

Case Report

“Incremental Syringe” A Novel, User-Friendly Syringe to Inject Botulinum Toxin with Improved Accuracy, Precision, and Ease

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Citation: Gillispie G, McLouth C, Brown P, Majid Mirzazadeh M (2019) “Incremental Syringe” A Novel, User-Friendly Syringe to Inject Botulinum Toxin with Improved Accuracy, Precision, and Ease. J Urol Ren Dis: JURD-1133. DOI: 10.29011/2575-7903.001133

Received Date: 18 December, 2018; **Accepted Date:** 09 January, 2019; **Published Date:** 15 January, 2019

Abstract

Purpose: Traditional syringes require users to visually estimate the volumes contained within. This is problematic as the user's vision can be required elsewhere, such as when viewing a monitor during onabotulinumtoxinA injections for the treatment of detrusor overactivity. Visual monitoring can also be insufficient for procedures requiring high accuracy and/or precision. An incremental syringe, which provides the user with audible and tactile feedback each increment, has been developed to resolve this problem. The purpose of this study was to compare the incremental syringe to a traditional syringe for accuracy and precision.

Methods: Fourteen volunteers dispensed eight consecutive 1.0 mL boluses of water using both syringe types and the weight of each bolus was recorded. This experiment was repeated for 14, 18, and 23-gauge needles.

Results: Bolus volumes were lower than intended by 3.0% and 2.4% for traditional and incremental syringes, respectively ($p = 0.030$). The coefficient of variation was 4.3% for the traditional syringe and 2.0% for the incremental syringe ($p < 0.001$). Lower variation both between and within operators was found for the incremental syringe by multiple analyses.

Conclusions: The incremental syringe's main advantage is its ease of use without visual monitoring. The results of this study indicate it is at least as accurate and precise as the syringes currently in use, if not more so, making it a promising medical device for the future

Keywords: Accuracy; Dosing; Feedback; Medical Device; Precision; Syringe

Introduction

Detrusor Overactivity (DO) is a common finding in both neurological disorders such as multiple sclerosis or spinal cord injuries and in other, non-neurological conditions. Patients with DO suffer from both an increased frequency and urgency of urination, high detrusor pressures, and incontinence. These symptoms both detract from patient quality of life and put the upper urinary tract at risk. Traditionally, anticholinergic treatments and more recently β_3 agonists are second line of treatment, after conservative measures

have failed. However, the common adverse side-effects and patient noncompliance remain major issues. More recently, minimally invasive intradetrusor injections of onabotulinumtoxinA (BOTOX, Allergan Inc.) has been added as the third line of therapy when neuromodulation medications fail, or a patient cannot tolerate them. These injections have been shown in multiple studies to successfully reduce DO and the associated urinary incontinence and as a result have gained widespread acceptance and usage [1,2].

Intradetrusor injection of onabotulinumtoxinA is an effective and overall easy procedure to perform in office or operating room setting. For this procedure, patients' bladders are

treated with a maximum of 30 independent 1 mL injections of onabotulinumtoxinA and saline [3]. These injections are spread across the bladder, approximately 2 mm deep and 1 cm apart, in equivalent 1 mL (or 0.5 mL) volumes excluding the trigone and bladder dome. Achieving the proper depth, spacing, and injection volume are all important to ensure a procedure's success [3]. The syringe must also be visualized to monitor injection volume. Simultaneous viewing of both the screen and the syringe is not possible, requiring assistance from nursing staff who may not have the proper space or angle of vision. This can result in both inaccurate injections and a high variance from one injection to the next.

Syringes are one of the most commonly used medical devices in the world today. They are cheap, simple, and widely accepted in medical practice. However, syringes have a major flaw which is often overlooked: the user is required to visually "eyeball" how much fluid has been aspirated or ejected. This can have negative consequences for the accuracy of dosage, the speed of the procedure, and the device's ease of use for many procedures. Once an excess of a medication is injected into the body, there is no way to bring it back. Certain medications can be dangerous if overdosed even by small amount while others lose their effectiveness if under-dosed [4-6]. The literature on syringe accuracy and precision is somewhat limited, but in general both have been found to decrease with smaller volumes and larger syringe sizes [7-9]. OnabotulinumtoxinA injections for DO represent a troublesome example for each of these considerations. The user's vision is required elsewhere, over- and under- dosing are both detrimental to the procedure, and a small volume is being repeatedly injected from a larger syringe.

An incremental syringe (Medallion IZOOff, MeritMedical, South Jordan, UT) has been designed and prototyped in an attempt to simultaneously improve on the accuracy and precision of current syringes while eliminating the need for visual monitoring during aspiration and injection (Figure 1). The incremental syringe provides tactile (a slight resistance) and audible (a "click") feedback after each increment. The plunger has added appendages which briefly increase the force required to advance the plunger upon entering the barrel of the syringe. Once this added resistance is overcome, the appendages make a clicking noise as they snap back into place. The syringe will then operate like a traditional syringe until the next increment/appendage is reached. In the case of onabotulinumtoxinA for overactive bladders, it has been proposed that the incremental syringe can increase dosage accuracy and precision, reduce procedural difficulty, reduce procedure time, and eliminate the need for an assistant. The aim of this study is to compare the accuracy and precision of a 10 mL incremental syringe with 1.0 mL increments to that of a traditional syringe of the same size for 1.0 mL injections.

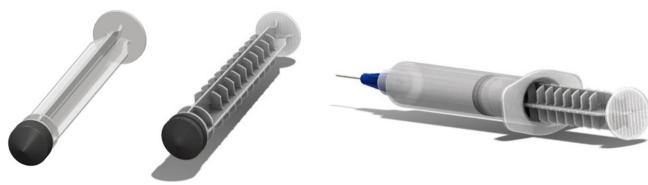


Figure 1: 3D rendering of a traditional syringe plunger (left), an incremental syringe plunger (center), and a syringe with an incremental plunger included (right).

Materials and Methods

This study used 10 mL BD Syringes [Becton, Dickinson and Company, Franklin Lakes, NJ]. Half of the syringes were converted from traditional to incremental syringes by switching out the original plunger with the prototyped incremental design (Figure 2). Fourteen volunteer graduate students served as syringe operators. For the incremental syringe, operators were instructed to rely on the audible and tactile feedback, although their vision was not physically restricted. Operators withdrew 9.0 mL of water and then injected it 1.0 mL at a time for eight consecutive milliliters. The first milliliter (from 10 to 9 mL) and the last milliliter (from 1 to 0 mL) were not used. Injections were done into a cup with a plastic wrap seal over the top to prevent splashing. Between each injection, weight was recorded using a Practum balance [Sartorius, Goettingen, Germany]. Afterwards, weight was converted to volume using the specific gravity of water, assumed to be 1000 mg/mL. In addition to the two syringe types, three needle sizes were also evaluated: 14, 18, and 23 gauges. Each operator performed the assessment for all needle size and syringe style combinations. The order of testing was randomized for each operator to minimize the effect of learning. However, because the operators were not healthcare professionals or regular syringe users, operators were given the opportunity to practice before testing to familiarize themselves with the syringes, the different needle sizes, and the new incremental plunger.



Figure 2: Photograph of traditional (left) and incremental (right) syringes with 14 (top), 18 (middle), and 23 (bottom) gauge needles.

Syringe accuracy is how well a syringe delivers a set volume. In this study it was quantified by measuring the error. Error was defined as the difference between the actual bolus volume and the intended volume, expressed as a percentage of the intended volume:

$$\text{Error (\%)} = \frac{\text{average bolus volume} - \text{intended volume}}{\text{intended volume}} * 100$$

Syringe precision is how consistently a syringe delivers the same volume, regardless of how accurate that volume is. In this study it was defined by the standard deviation of a set of injections:

$$\text{Standard Deviation} = \sqrt{\frac{\sum(\text{single bolus volume} - \text{average bolus volume})^2}{\text{Number of boluses}}}$$

Standard deviation is also sometimes normalized by the average volume and reported as a coefficient of variation. This is useful in order to compare precision across different bolus volumes and was defined in this study as:

$$\text{coefficient of variation (\%)} = \frac{\text{standard deviation of bolus volumes}}{\text{average bolus volume}} * 100$$

It is important to note that the absolute value of error is negatively related to accuracy and both standard deviation and coefficient of variation are negatively related to precision. For example, a large magnitude error represents a low accuracy and a high standard deviation represents a low precision. Data was analyzed using SAS software (Version 9.4, SAS Institute Inc., Cary, NC). An alpha level of $p < 0.05$ was considered statistically significant unless stated otherwise. Mixed models were used to simultaneously determine the impact of syringe type and needle gauge on accuracy while controlling for the presence of non-independent observations (i.e., each operator performed multiple injections). Follow-up comparisons were used to better characterize the difference between syringe type and needle gauge. Tests for homogeneity of variance were used to determine differences in precision between syringe types and needle gauges. To make comparisons within and across operators, needle size was ignored and data from different gauge needles were pooled together. To compare between syringe types within each individual operator, a t-test was used to test for accuracy (i.e., mean difference) while an F-test was used for precision (i.e., equality of variances). Since this was done for every operator, a Bonferroni correction was applied to control for multiple comparisons (14 comparisons; corrected alpha level = 0.0036). A Sign Test was also conducted to examine the effect of syringe type at the operator level. Lastly, analyses were

carried out to see if the incremental syringe reduced the variation between operators for accuracy and precision. For accuracy, a one-way ANOVA was carried out between operators for both the incremental and traditional syringe with a post-hoc Tukey's HSD test if applicable. Differences in operator accuracy were further analyzed by averaging the accuracies of each individual operator and using this average as a single value. An F-test was applied to the group of averages to test if the variation between operators was the same for both syringe types. An F-test was also conducted for the incremental and traditional syringe separately on the individual operators to investigate if precision varied significantly between operators.

Results

In all, 8 measurements were made per test, 48 per operator, 224 per needle size, 336 per syringe type, and 672 in total. The average bolus volume was 0.97 ml which is 3% lower than the intended volume. Under dosing was common, with only 10.0% of injections being greater than 1.0 ml. Overall, the incremental syringe was more accurate than the traditional syringe ($p = 0.030$). This difference is non-significant when analyzing 14 gauge ($p = 0.189$), 18 gauge ($p = 0.216$), and 23 gauge ($p = 0.221$) needle sizes separately due to the loss of statistical power. The standard deviation of bolus volumes, which was used as a proxy for precision, was approximately three times higher for the traditional syringe than for the incremental syringe ($p < 0.001$). This remains true when analyzing 14 gauge ($p < 0.001$), 18 gauge ($p < 0.001$), and 23 gauge ($p < 0.001$) needle sizes separately. Needle size did not affect accuracy ($p = 0.775$) or precision ($p = 0.603$) for the traditional syringe. Similarly, needle size had no effect on the accuracy ($p = 0.425$) or precision ($p = 0.094$) of the incremental syringe. These results are summarized in (Tables 1, 2).

	Mean Volume [mL] (Error [%])		p value
	Traditional Syringe	Incremental Syringe	
14 Gauge Needle	0.9682 (-3.2%)	0.9739 (-2.6%)	0.189
18 Gauge Needle	0.9720 (-2.8%)	0.9774 (-2.3%)	0.216
23 Gauge Needle	0.9708 (-2.9%)	0.9762 (-2.4%)	0.221
p value	0.775	0.425	
All Needle Sizes	0.9703 mL (-3.0%)	0.9758 mL (-2.4%)	0.030

Table 1: Accuracy of Traditional and Incremental Syringes with various needle sizes.

	Volume S.D. (Coefficient of Variation [%])		
	Traditional Syringe	Incremental Syringe	p value
14 Gauge Needle	0.0346 (3.6%)	0.0109 (1.1%)	<0.001
18 Gauge Needle	0.0461 (4.7%)	0.0282 (2.9%)	<0.001
23 Gauge Needle	0.0443 (4.6%)	0.0181 (1.9%)	<0.001
p value	0.603	0.094	
All Needle Sizes	0.0417 (4.3%)	0.0191 (2.0%)	<0.001

Table 2: Precision of Traditional and Incremental Syringes with various needle sizes.

To examine the effects of syringe type within individual users, data was pooled by needle size and separated by operator. No individual's accuracy showed a statistically significant difference between syringe types. However, 11 out of the 14 operators showed better precision with the incremental syringe ($p < 0.001$ for each). A Sign Test was also conducted and, in terms of absolute magnitudes, 13 of 14 operators were more accurate with the incremental syringe ($p = 0.0018$), (Figure 3) and 13 of 14 were more precise with the incremental syringe ($p = 0.0018$), (Figure 4). Comparisons across individuals were made for both syringe types to see if the incremental syringe reduced differences in accuracy and precision between individuals. As seen in (Figure 3), operator error had a range of 4.7% (from -4.2% to +0.5%) for the traditional syringe and 0.8% (from -2.8% to -2.0%) for the incremental syringe. For the traditional syringe, a one-way ANOVA with a post- hoc Tukey's HSD test revealed one user (operator 14) was found to have a significantly different accuracy when compared to the other operators ($p = 0.0341$). The same analysis done on the incremental syringe showed no differences in accuracy between operators ($p = 0.951$). To investigate further, all injections were grouped by syringe type and operator and then averaged in order to assign each operator one error value for the traditional syringe and one for the incremental syringe. An F-test comparing the variability of these averages for the two syringe types ($n = 14$) revealed significantly lower variation between the incremental syringe averages when compared to the traditional syringe averages ($p < 0.001$). Precision was also found to be more consistent between operators for the incremental syringe compared to the traditional syringe (Figure 4). Operator precision, measured as coefficient of variation, had a range of 7.1% (from 1.8% to 8.9%) for the traditional syringe and 4.1% (from 0.9% to 5.0%) for the traditional syringe. Levene's test for Homogeneity showed

the variance of operators' injections to be significantly different from each other when comparing across the traditional syringe ($p = 0.003$). The same test found no significant differences between operators for the incremental syringe, although this was trending towards significance ($p = 0.053$).

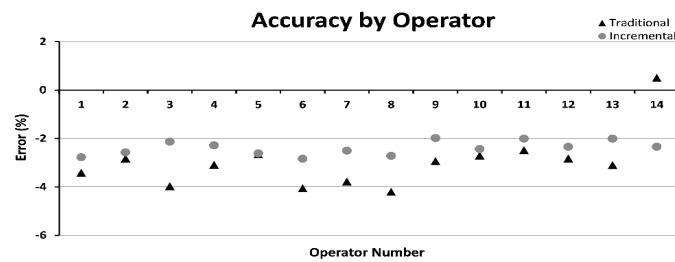


Figure 3: Accuracy for traditional versus incremental syringes, separated by individual operators and pooled by needle size.

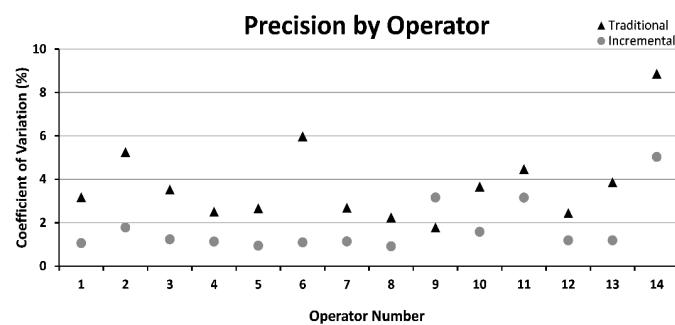


Figure 4: Precision for traditional versus incremental syringes, separated by individual operators and pooled by needle size.

Discussion

The International Organization for Standardization (ISO) requirements for syringe accuracy currently stand within approximately 5% of the intended volume [10]. Both the traditional and incremental syringes were within ISO standards at -3.0% and -2.4%, respectively. When examining this study's results for the traditional syringe alone, accuracy and precision were similar or slightly improved compared to previous studies. Only one previous study has tested 1.0 mL injections by a traditional 10 mL syringe and found an error of -3.0% and a coefficient of variation of 4.3%, both of which were the same for the traditional syringe in this study [7]. Needle size did not affect accuracy or precision for the either syringe type. Resistance to flow in a tube is largely a function of the tube's diameter. One concern regarding the incremental syringe's design was that if fluid resistance was too high, operators would not be able to distinguish the increased resistance at each increment from the resistance to fluid flow. There were also concerns that if fluid resistance was too low, the pressure required to overcome

each increment would cause the user to overshoot the following increment. The lack of differences between needle sizes for both accuracy and precision suggest it should be suitable for use with various needle sizes. This is possibly due to users being able to rely on the auditory "click" feedback in addition to the tactile resistance felt at each increment.

Overall, the incremental syringe showed an at least equivalent, potentially improved, accuracy relative to the traditional syringe. Differences in precision between the two syringes were much more pronounced with the incremental syringe markedly outperforming the traditional syringe. While statistical significance was reached in many cases, it should be noted that these differences may not be clinically significant for treatment of DO or other medical procedures. For example, the accuracy improvement of the incremental syringe (from -3.0% to -2.4% error) only amounts to 0.006 mL for a 1.0 mL injection. Precision showed differences that would be more relevant clinically as standard deviations were about 3 times larger for the traditional syringe than they were for the incremental syringe. With such a high precision and less dependence on operator performance, it is possible that a small correction to the incremental syringe design could reduce the volume error from -2.4% to near zero. The incremental syringe also reduced the impact individual operators had on dosing, which can be seen in (Figures 3,4). The range of operator accuracies and precisions were smaller for the incremental syringe than for the traditional syringe. Several statistical analyses were able to detect differences between operators for the traditional syringe, but not for the incremental syringe. This indicates the incremental syringe could be beneficial in reducing dosing differences between users. In terms of clinical significance, it can be stated with certainty that the incremental syringe was at least as accurate and as precise as the traditional syringe. Its improved ease of use alone could justify its implementation for many applications such as those in which the user is unable to visually monitor the syringe during injection or aspiration. Reading the syringe volume can be difficult or even impossible if the operator's view is obstructed, if the lighting is poor, if the positioning is awkward, or if he or she needs to simultaneously view other important information such as medical imaging. The incremental syringe could also be beneficial in time sensitive procedures such as for trauma and military field deployment. The preset increments are also convenient for procedures which require numerous injections from the same syringe, for instance in the case of onabotulinumtoxinA for overactive bladders.

This study had several limitations which should be considered. For one, subjects were graduate students and were not as experienced as the health professionals who ordinarily handle syringes. Injections were also given consecutively from the same syringe. When a subject over or under dosed on a particular injection, the following one would be more likely to be incorrect

in the opposite direction. This makes the results of this study more applicable when compared to multiple injection procedures such as onabotulinumtoxinA for overactive bladders, but less so for procedures which have only one injection per syringe. Experience may also have played a role in operator performance. All operators had prior experience with traditional syringes, but none had used an incremental syringe previously. Operators were given the opportunity to practice with both syringe types prior to testing, but it is possible that further familiarity with the incremental syringe would have improved its results. Simultaneously, the observer effect may have played a role in this study. Participants were aware they were being observed for accuracy and may have been more careful than they would have otherwise. Accuracy and precision for both syringe types may have been artificially inflated as a result, although it is possible the traditional syringe would be more prone to mistakes of carelessness. Lastly, the subjects were under ideal conditions for their injections. Lighting was excellent, subjects did not have to reach far or awkwardly position themselves, and subject could easily adjust their angle of vision to their preference. However, this is often not the case for bladder injections of onabotulinumtoxinA and many other procedures. The precision and accuracy of injections for either or both syringes may suffer under more difficult conditions.

In conclusion, a novel syringe has been designed to provide users with tactile and audible feedback after each set volume increment is dispensed. This allows the incremental syringe to be utilized without visual monitoring of the syringe volume. When compared to a traditional syringe, the incremental syringe showed slight improvement in accuracy, significant improvement in precision, and a decreased variability between operators. The magnitudes of these improvements are potentially not of clinical importance for all applications, but still show the incremental syringe to be a viable clinical device. The data presented in this study, along with the incremental syringe's ease of use, make it a promising medical device for the future.

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