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BOTULINUM TOXIN: INDICATIONS IN UROLOGY

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ABSTRACT

Background: Overactive bladder (OAB) is a syndrome characterised by urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology. Neurogenic detrusor overactivity (NDO) is secondary to a neurological dysfunction, either congenital or acquired, that may determine the occurrence of urinary symptoms similar to OAB's. Both conditions have negative impact in the health-related quality of life of the patients causing reduced work productivity, poorer quality of sleep and higher rates of anxiety and depression.

Objectives: To assess the safety and effectiveness of intravesical botulinum neurotoxin (BoNT) injections in patients with OAB and NDO along with number of injections, the dosage and the adverse effects (AE). Additionally, a demographic characterisation of the studied population was performed.

Methods: A retrospective study was conducted at the Urology and Renal Transplantation Department, Coimbra University Hospital Center with the patients with OAB and NDO submitted to BoNT injections between January 1st of 2015 and December 31st of 2018. Statistical analysis was performed using SPSS, 26.0.

Results: The number of patients was 133: 76,7% women and 23,3% men. The average age was 64,5 ± 15,24 years. Regarding the diagnosis, 71,4% had OAB while 28,6% had NDO.

The mean number of injections per patient was 1,83 ± 1,08 (min 1; max 6) and 50,4% of the patients underwent more than 1 injection. The mean BoNT dose used was 124,83 ± 42,96 for OAB and 190,43 ± 20,48 for NDO. AE occurred in 7%. The average time between treatments was 13,15 ± 5,77 months for OAB and 12,41 ± 5,79 for the neurogenic group. At the end of the study, 70,7% maintained the treatment, 7,6% suspended and 3,8% were discharged.

Discussion: Comparing OAB and NDO, statistically significant relationships were found in the mean number of injections ($p<0.001$) and in the mean BoNT dose used ($p<0.001$). A statistically significant difference was also found between the interval between the first two treatments and the interval between the second and third injections ($p=0,027$). There were no statistically significant differences between the maintenance or suspension of treatment or hospital discharge considering the diagnosis, the gender or the age of the patients.

Conclusion: BoNT injections are a safe and valuable treatment for OAB and NDO, regardless of the age of the patients. AE related to the procedure are uncommon. NDO patients needed more injections to control the symptoms and therefore a longer treatment.

Keywords: overactive bladder; neurogenic; idiopathic; detrusor overactivity; botulinum neurotoxin; urinary incontinence.

RESUMO

Introdução: A Bexiga Hiperativa (OAB) é um síndrome caracterizado pela presença de urgência urinária, geralmente acompanhada de aumento da frequência diária e noctúria com ou sem incontinência urinária de urgência, na ausência de infeção do trato urinário ou de outra patologia evidente para estes sintomas. A hiperatividade neurogénica do detrusor (NDO) é secundária a uma disfunção neurológica, quer congénita como adquirida, que pode condicionar a existência de sintomas urinários semelhantes à OAB. Ambas as condições têm um impacto negativo na qualidade vida relacionada com a saúde causando diminuição da produtividade no trabalho, sono não reparador e taxas altas de ansiedade e depressão.

Objetivos: Avaliar a segurança e efetividade das injeções intravesicais de toxina botulínica (BoNT) em doentes com OAB e NDO, bem como o número de injeções, a dose utilizada e os efeitos adversos (AE). Adicionalmente, foi realizada uma caracterização demográfica da população estudada.

Métodos: Foi conduzido um estudo retrospetivo no Serviço de Urologia e Transplantação Renal, do Centro Hospitalar da Universidade de Coimbra com os doentes com OAB e NDO submetidos a injeções de BoNT entre o dia 1 de janeiro de 2015 e 31 de dezembro de 2018. A análise estatística foi realizada utilizando o SPSS, 26.0.

Resultados: O número de doentes era 133: 76,7% mulheres e 23,3% homens. A idade média era de 64,5133 ± 15,24 anos. Quanto à etiologia, 71,4% tinham OAB enquanto que 28,6% tinham NDO. O número médio de injeções por doente foi de 1,83 ± 1,08 (min 1; max 6) e 50,4% dos doentes foram submetidos a mais de 1 injeção. A dose média de BoNT usada foi de 124,83 ± 42,96 nos casos de OAB e 190,43 ± 20,48 para a NDO. Os AE ocorreram em 7%. O tempo médio entre tratamentos foi de 13,15 ± 5,77 meses para a OAB e 12,41 ± 5,79 para o grupo com distúrbio neurogénico. No fim do estudo, 70,7% mantiveram o tratamento, 7,6% suspenderam e 3,8% tiveram alta médica.

Discussão: Comparando os subgrupos com OAB e NDO, foram encontradas relações estatisticamente significativas no número médio de injeções ($p<0,001$) e na dose média de BoNT usada ($p<0,001$). Foi também encontrada diferença estatisticamente significativa entre o intervalo entre os primeiros dois tratamentos e intervalo entre a segunda e terceira injeções ($p=0,027$). Não foi encontrada diferença estatisticamente significativa entre a manutenção ou suspensão do tratamento ou alta médica tendo em conta o diagnóstico, o género ou idade dos doentes.

Conclusão: As injeções de BoNT são seguras e constituem um tratamento de grande importância para a OAB e NDO, independentemente da idade dos doentes. Os AE

relacionados com o procedimento são incomuns. Os doentes com NDO necessitaram de mais injeções para controlar os sintomas e, consequentemente, de um tratamento mais longo.

Palavras-chave: bexiga hiperativa; neurogénica; idiopática; hiperatividade do detrusor; toxina botulínica; incontinência urinária.

INTRODUCTION

Overactive bladder (OAB) is a syndrome defined by the International Continence Society (ICS) as “urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology” (1).

Detrusor overactivity (DO) is linked to OAB and is an urodynamic observation that consists in involuntary detrusor contractions during filling cystometry, which may be spontaneous or provoked (1,2). According to the ICS, DO can also be categorised in two subgroups: neurogenic, if there is evidence of a relevant neurological cause like Parkinson disease, multiple sclerosis, spinal cord injury or congenital conditions (1,3); or idiopathic, if there is no associated identifiable disease (2,3).

Neurogenic detrusor overactivity (NDO) frequently occurs in patients with neurological conditions, who usually also have vesicourethral function impairment (4,5). These patients can also experience symptoms of frequency, urgency or urge urinary incontinence (6). While OAB is a clinical diagnosis, in the evaluation of NDO is essential to conduct an urodynamic study, in order to assess the underlying neurological dysfunction and, therefore, to ascertain the appropriate treatment (1,6). NDO patients have a higher risk of urological complications such as hydronephrosis, vesicourethral reflux, urolithiasis or urosepsis (6). Therefore, the main goal managing NDO patients is to preserve the upper urinary tract function (4,6).

Both conditions pose a negative impact in the health-related quality of life of the patients causing reduced work productivity, poorer quality of sleep and higher rates of anxiety and depression (7).

The initial standard treatment consists in patient education and behavioural modifications including reduced intake of caffeine and alcohol, scheduled voiding and pelvic floor muscle strengthening (8). If this approach is not effective, it is necessary to implement medical treatment.

The first-line pharmacological treatment consists of antimuscarinic agents (9). Although they are effective controlling the symptoms, they are frequently discontinued due to adverse effects (AE) including dry mouth, constipation, drowsiness and blurred vision (9,10).

Alternatively, a β_3-adrenoreceptor agonist has also been used on the management of OAB and NDO symptoms. As reviewed by Deeks and Allison and Gibson, the effectiveness of this agent is consistent, but with less AE, when compared with antimuscarinic drugs (11,12).

When the conventional pharmacological therapies are not effective, there are third-line treatments including neuromodulation and intravesical botulinum toxin injections (9).

Neuromodulation consists in an external electrical impulse that stimulates the sacral nerve plexus to regulate bladder and pelvic muscles function. It can be done by peripheral tibial nerve stimulation or by sacral neuromodulation with an implanted electrical pulse generator (9,13).

Furthermore, intravesical botulinum toxin injections are also a minimally invasive third-line procedure for OAB and NDO treatment. Botulinum neurotoxin (BoNT) is produced by the gram-positive anaerobic bacteria *Clostridium botulinum* and there are seven different serotypes (A-G). Botulinum neurotoxin A (BoNT/A) is the most frequently used in the urologic field whether the use of the other serotypes in this area is not approved (14,15). BoNT/A is composed of a 100kDa heavy chain polypeptide linked by a disulphide bond to a 50kDa light chain (15,16). BoNT/A mechanism of action consists of inhibition of acetylcholine release from the pre-synaptic membrane, resulting in a neuromuscular blockage and temporary muscular acontractility (4). Besides, it is suggested BoNT/A inhibits the release of other neurotransmitters and neuropeptides and has a down-regulating role in the expression of purinergic and capsaicin receptors on afferent neurons within the bladder (15). In addition, it is described a central nervous system effect through retrograde axonal transport, resulting in an attenuation of central sensitisation, meaning BoNT/A does not only present a peripherical action (17).

BoNT/A injections can be performed as an outpatient procedure. First, the patients should be screened for urinary tract infections (UTI) and acute urinary retention (AUR). The injections are then performed using a flexible or rigid cystoscope after instillation of lidocaine gel into the bladder (18). Often it can be performed in a day case setting, under general anaesthesia (19). The most common AE are site injection pain, UTI, AUR, mild haematuria, increased post-void residue and *de novo* intermittent self-catheterisation (8,20).

However, BoNT injections are usually well tolerated with low incidence of AE. This procedure has been proved to be effective on the management of refractory symptoms and should be considered in both NDO and OAB (5,21).

The objective of this study was to review the experience with BoNT injections at Urology and Renal Transplantation Department, Coimbra University Hospital Center between January 2015 and December 2018.

METHODS

The present work is a retrospective study conducted at Urology and Renal Transplantation Department, Coimbra University Hospital Center with patients with OAB and NDO submitted to BoNT injections between January 1st of 2015 and December 31st of 2018.

There were selected 172 patients of which 39 were excluded, because it was not possible to access their medical files.

The medical information collected from the 133 remaining patients was organised in a database. The data collected from the medical files included the gender and age of the patients, the diagnosis, the number of injections of each patient and the respective BoNT doses used, as well as the time interval between procedures; the reported adverse effects related to the procedure and the outcome at the end of the study were also collected.

Statistical analysis was performed using SPSS software version 26 for Microsoft Windows. The Chi-square test, independent-samples T-test, Mann-Whitney U, Z score and one-way ANOVA were applied to assess statistical significance. A p-value <0,05 was considered statistically significant.

RESULTS

From a sample of the eligible 133 patients, 102 (76,7%) were women and 31 (23,3%) were men. The mean age of the patients was 64,50 years with a standard deviation (SD) of 15,24 years (**Figure 1**). The minimum age was 23 years, whereas the maximum was 89 years old. The total number of procedures was 243.

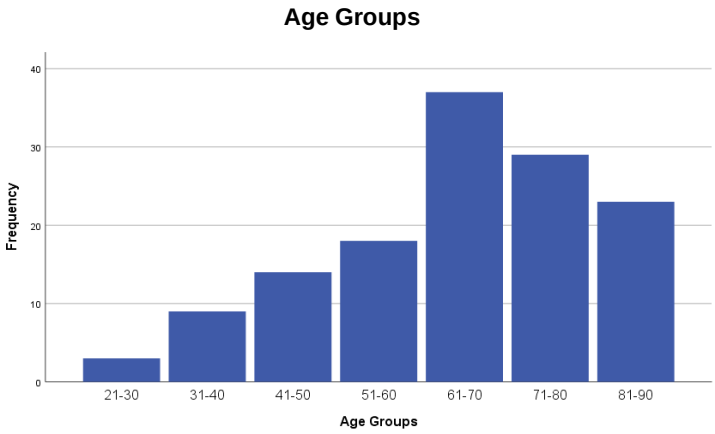

Figure 1. Frequency of the number of patients by age group

The relative percentage of women and men by age group was calculated. It was found that, in this sample, there was no statistically significant difference between the gender and the age group through the z-score (**Table 1**).

Table 1. Relative percentage of women and men by age group

		Age Groups						
		21-30	31-40	41-50	51-60	61-70	71-80	81-90
Gender	Feminine	1.5%	6.0%	9.8%	9.8%	21.8%	18.0%	9.8%
	Masculine	0.8%	0.8%	0.8%	3.8%	6.0%	3.8%	7.5%

Regarding the aetiology, 71,4% of the patients had OAB and 28,6% had NDO. Within NDO, the most frequent causes were spinal cord injury (8,3%) and multiple sclerosis (8,3%), followed by spina bifida (2,3%) and syringomyelia (2,3%); 3,2% had other neurological causes such as spinal cord infarction, infiltrative tumours of the neuroaxis, cerebrovascular disease or Parkinson's disease; in 4,5%, it was impossible to ascertain the neurological cause (**Figure 2**).

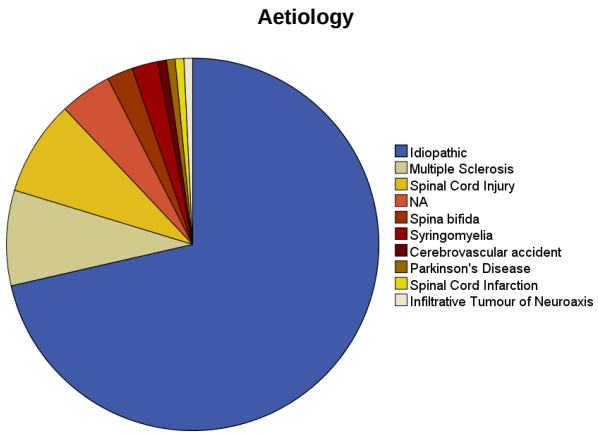

Figure 2. Percentage of different aetiologies

Concerning the BoNT dose, the mean number of units used for OAB patients was 124,83 with an SD of 42,96 and for NDO patients was 190,43 with an SD of 20,48. Through the Mann-Whitney U test it was verified that there were statistically significant differences between the groups aforementioned ($p<0.001$).

The mean number of injections per patient was 1,83 with a SD of 1,08 and the minimum was 1 injection and the maximum was 6. The majority of patients (50,4%) were submitted to more than 1 injection. Within the subgroups, the mean number of injections was 1,58 with an SD of 0,78 for OAB and 2,45 with an SD of 1,43 for NDO (**Figure 3**).

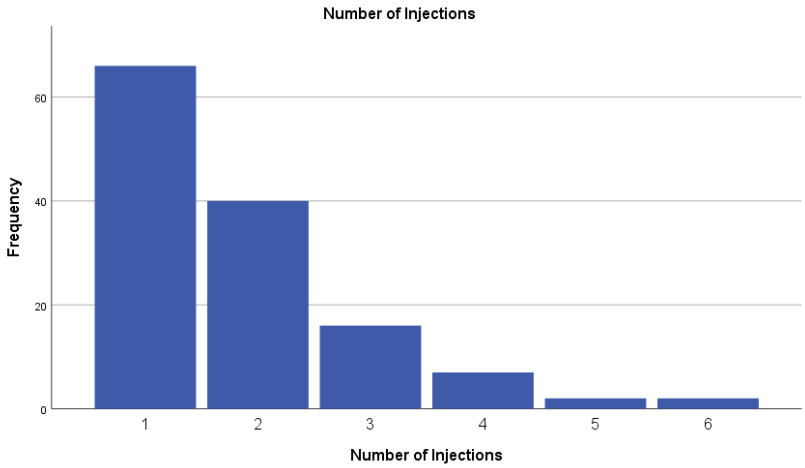

Figure 3. Frequency of the number of injections per patient

A Mann-Whitney U test was applied and it was found a statistically significant difference between the median number of injections for OAB and NDO ($p<0.001$).

Using the Chi-square test, it was verified that the age of the patients and the number of injections were unrelated (p=0.293) (**Table 2**).

Table 2. Statistical relationship between the patient's age and the number of injections

		Age groups		
		<=50	>50	Total
Number of injections	1	10	56	66
	>1	16	51	67
Total		26	107	133

Chi-square test (p=0,293)

Through the previously mentioned test, it was found that the number of injections was also unrelated with the patients' gender (p=0,385).

The average time between treatments was 13,15 ± 5,77 months (min 4; max 26) for OAB patients and 12,41 ± 5,79 months (min 4; max 34) for the neurogenic causes. However, through the independent-samples T-test, it was verified that the difference between these groups was not statistically significant (p=0,51). Among women, the average time between treatments was 12,86 ± 6,18 months (min 4; max 34), whereas in men was 12,85 ± 4,30 months (min 6; max 23). Considering the age, patients of 50 years or less had an average time between treatments of 13,5 ± 6,38 months (min 7; max 34); within patients above 50 years, the average time interval was of 12,57 ± 5,49 months (min 4; max 32). Using the independent-samples T-test, it was concluded that there was no influence of the gender (p=0,997) or age (p=0,437) of the patients in the time between treatments. The time interval when the BoNT dose used ranged from 100 units to 150 units was of 12,59 ± 5,17 months (min 4; max 26); conversely, with doses ranging from 200 to 250 units, the mean time interval was of 13,06 ± 6,23 months (min 4; max 34). There was no influence of the BoNT dose used on the time interval between treatments (p=0,670) (**Figure 4**).

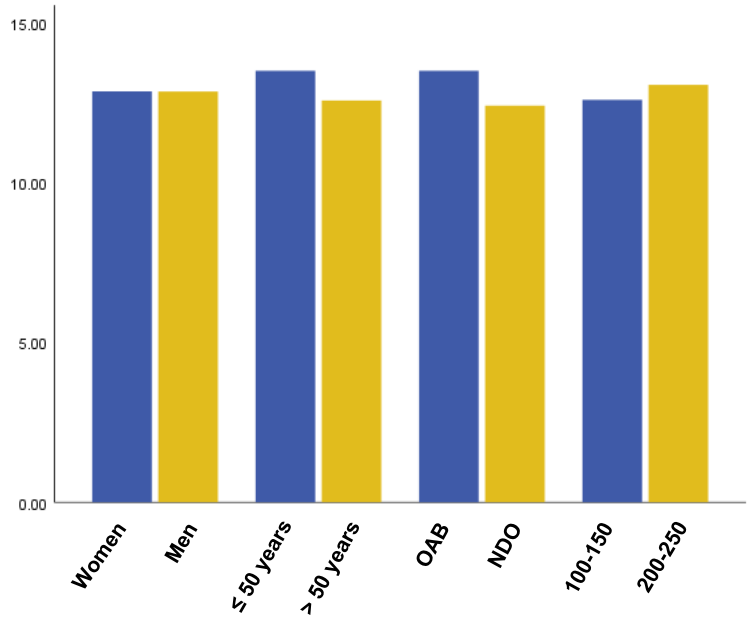

Figure 4. Average time between treatments in months for gender, age, diagnosis and BoNT dose

To assess differences in the average time between treatments, one-way ANOVA test was used. It was verified that there was a statistically significant difference between groups (p=0,015). In order to understand which of the specific groups differed, was applied a post-hoc analysis with Tukey's test that only showed a statistically significant difference between the first two treatments and the second and third injections (p=0,027).

Regarding AE related to BoNT administration, they occurred in 7% of the procedures; of which 4,5% reported UR, 1,6% UTI and 0,8% haematuria; in 93% of the procedures there were no complications associated with the procedure (**Figure 5**).

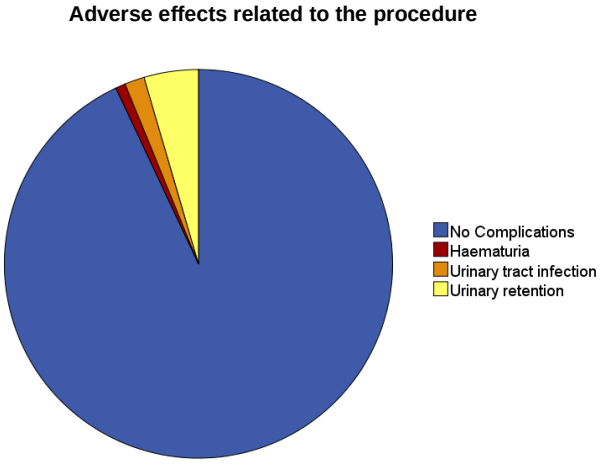

Figure 5. Percentage of adverse effects related to the procedure

Using the Chi-square test it was found the occurrence of AE was not influenced by the diagnosis (p=0.416) (**Table 3**).

Table 3. Statistical relationship between diagnosis and the occurrence of adverse effects

		Diagnosis		
		OAB	NDO	Total
Adverse effects	Yes	12	5	17
	No	137	89	226
Total		149	94	243

Chi-square test (p=0,416)

There were also found no correlations between the occurrence of AE and the gender (p=0,297) and between the occurrence of AE and the age of the patients (p=0,684).

Through the Chi-square test it was verified the occurrence of AE was unrelated to the BoNT dose used (p=0,190).

Using the test previously mentioned, it was verified there was no relationship between the number of injections and the occurrence of AE (p=0,167).

Regarding the different outcomes at the end of the study, 70,7% of the patients were still in treatment, 7,5% suspended BoNT injections and 3,8% had been discharged; in 18% of the patients was impossible to assess the outcome (**Figure 6**).

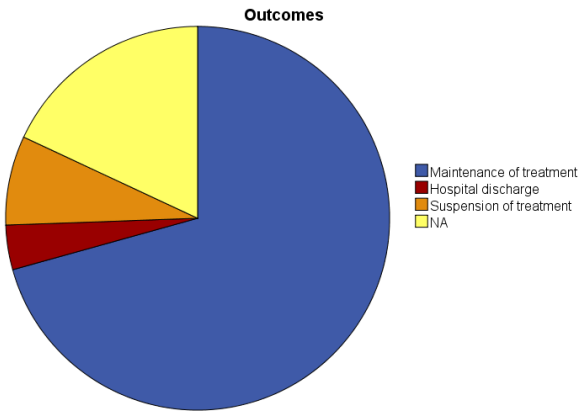

Figure 6. Percentage of the different outcomes at the end of the study

The reasons why patients suspended the treatment were the partial improvement of the symptoms, no significant benefit of the toxin when compared to anticholinergics or the switch to an alterantive treatment like neuromodulation; the medical discharges were due to poor general condition of the patients related to their comorbidities and advanced age. Through the

Chi-square test, it was verified that the gender did not influence the outcome (p=0,733), neither did the diagnosis (p=0,624) nor the age of the patients (p=0,212).

DISCUSSION

OAB is a syndrome characterised by the presence of urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.(1) Nevertheless, urgency urinary incontinence affects approximately one-third, mainly female (22).

NDO patients can also experience symptoms of frequency, urgency or urge urinary incontinence (6). Urodynamic studies are essential when evaluating patients with neurological diseases that affect the vesicourethral function, in order to assess the underlying neurological dysfunction and ascertain the appropriate treatment (1,6). NDO patients may have a higher risk of urological complications such as hydronephrosis, vesicourethral reflux, urolithiasis or urosepsis (6). Therefore, the main goals managing NDO patients is, not only the improvement of the health-related quality of life controlling the symptoms, but also to preserve the upper urinary tract function (4,6).

Furthermore, it is known that some OAB patients may have idiopathic detrusor overactivity (IDO) but in others this finding is not present (4).

The symptoms of OAB and NDO have been shown significatively associated with a decreased health-related quality of life and have a major impact in patients' daily activities coursing with social embarrassment and avoidance and limiting behaviour (5,21,23).

OAB is a common disorder, with a prevalence similar between both women and men, ranging from 10% to 20% in several studies in this area (8,24,25). At younger ages, OAB prevalence is suggested to be higher in women than men, but this difference seems to be attenuated as age advances (22). Also, it appears the prevalence usually increases with age, in both genders (10,23). However, the information on this topic is often discrepant probably due to the inconsistent definitions of OAB and NDO used between studies, showing the importance of terminology standardisation and its impact on epidemiological studies.

The patients eligible to this work were mainly women (76,7%) and the average age of the sample was 64,5 ± 15,24 years old. The percentage of patients was increasing up to the age of 70 years, as expected (13,25); and, although there was no statistically significant difference, the relative percentage of women is always higher than men, for all age groups. However, it is important to mention, as a limitation, that the study sample was obtained from medical records so only includes patients who sought medical help for this problem.

In this study, 71,4% of the patients had OAB. The remaining 28,6% had DO secondary to a neurological disease, such as spinal cord injury or multiple sclerosis. This is in accordance with several studies because, although OAB aetiology is complex and poorly understood, the vast majority of detrusor overactivity is idiopathic (9,19).

Regarding the dose range, some studies suggest patients with OAB benefit with dosage between 100-150 units while patients with NDO need higher doses (5,8,21). This information meets the results found in this study, where the average units used for OAB patients was 124,83 ± 42,96 and for NDO patients was 190,43 ± 20,48, with a statistically significant difference between the groups (p=0,000).

According to some authors, the benefits of BoNT injections can be seen from three to twelve months (26,27). In this study, the average time between treatments was 13,15 ± 5,77 months for the patients with OAB and 12,41 ± 5,79 months for those with NDO, without statistically significant differences between these groups. It is also described the duration of effect is usually dose-dependent (15,28). However, in this study was not found a relationship between the time inter-injections and the BoNT dose used (p=0.670). There was also no influence of the gender (p=0.997) or age of the patients (p=0.437) in the time between injections.

One-way ANOVA was used to assess differences in the average time between treatments; it was concluded there was a statistically significant difference between the groups (p=0,015) and through Tukey *post-hoc* was verified this difference only occurred between the first two treatments and the second and the third injections (p=0,027). Considering that, in this work, was not found a relationship between the studied variables and the time between injections, further studies would be needed to understand what may have caused this difference.

Concerning the number of treatments, the average number of injections per patient was 1,83 ± 1,08. Most patients underwent more than 1 injection. The mean number of injections was 1,58 ± 0,78 for OAB and 2,45 ± 1,43 for NDO. It was found a statistically significant difference between the median number of injections for each subgroup (p<0.001), concluding that patients with NDO needed, in average, a higher number of injections and therefore to maintain a longer treatment. In this study, it was not found a relationship between the number of injections with the gender or the age of the patients.

A meta-analysis showed that repeated treatments do not lead to a decrease in the effectiveness either clinical or from the urodynamic point of view; furthermore, there is no evidence of development of clinical intolerance towards the toxin (29).

AE occurred in 7% of the procedures. UR and UTI were the most reported, followed by haematuria. This is in line with several studies where these are the most commonly mentioned AE. Some systemic AE have been described as related to this procedure including constipation, transitory asthenia or dry mouth, but they are very infrequent and were also not observed in this study (19). AUR following BoNT injections is usually transient and requires temporary clean intermittent catheterisation until the patient returns to his prior voiding state (9,20). According to Duthie and colleagues, higher doses (300 units) were found to be

associated with higher rates of AE, specifically UR (19). However, in this study it was verified the occurrence of AE was unrelated to the BoNT dose used (p=0,190). This could be explained by the fact that, in the sample studied, there were no patients submitted to such high doses of BoNT. The occurrence of UTIs is usually associated with higher post-void residual volumes, but in this study this parameter was not evaluated (20,28). Haematuria often occurs in the first week after the procedure and is related to the injection itself; in general it is mild and self-resolving so no intervention is usually necessary (19,20).

Some studies suggested higher rates of AUR were related with the diagnosis, being more common in patients with NDO (15,30). That was not verified in this work, where the occurrence of AE was not related to the cause (p=0.416). On the other hand, the gender of the patients was also not related with AE observed, though Kuo *et al.* suggested that male gender was a risk factor for increased AE related to the procedure (31). Although BoNT injections have been proved to be safe in elderly, some authors described higher rates of AE in this age group, probably related to their comorbidities (26,32); however, in this study, the age of the patients did not influence the occurrence of AE (p=0,684).

Regarding the different outcomes assessed at the end of the study, most patients were still in treatment (70,7%); suspension of the injections occurred in 7,5% and 3,8% had been discharged; in 18%, it was not possible to assess the outcome. There were no statistically significant differences between the maintenance or suspension of treatment or hospital discharge considering diagnosis, gender or age of patients.

Although there are some noteworthy conclusions at this study, there are some limitations associated with retrospective studies that should be considered; namely, the data collected from medical records was dependent of an accurate record-keeping and the sample selection bias, as already mentioned above. Also, it would have been important to assess other variables such as tolerability of the patients towards the procedure, the urodynamic studies results when appropriate, the BoNT brand used and its costs and the satisfaction of the patients with this treatment when compared with other lines of treatment, as it has been described in the literature that these could provide interesting results (33–35).

Nevertheless, BoNT injections are a safe treatment for both OAB and NDO, regardless of the age of the patients, with low incidence of AE. Therefore, BoNT injections should be considered as an effective treatment in the management of patients with refractory symptoms.

REFERENCES

1. Haylen BT, Ridder D de, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/ International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction. Neurourol Urodyn. 2010;29:4–20.

2. Harris S, Rizzolo D. Botulinum toxin as a treatment for refractory overactive bladder. J Am Acad Physician Assist. 2016;29(2).

3. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61(1):37–49.

4. Karsenty G, Denys P, Amarenco G, De Seze M, Gamé X, Haab F, et al. Botulinum Toxin A (Botox®) Intradetrusor Injections in Adults with Neurogenic Detrusor Overactivity/Neurogenic Overactive Bladder: A Systematic Literature Review. Eur Urol. 2008;53(2):275–87.

5. Chancellor MB, Patel V, Leng WW, Shenor PJ, Lam W, Globe DR, et al. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2013;81(8):841–8.

6. Kennelly MJ, Devoe WB. Overactive Bladder : Pharmacologic Treatments in the Neurogenic Population Pharmacologic Treatments for Overactive Bladder. 2008;10(3):182–91.

7. Mckellar K, Bellin E, Schoenbaum E, Abraham N. Prevalence, Risk Factors, and Treatment for Overactive Bladder in a Racially Diverse Population. Urology. 2019;126:70–5.

8. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol. 2015;193(5):1572–80.

9. White N, Iglesia CB. Overactive Bladder. Obstet Gynecol Clin North Am. 2016;43(1):59–68.

10. Yamada S, Ito Y, Nishijima S, Kadekawa K, Sugaya K. Basic and clinical aspects of antimuscarinic agents used to treat overactive bladder. Pharmacol Ther. 2018;189:130–48.

11. Deeks ED. Mirabegron: A Review in Overactive Bladder Syndrome. Drugs. 2018;78(8):833–44.

12. Allison SJ, Gibson W. Mirabegron, alone and in combination, in the treatment of overactive bladder: real-world evidence and experience. Ther Adv Urol. 2018;10(12):411–9.

13. Leron E, Weintraub AY, Mastrolia SA, Schwarzman P. Overactive Bladder Syndrome: Evaluation and Management. Curr Urol. 2017;11(3):117–25.

14. Lew MF. Review of the FDA-Approved Uses of Botulinum Toxins , Including Data Suggesting Efficacy in Pain Reduction. 2002;142–6.

15. Hsieh PF, Chiu HC, Chen KC, Chang CH, Chou ECL. Botulinum toxin A for the treatment of

overactive bladder. Toxins (Basel). 2016;8(3):1–12.

16. Li B, Peet NP, Butler MM, Burnett JC, Moir DT, Bowlin TL. Small molecule inhibitors as countermeasures for botulinum neurotoxin intoxication. Molecules. 2011;16(1):202–20.

17. Papagiannopoulou D, Vardouli L, Dimitriadis F, Apostolidis A. Retrograde transport of radiolabelled botulinum neurotoxin type A to the CNS after intradetrusor injection in rats. BJU Int. 2016;117(4):697–704.

18. Irvine CA. Botox prescribing information. Allergan, Inc.; 2019.

19. Duthie J, Wilson DI, Herbison GP, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Libr. 2011;(12).

20. Leu R, Stearns GL. Complications of Botox and their Management. Curr Urol Rep. 2018;19(11):4–7.

21. Chapple C, Sievert KD, Macdiarmid S, Khullar V, Radziszewski P, Nardo C, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: A randomised, double-blind, placebo-controlled trial. Eur Urol. 2013;64(2):249–56.

22. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-Based Survey of Urinary Incontinence , Overactive Bladder , and Other Lower Urinary Tract Symptoms in Five Countries : Results of the EPIC Study. 2006;50:1306–15.

23. Fowler CJ, Auerbach S, Ginsberg D, Hale D, Radziszewski P, Rechberger T, et al. OnabotulinumtoxinA Improves Health-Related Quality of Life in Patients With Urinary Incontinence Due to Idiopathic Overactive. 2012;62:148–57.

24. Vaughan CP, Johnson TM, Ala-Lipasti MA, Cartwright R, Tammela TLJ, Taari K, et al. The Prevalence of Clinically Meaningful Overactive Bladder : Bother and Quality of Life Results from the Population-Based FINNO Study. Eur Urol. 2011;59(4):629–36.

25. Eapen RS, Radomski SB. Review of the epidemiology of overactive bladder. Res Reports Urol. 2016;8:71–6.

26. Kuo HC, Liao CH, Chung SD. Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: Risk factors and influence on treatment outcome. Eur Urol. 2010;58(6):919–26.

27. Brubaker L, Gousse A, Sand P, Thompson C, Patel V, Zhou J, et al. Treatment satisfaction and goal attainment with onabotulinumtoxinA in patients with incontinence due to idiopathic OAB. Int Urogynecol J. 2012;23(8):1017–25.

28. Dmochowski R, Chapple C, Nitti VW, Chancellor M, Everaert K, Thompson C, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: A double-blind, placebo

controlled, randomized, dose ranging trial. J Urol. 2010;184(6):2416–22.

29. Yokoyama T, Chancellor MB, Oguma K, Yamamoto Y, Suzuki T, Kumon H, et al. Botulinum toxin type A for the treatment of lower urinary tract disorders. Int J Urol. 2012;19(3):202–15.

30. Bauer RM, Gratzke C, Roosen A, Hocaoglu Y, Mayer ME, Buchner A, et al. Patient-Reported Side Effects of Intradetrusor Botulinum Toxin Type A for Idiopathic Overactive Bladder Syndrome. 2011;68–72.

31. Jiang Y-H, Ong H-L, Kuo HC. Predictive factors of adverse events after intravesical suburothelial onabotulinumtoxinA injections for overactive bladder syndrome - a real-life practice of 290 cases in a single center. Neurourol Urodyn. 2015;32(September).

32. Komesu YM, Amundsen CL, Richter HE, Erickson SW, Ackenbom MF, Andy UU, et al. Refractory urgency urinary incontinence treatment in women: impact of age on outcomes and complications. Am J Obstet Gynecol. 2017;218(1).

33. Sussman D, Patel V, Popolo G Del, Lam W, Globe D, Pommerville P. Treatment Satisfaction and Improvement in Health-Related Quality of Life With OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity. 2012;(December 2011).

34. Sahai A, Dowson C, Khan MS, Dasgupta P. Improvement in quality of life after bptulinum toxin-A injections for idiopathic detrusor overactivity. BJU Int. 2009;103:1509–15.

35. Reynolds WS, Fowke J, Dmochowski R. The Burden of Overactive Bladder on US Public Health. 2016;8–13.