Intravesical injection of botulinum toxin A for treatment of overactive bladder in anticoagulated patients: Is it safe?

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ABSTRACT

Objective: This study aimed to identify the complication rate, specifically bleeding, in patients who received anticoagulation undergoing intravesical botulinum toxin A injections.

Material and methods: This study included all patients (n=430) undergoing intravesical injection of botulinum toxin A in a single secondary care center between January 2013 and December 2018. We recorded the use of anticoagulants/antiplatelets and complications. Logistic regression was used to investigate the association between anticoagulant/antiplatelet use and the complications arising, while controlling for age and sex.

Results: We identified 430 procedures in 94 men and 336 women (mean age, 60 years). A total of 79 patients received anticoagulants (18%). Aspirin was the most common anticoagulant (52%). Complication rate in anticoagulated patients was 6% (n=5), and it was 2% in those not on anticoagulants/antiplatelets (n=7). Complications were over 3 times more likely in patients who received anticoagulants/antiplatelets (odds ratio=3.233; 95% confidence interval=0.873, 11.38; p=0.067). There was no difference in the complications between patients with idiopathic symptoms and those with neuropathic overactive bladder. No patients required further surgical intervention, and all except 1 were Clavien–Dindo grade I–II with no mortalities.

Conclusion: Anticoagulated patients undergoing intravesical injections have higher complication risks; however, the treatment outcome is unaffected with no significant morbidity/mortality. This is the first study to demonstrate safe outcomes for this subgroup and can assist in decision making and consenting.

Keywords: Anticoagulant; antiplatelet; intravesical botulinum toxin A; postoperative complications; overactive bladder.

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Introduction

Botulinum toxin A is a proven effective and minimally invasive treatment for overactive bladder (OAB), refractory to medical therapies.[1] Since the licensing of botulinum toxin A by the medicines and healthcare products regulatory agency in September 2012, there has been no formal guideline to aid the surgeons in the management of patients receiving concomitant antiplatelet or anticoagulant therapy.

Although cystoscopic intravesical botulinum toxin A injection is carried out in clinics and regularly performed under a local anesthetic, there are still potential complications (20%–43%).[2] Hematuria is well documented and common with urinary tract instrumentation and injection (3.6%–5.2%); however, there is a lack of evidence quantifying the duration and severity. This may be concerning in anticoagulated patients.[3-5] Currently, there are no studies or specific guidelines regarding the concomitant use of anticoagulant therapies and intravesical botulinum toxin A. Owing to the theoretical bleeding risk, patients taking antiplatelets/anticoagulants were either excluded from trials[6] or had these medications ceased 1 week before the procedure.[7]

The aim of this single-center retrospective study was to explore the complications of intravesical botulinum toxin A with concomitant antiplatelets/anticoagulants.

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Material and methods

Study participants and ethical approval

This study was registered as an original project with the clinical governance board at Morriston Hospital (Audit number 1718106) and formal approval was obtained from them with the aim of ensuring that the complication rate in anticoagulated patients was not unduly high. Because this was a local retrospective audit project, separate ethical approval was not required. Patients were identified from procedure lists using name and hospital identification number between January 2013 and December 2018. The following standard information was collected: age, gender, indication where documented, dose given, perioperative use of anticoagulant with the reason for prescribing, and postoperative complications. Patients were not asked to stop antiplatelets/anticoagulants before their procedure and were informed of the bleeding risk at the time of consent. They were specifically informed of a possible increased bleeding risk as part of a standard consent process in the United Kingdom of tailoring consent for risks to each individual since the Montgomery versus Lanarkshire case in 2015.[8] International normalized ratio was checked in patients on warfarin, and the procedure was not continued if the patient was outside of their therapeutic range. Data were retrieved from electronic medical records (operation notes, discharge summaries, clinic letters, GP records, and medication records) and analyzed.

Procedure

Procedures were carried out mainly under a local anesthetic in a flexible cystoscopy clinic using an 18-Fr flexible cystoscope with a single-use, 27-gauge needle with outer sheath for cystoscopes. Some procedures were performed under a general anesthetic in patients deemed fit at patient request. This was performed with a 21-Fr rigid cystoscope and a single-use, 23-gauge Cook cystoscopic injection needle. None of the patients treated had a high spinal injury, so the risk of autonomic dysreflexia was not a factor in the anesthetic decision.

Regardless of dose, the botulinum toxin A was diluted in normal saline and injected in 1-mL aliquots in the bladder. The procedure was covered with 2 doses of oral 500 mg ciprofloxacin (1 dose pre- and 1 postprocedure).

Main Points:

- Anticoagulation can be safely continued when performing intravesical botulinum toxin injection.
- Complications do not increase when using concurrent anticoagulation and botulinum toxin.
- There are no other studies on this combination of treatments.

Study outcomes

The end point was considered to be any complication within 30 days that required the patient to seek medical attention. Complications were classified as follows: visible hematuria, acute urinary retention (painful inability to void regardless of volume) or post void residuals requiring clean intermittent self-catheterization, urinary tract infection (UTI), weakness, allergic reaction, and failure of treatment. Mostly, these were recorded in the electronic records as acute attendance. UTI was assessed by either the patient reattending acutely or having a urine sample sent in 30 days postoperatively. The complications were also graded per the Clavien–Dindo system.[9]

Statistical analysis

Logistic regression was used to investigate the effect of antiplatelets/anticoagulants on complications. The results are presented as odds ratios (ORs), with above 1 corresponding to a harmful effect. Age and sex were included as covariates to control for potential confounding.

All the statistical analysis was performed using the R version 3.5 (R Core Team [2018]. R is a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported using mean and range and categorical variables as percentages. For unadjusted comparison between those who experienced complications and those who did not, Chi-squared and *t*-tests were used to assess for statistically significant differences in the categorical and continuous variables, respectively. Logistic regression was used to formally determine the association of concurrent anticoagulation use and postoperative complication, with the OR being reported alongside a 95% confidence interval and p value.

Simple comparisons of complication groups (yes/no) by age (*t*-test), anticoagulant use (Chi-squared test of association), and type of anticoagulant (Chi-squared test of association) are provided, but these do not account for confounding as in the multivariable logistic regression model.

Results

Baseline characteristics

A total of 430 procedures were carried out in 208 patients over a 6-year period. The majority of procedures (78%) were in female patients. The mean age was 60 years old (range, 21–91 years).

The indication for botulinum toxin A was recorded in 397 patients, with 250 (63%) being for idiopathic OAB and the remaining 147 for neuropathic OAB. The dose given was dependent on the indication and any previous dosing and was recorded in 351 procedures. The median dose of botulinum toxin A given to the patients with idiopathic OAB was 100 units, and it was 300 units for patients with neuropathic OAB.

Table 1. Anticoagulants/antiplatelet agents being taken by patients referred for intravesical botulinum toxin A injections

Category	Type of anticoagulant/antiplatelet	Number of patients	Total
Single AP	Aspirin	41	
	Clopidogrel	12	53
Dual AP	Aspirin + Clopidogrel	3	
	Aspirin + Ticagrelor	2	5
Warfarin	Warfarin	11	11
LMWH	Enoxaparin	2	
	Tinzaparin	2	4
DOAC	Apixaban	2	
	Dabigatran	2	
	Rivaroxaban	2	6

AP: antiplatelet; DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin

Table 2. Indications for anticoagulant/antiplatelet therapy in patients undergoing intravesical botulinum toxin A injections

Indication	Number of patients
Cerebrovascular disease	18 (23%)
Atrial fibrillation	12 (15%)
Ischemic heart disease	11 (14%)
Venous thromboembolism	6 (8%)
Valve disease	2 (2.5%)
Retinal artery occlusion	2 (2.5%)
Peripheral vascular disease	1 (1.25%)
Primary prevention	1 (1.25%)
Postoperative	1 (1.25%)
Migraine	1 (1.25%)
Not stated	24 (30%)

For data analysis, the number of procedures rather than the number of different patients was used as the denominator.

Anticoagulation

A total of 18% of the patients were receiving antiplatelet or anticoagulant therapy (79/430) (Table 1).

These were prescribed for a variety of indications but the majority of indications were cerebrovascular events or atrial fibrillation (Table 2). Unfortunately, in one-third of cases, the indication for antiplatelet/anticoagulant was not clear from the notes.

Complications

A total of 12 (3%) patients experienced a complication within 30 days after intravesical injection of botulinum toxin A (Table 3). Moreover, 4 other patients were recorded as not responding to treatment but were not included as complications because this did not fit the Clavien–Dindo grading system. A total of 11 complications were Clavien–Dindo grade I–II; 1 patient with urosepsis required intensive treatment unit support and is, therefore, grade IV. This patient was on dual antiplatelet therapy (aspirin and ticagrelor), but the complication was not related to bleeding. Because there is only 1 procedure performed in a patient on ticagrelor (a potent antiplatelet), it is impossible to determine if this is a specific independent risk factor for high-grade complications.

There were no reported incidents of allergic reaction or weakness, which correlates to the reported low risk of systemic side effects with intravesical injection.

Relationship between antiplatelet/anticoagulant and complications

In total, 8 of the 351 procedures in patients who were not on antiplatelet/anticoagulant medications resulted in a complication (2%). Moreover, 5 procedures in patients who received antiplatelets/anticoagulants experienced a complication (6%; 5/79). Although less adverse events were recorded after the procedures were performed on those who received antiplatelets/anticoagulants, the percentage is higher owing to the relatively low numbers of patients on these medications. A summary of complications by age, sex, and complication is shown in Table 4, and Figure 1 demonstrates the total complications subdivided by antiplatelet/anticoagulant use. Table 4 suggests the evidence for an association between antiplatelet/anticoagulant use and complications (p=0.05 from the Chi-squared test), although this does not control for age/sex. Complications were over 3 times more likely in those who underwent the procedures while on antiplatelets/anticoagulants (OR=3.233). There was some evidence that this association is at the population level (95% confidence interval=0.873, 11.38; p=0.067), although this falls outside the nominal threshold of statistical significance. The confidence in-

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Table 3. Total complications in patients undergoing intravesical injection of botulinum toxin A

Complication	Clavien–Dindo grade	Number of patients	Total
Hematuria	II		
Anticoagulated		4	
Nonanticoagulated		0	4
UTI	II		
Anticoagulated		0	
Nonanticoagulated		2	2
Urosepsis	IV		
Anticoagulated		1	
Nonanticoagulated		0	1
Retention	II		
Anticoagulated		0	
Nonanticoagulated		4	4
Pain	I		
Anticoagulated		0	
Nonanticoagulated		1	1
			12

UTI: urinary tract infection

Table 4. Summary of complications by age, sex, and whether and which anticoagulants were taken

	No n=418 (%)	Yes n=12 (%)	p
Age	60.3 (13.4)	63.0 (15.2)	0.554
Sex			0.305
Female	328 (78.5)	8 (66.7)	
Male	90 (21.5)	4 (33.3)	
Anticoagulant			0.050
No	344 (82.3)	7 (58.3)	
Yes	74 (17.7)	5 (41.7)	
Anticoagulant type			0.044
None	347 (83.0)	7 (58.3)	
Antiplatelet	52 (12.4)	3 (25.0)	
Warfarin	9 (2.15)	2 (16.7)	
DOAC	6 (1.44)	0 (0)	
LMWH	4 (0.96)	0 (0)	

DOAC: direct oral anticoagulant; LMWH: low-molecular-weight heparin

terval was wide at this instance, which was expected because only 12 patients showed complications.

All the 4 bleeding complications occurred with antiplatelets/anticoagulants (Figure 2). Moreover, 2 reported postprocedure hematuria episodes in the antiplatelet/anticoagulant group were in the same patient on warfarin; therefore, although reported here as a complication, it was not significant to prevent this patient from continuing the treatment. In fact, 4 complications were observed in patients who had a repeat procedure. The patients who were not on antiplatelets/anticoagulants and had UTI/retention did not experience a complication in the subsequent procedure. The patient on warfarin had intermittent hematuria after 2 intravesical botulinum toxin A procedures.

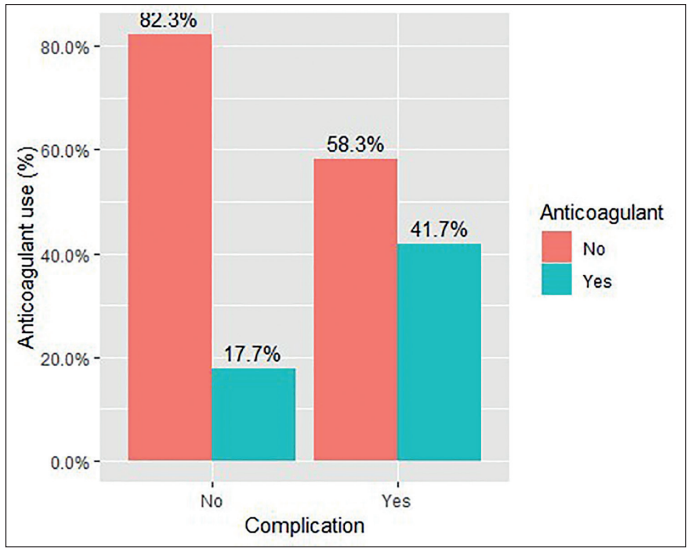

Figure 1. Complication rate subdivided by anticoagulant use

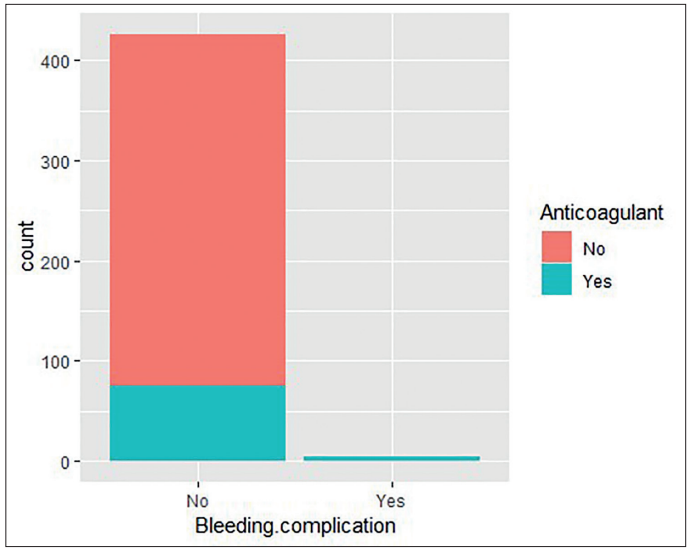

Figure 2. Number of bleeding complications subdivided by anticoagulant use

The dose given to these patients does not seem to be a factor because the 2 patients with bleeding complications had been given 100 units of botulinum toxin A and 2 received 200 units.

Considering different antiplatelets/anticoagulants as a factor, 2 patients with bleeding complications after procedures who were on antiplatelets/anticoagulants involved warfarin and other 2 patients involved antiplatelets; none were involved in the direct oral anticoagulant group (Figure 3).=

Other factors relating to complications

We also considered indication for botulinum toxin A, dosing, and subsequent complications. This further reduced the numbers, making the formal data analysis difficult.

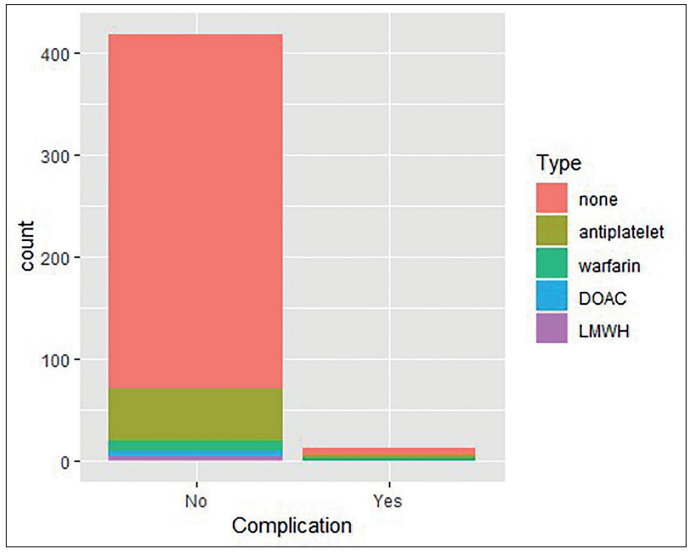

Figure 3. Complication rate subdivided by whether and which anticoagulant was used

The indication for botulinum toxin A was recorded in 397 patients. In total, 54 (22%) from the group receiving botulinum toxin A for idiopathic OAB symptoms and 21 (14%) from the group with neuropathic OAB were on antiplatelet/anticoagulant medications. A total of 6 complications occurred in the group receiving botulinum toxin A for idiopathic OAB; 2 of these were bleeding complications and 4 were other complications (AUR and pain). Moreover, 6 complications also occurred in the neuropathic OAB group, 2 bleeding and 4 other complications (infection and AUR). This does not support an increased risk in 1 particular group of patients regarding indication for botulinum toxin A.

The dose given at the time of the procedure also does not seem to influence the overall subsequent complications. A total of 10/12 patients with complications had the dose recorded accurately in the operation note. The dose ranged from 100 to 300 units, with a median of 200 units. For bleeding complications, the dose given was 100 units in 2 patients and 200 units in the other 2. The complication that was the most likely to reflect a link between the dose and the number of complications is urinary retention. Unfortunately, the dose was not recorded in 2 patients with retention. The remaining 1 patient 100 units and the other had 200 units. Overall, 3 cases of AUR were in patients with idiopathic OAB and 1 in a patient with neuropathic OAB. AUR was more likely in male patients (75% occurred in male patients).

Discussion

Intravesical injection of botulinum toxin A is now included in the National Institute for Clinical Excellence guidance for both

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men and women with refractory OAB symptoms.[10,11] Of particular mention is the potential requirement to perform clean intermittent self-catheterization, while there is no mention of the risk of bleeding as a potential contraindication. However, when undertaking any procedure, we must take into account the individual comorbidities to fully counsel the regarding risks.

In this study, the average age of 60 years and the female preponderance fit within the standard population receiving intravesical botulinum toxin A.[3]

According to a national statistics survey, 5% of women and 8% of men were prescribed an antiplatelet agent in 2015/2016,[12] and 17,000 prescriptions in 1 month during 2015 were for anticoagulants.[13] Antiplatelet/anticoagulant therapy is often prescribed for potentially life-threatening and life-changing conditions. In some, stopping anticoagulation can cause a life-threatening thrombus. They, therefore, need to be carefully managed perioperatively to avoid both thromboembolic and bleeding events. It has been reported that 90% of bleeding occurs during the first 4 postsurgical days. In a study evaluating a variety of procedures, it was found that aspirin increases the bleeding without reducing the arterial thrombotic events compared with placebo,[14] but this is not necessarily the case in patients who require antiplatelets/anticoagulants for other diseases. Aspirin was the most common agent encountered here (52%), with cerebrovascular disease being the most common indication. There is a risk of cerebrovascular accident if anticoagulation for atrial fibrillation is ceased, and this should be done with caution.

There are 4 principles for managing antiplatelets/anticoagulants perioperatively: 1) defer surgery until antithrombotic agents are not needed, 2) stop the antithrombotic agents before surgery and restart after, 3) continue through the surgical procedure, or 4) administer alternatives with less risk of bleeding ("bridging").[15] This often requires liaising with other specialties, which can delay the procedure. Reversal of warfarin can be difficult, requiring monitoring and, in some cases, admission. Recommencing warfarin postoperatively and providing monitoring until they reach therapeutic anticoagulation can be unreliable. All of this can be avoided if a patient is able to continue antiplatelets/anticoagulants while undergoing a procedure. The European Association of Urology has provided some recommendations regarding these issues but not specifically for intravesical botulinum toxin A.[15] There is a definite risk to patients in stopping/changing the anticoagulant therapy perioperatively (both from triggering embolic/thrombotic events and from potential adverse reactions to new prophylactic medications), but no clear indication has been provided in the literature about the risks of continuing their medications for botulinum toxin A injection.

When deciding which path to follow, it is important to know the relative bleeding risk of certain procedures. Since the licensing of intravesical botulinum toxin A injection in 2012, there has been no specific advice, and the decision to discontinue the antiplatelets/anticoagulants has been subject to local guidance and risk/benefit consideration for the individual patient, with no available literature to guide this decision. The risks of bleeding in general after the procedure are reported as 3.6%–21%.[3-5]

Here the risk of a bleeding complication requiring medical attention was 1% (5% of patients on antiplatelet/anticoagulant treatment). These numbers are well within those reported in the literature, in which anticoagulated patients are excluded,[3,4] implying no additional risk if a patient continues their antiplatelet/anticoagulant therapy during their treatment. In addition, multivariate logistic regression analysis demonstrated an increase in the complication risk within this patient group, but this failed to reach statistical significance because of the small number of complications overall. Finally, where complications did occur, these were predominantly Clavien–Dindo grade I–II and did not require surgical intervention. This is supported by the patients who experienced a complication and still received further botulinum toxin A injections.

The overall risk of urinary retention was also approximately 1%, less than expected. This might be underreported because all the patients were taught intermittent self-catheterization preoperatively and would have a supply of catheters at home, implying that they may not seek medical help. This may not have been recorded in the follow-up letters and, as this is a retrospective audit, it could not be accurately assessed with questionnaires because some patients were reviewed 6 years postprocedure.

Collectively, these findings demonstrate that intravesical botulinum toxin A injection is safe within this cohort who continues antiplatelets/anticoagulants, although the patients should be adequately counseled regarding the increase in risk of mild postoperative complications before giving informed consent.

The major strength of this study is that it explores a question for which there is currently a paucity of evidence within the published literature. However, the findings are limited by a number of potential sources of bias, including its retrospective nature. Although the study is informative in itself, the low number of complications within the cohort provides limited statistical power to detect the associations. However, it is probable that with a larger dataset, the increased risk of complications among the anticoagulated patients would achieve statistical significance. Furthermore, large and ideally prospective studies are, therefore, required to increase the power, and they will enable us to address the question of the bleeding risk specifically.

In conclusion, this is the first study to confirm that intravesical botulinum toxin A injection is a safe and well-tolerated proce-

dure in patients on anticoagulant medication. Although these patients are at an increased risk of postoperative complications, the rate remains low and the complications are mild. This, at the very least, enables a more informed consent process for these patients.

A wider discussion regarding the policy should be encouraged with other centers participating in further data analysis. Sharing data could improve the statistical power and enable a more rigorous patient counseling. A multicenter agreement on a pathway to standardize the practice will also potentially pave the way for randomized controlled trials if there is a consensus that continuing the antiplatelets/anticoagulants during botulinum toxin A treatment is a safe practice.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Audit Department of Morriston Hospital (Audit number 1718106).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.K., A.Y.; Design – G.K., A.Y.; Supervision – G.K.; Resources – G.K., A.Y.; Materials – G.K., A.Y.; Data Collection and/or Processing – H.W., O.L., A.S.; Analysis and/or Interpretation –H.W., A.S.; Literature Search – H.W., O.L.; Writing Manuscript – H.W., N.B.; Critical Review – H.W., G.K., A.Y.; Other – H.W., G.K.

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