population, only three (4%) reported not controlling the INR value prior to or on the day of injections. Of the remaining 71 respondents (89%), the safe INR value for BTX injections was reported as ≤2.0 by 32 (45%), ≤2.5 by 27 (38%), and ≤3.0 by 12 (17%) respondents. Neurologists seemed to be more conservative than PM&R physicians because majority of them (80%) were injecting BTX in patients with an INR value ≤2.0 (0=0.039). A majority of these respondents (46%) reported controlling the INR value the day before the injection. Only one respondent (PM&R physician) reported determining a safe INR value by calculating the average of the value of the last 5 days before the injection. One respondent (neurologist) reported ceasing warfarin treatment 3 days before injection and starting low-weight heparin administration. Thirteen respondents reported injecting superficial and huge muscles such as the biceps, gastrocnemius, and hamstrings regardless of the INR value. Forty-one (55%) of the respondents (n=74) reported altering some portion of their routine injection technique in anticoagulated patients (Table 4). These alterations include using a smaller needle size, injecting without a guide, and refusing to inject deep compartment muscles (9 respondents).

Among the respondents who were injecting deep muscles (n=65), 14 (22%) reported having at least one prior complication of bleeding or ecchymosis as a result of injecting BTX in an anticoagulated patient. Two respondents reported having five previous complications, the other three recalled two, and the remaining nine reported a single complication. Only one

respondent reported having a single complication of compartment syndrome previously because of BTX injections into the deep muscles.

Discussion

Our survey of 80 physicians demonstrated that there is considerable practice variability in normal injection techniques among Turkish physicians. The survey also documented that the majority of physicians remained cautious and restricted the administration of BTX injections in some way for anticoagulated patients. These restrictions were quite varied, including refusal to perform BTX, limiting BTX to superficial muscles, altering the routine injection techniques, and requiring a safe INR value prior to or on the day of injections. The survey demonstrated that a majority of physicians controlled INR value prior to or on the day of injections. Although the responses regarding the safe INR value varied, most physicians perform injections if the INR value is below the therapeutic range (≤ 2.0), whereas others refuse injections if the INR value is higher than the therapeutic range (>3.0). The survey also suggested that physicians rarely experienced bleeding complications as a result of BTX injections in anticoagulated patients.

Considering the issues of time, money, and target population, we decided that an e-mail survey approach is best suited for this research project (7,8). Recent studies have demonstrated an increase in web-based response rates compared with paperbased response rates (9). We considered all conceptual and methodological issues associated with designing and conducting e-surveys (7,8). To improve the response rates, we used some recommended strategies, including sending up to three reminders, personalizing the emails, adding the updated response rate to reminder emails, stating the average time it would take to complete the survey, engagement by having an easily accessible link to the survey, and transparency of survey length and completion by targeting the correct, and thereby, interested population (8). Using these strategies provided us the ability to reach a large number of potential respondents quickly and cheaply and to receive completed surveys in a correspondingly short amount of time.

Our survey demonstrated that only 7% of the respondents refuse performing BTX injections in anticoagulated patients. On the other hand, only 4% of them administer BTX injections re-

gardless of the INR value. Others uniformly restrict BTX injections because of concerns about bleeding in these patients. A high majority of physicians avoid administering BTX injections in patients with an INR value above the therapeutic range (≥3.0). Furthermore, approximately half of the physicians administer injections only in patients with an INR value below the therapeutic range (<2.0). Thus, these physicians withhold administering an anticoagulant medicine before performing BTX injections to reach the safe INR value. However, the discontinuation of antithrombotic treatments in the patients with therapeutic INRs may expose them to potentially devastating thrombotic complications (10). It is certainly much more harmful than bleeding complications from BTX injections (11). In fact, a total of 25 bleeding or ecchymosis complications from BTX injections in anticoagulated patients were recalled by 14 respondents. Because this number spans the collective memory of all respondents and most of the respondents had many years of experience in administering BTX injections in many patients, this number would be thousands of procedures performed over several decades. Although the respondents provided no details of the bleeding complications, they are likely to be significant enough to be remembered. However, it is not clear whether bleeding complications have caused the formation of hematomas. Nevertheless, the paucity of such reports suggest that significant bleeding after BTX injection occurred rarely in patients with an INR value within the therapeutic range. Because only 4% of the respondents were reported to perform BTX injections regardless of the INR value, the risk of bleeding in patients with an INR value above the therapeutic range remains unclear. On the other hand, although only one respondent reported to have experienced compartment syndrome in a single patient, the awareness of this possibility is crucial because this syndrome needs prompt diagnosis and intervention (12). However, it is difficult to comment about the occurrence of this syndrome because the details of this complication such as the INR value at the time of injection, localization of the injected muscles, or existence of comorbid conditions are not provided. Thus, future studies using imaging techniques to assess the complications of bleeding from BTX injections in anticoagulated patients are required to establish a "safe" INR value.

The association between bleeding complications and the technique used for guiding toxin injections remain unclear. Our survey demonstrated that many Turkish physicians alter their routine injection techniques in anticoagulated patients in an attempt to prevent bleeding complications. Although this approach theoretically may reduce bleeding complications, a further study is warranted to demonstrate clear relations. Also, the risk of gauge of needle to use remains unclear, but most respondents reported using a smaller caliber needle to avoid bleeding complications in these patients. This approach seems to be extremely logical because it has been recommended to use the smallest caliber needle possible to minimize tissue damage and prevent the risk of bleeding complications from intramuscular injections in anticoagulated patients (1,6,13). This issue should also be considered in future research.

Although it was not our primary goal, this survey also documented normal BTX administration techniques used by Turkish

physicians in a routine clinical setting. There was a wide variance in practice regarding the type of guidance and needle they used for injecting BTX for adult spasticity. There were also significant differences between physicians in the field of PM&R and neurology. It is noteworthy that 42% of the respondents were performing injections by palpation and surface landmarks for guiding toxin injections. The correct placement of the needle within the muscular structure is crucial for the efficacy of BTX injections. Generally, manual needle placement based solely on anatomical landmarks and palpation is considered to be an acceptable technique for the large and superficial muscles, particularly if administered by experienced clinicians. However, instrumental guidance has been recommended for small and deep-seated muscles (10). Moreover, most recent randomized controlled studies have proved with evidence that guidance with EMG, ES, or US improves the therapeutic efficacy of BTX therapy compared with manual placement (14,15). The reasons why most Turkish physicians do not use instrumental guidance routinely may be because of the procedural difficulty, time required, and technical inadequacies in clinical settings (13,14).

There are some limitations of this study. The limited access of the survey only to the physicians with a computer, internet access, or an e-mail account may be a drawback of this methodology. Thus, the sample used in the current study may limit the ability of the results to be generalized to all physicians across Turkey. Because the real number of physicians who treat adult spasticity with BTX injections across Turkey is unknown, it is difficult to estimate the success of this survey regarding the response rates. Another limitation of the study is that it is difficult to analyze the associations between bleeding complications and approaches of physicians because of the small sample size and presence of many cofactors influencing the complications.

Conclusion

This survey demonstrated that Turkish physicians are conservative in checking INR values before administering BTX injections in patients receiving anticoagulant medications. Most of them did not administer BTX injections when INR values exceeded 3.0. Caution may be warranted in making more generalized conclusions from our findings with respect to other clinicians all over the world because of the potential for differences in injection techniques between countries. Studies are underway to image hematoma size following BTX injections in the deep compartment. These studies will help to develop a consensus statement for BTX injections in this patient population that would lead to more homogeneous practices.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University Medical Faculty.

Informed Consent: As this study was designed as an electronic survey, filling out the survey was considered as an implicit consent to participation in the study.

Peer-review: Externally peer-reviewed.

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Author Contributions: Concept - C.B., İ.F.; Design - A.Y.O., C.P., C.B., İ.F.; Supervision - C.P., C.B.; Resource - A.Y.O.; Materials - A.Y.O.; Data Collection and/or Processing - A.Y.O.; Analysis and/or Interpretation - A.Y.O., C.P., C.B., İ.F.; Literature Review - A.Y.O., C.P.; Writer - A.Y.O.; Critical Review - C.P., C.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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Appendix 1

We invite you to participate in the survey on "Standards of practice in anticoagulated individuals requiring botulinum toxin (BTX) injections for limb spasticity." Although BTX injections theoretically increases the risk of bleeding and hematoma formation, the degree of that risk has not been well examined, and no evidence-based guidelines exist regarding BTX injection procedures in anticoagulated patients. It has come to our attention that there is a wide variance in practice among Turkish physicians regarding the administration of BTX injections in patients on anticoagulant medications. The aim of this survey is to collect information regarding the special practices of Turkish physicians when treating spasticity with BTX injections in patients who are anticoagulated. This is part of a larger research project, which has been conducted in physicians across Canada. Determining the most common practice procedures may help the physicians to examine their practices in a greater context. This will also help to establish a baseline for future clinical studies and facilitate the development of evidence-based guidelines for BTX injections in this patient population. The average time it would take to complete the survey is estimated to be less than 10 min. You may access the survey directly here or through the link embedded in this e-mail. Once you begin the survey, you will be able to return to complete the survey if needed by clicking on the link provided. When you complete and submit the survey, you will not be able to modify or change answers. You can view the results after submitting the survey.

Confidentiality: This survey has received ethical approval from The survey does not include any personally identifiable information. Your information will be anonymous within the dataset. All data obtained from participants will be kept confidential and will only be reported in a non-attributable form. Primary data will be destroyed at the conclusion of the research. When the analyses are completed, the results will be shared with you.

Participation: Participation in this research study is completely voluntary. You have the right to refuse to participate entirely. By filling out the survey, you consent for the researcher to collect data from you, to release this data to others, and to publish and present data collected in this research.

If you have questions regarding this study or would like to be kept informed about the research, please contact: by e-mail (....) or by telephone (....).

I have read and understood the above consent form and desire of my own freewill to participate in this study.

- Yes
- No
- 1. Branch of your practice?
 - o PM&R
 - o Neurology
 - o Other
 - o Prefer not to respond
- 2. Working affiliation?
 - o University Hospital
 - o Training and Research Hospital

- o State Hospital
- Private practice
- o Other
- o Prefer not to respond
- 3. How many years of experience do you have administering BTX injections for patients with spasticity?
 - o Less than 1 year
 - o 1-3 years
 - o 3-5 years
 - o 5-10 years
 - o More than 10 years
 - o Other
 - o Prefer not to respond
- 4. How many adult patients with spasticity do you have on your roster?
 - o 0-10
 - o 0-30
 - o 30-50
 - o More than 50
 - o Other
 - o Prefer not to respond
- 5. What form of guidance do you use for injecting BTX in your clinical practice?
 - o Only electrical stimulation
 - o Only EMG
 - o Only ultrasound
 - o Electrical stimulation and EMG
 - o Electrical stimulation and ultrasound
 - o No guide
 - o Other
 - o Prefer not to respond
- 6. What type of needle do you mostly use for injecting BTX in your clinical practice?
 - o 22G
 - o 25G
 - o 27G
 - o Other
 - o Prefer not to respond
- 7. Are you aware about the complication of compartment syndrome in anticoagulated patients who were injected with BTX?
 - o Yes
 - o No
 - o Other
 - o Prefer not to respond
- 8. Are you aware about the complications of bleeding or ecchymosis in anticoagulated patients who were injected with BTX?
 - o Yes
 - o No
 - o Other
 - o Prefer not to respond

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9. Do you inject BTX in anticoagulated patients?o Yeso Noo Othero Prefer not to respond	Yes, prefer a smaller sizeNoOtherPrefer not to respond
10. Do you have the ability to measure an INR value prior to or on the day of BTX injections? o Yes o No o Other	 16. Do you change the type of guide you use for injecting a patient on warfarin? o Yes, prefer injecting without a guide o No o Other o Prefer not to respond
 o Prefer not to respond 11. Do you control an INR value prior to or on the day of BTX injections? o Yes o No o Other o Prefer not to respond 	 17. Do you inject muscles of the deep, distal upper, or lower extremity compartments (i.e., FDS, FDP, FDL, TP) in a patient on warfarin? o Yes o No o If it must be done o Other o Prefer not to respond
12. What is your comfort INR range for BTX injections? o <2.0 o <2.5 o <3.0 o <3.5 o <4.0 o <4.5 o Do not measure at all o Other	 18. If yes to the above question, have any of your patients (anticoagulated with warfarin+injected in deep compartment muscles) ever developed a compartment syndrome as a result of your injections? o Yes o No o Other o Prefer not to respond
 o Prefer not to respond 13. How recent an INR result do you use to determine whether or not the injections will be completed at their clinic visit? o Same day o The day before injection o 2–7 days o 8–14 days o Inject regardless of the INR value o Other o Prefer not to respond 	 19. If yes to the above question, how many complications of compartment syndrome have you had in the past year? 20. Have any of your patients (anticoagulated with warfarin+injected in deep compartment muscles) ever developed bleeding or ecchymosis as a result of your injections? o Yes o No o Other o Prefer not to respond
14. Are there any muscles that you do not inject regardless of the INR value in a patient? If yes, please list.15. Do you change the type of needle you use for injecting a	21. If yes to the above question, how many such complications (bleeding or ecchymosis) have you had in the past year?
natient on warfarin?	Thank you very much