Tolerance of salivary gland botulinum toxin A injection under local anesthesia for the treatment of sialorrhea in children: An observational study.

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Abstract

Objectives: The main objective of this study was to assess tolerance of botulinum toxin A injection into the salivary glands under local anesthesia in a pediatric population. Secondary endpoints comprised efficacy and side-effects.

Material and methods: A retrospective observational study included children treated between January 2013 and March 2020 for sialorrhea and/or pharyngeal salivary congestion. Children were identified from the botulinum toxin A injection database. The study included 162 injection sessions in 55 children. Injections were performed under local anesthesia with nitrous oxide, after clinical location of the site. Epidemiological and clinical data, injection tolerance on the FLACC scale, treatment response and complications were recorded.

Results: For submandibular gland injections, pain was absent in 81 cases, mild in 64, moderate in 4 and intense in 1. In parotid gland injections, pain was absent in 45 cases, mild in 89, moderate in 17 and intense in 1. Injection tolerance was significantly poorer ($p < 0.005$) in parotid than submandibular glands. Seventy-seven percent of the injections had a positive effect on sialorrhea. Fifteen patients presented transient adverse events: mainly dysphagia and paradoxical increase in sialorrhea.

Conclusion: Salivary gland botulinum toxin A injections in under local anesthesia were well-tolerated, safe and effective for children with sialorrhea and/or pharyngeal salivary congestion.

Keywords: Sialorrhea, botulinum toxin A, pediatric, local anesthesia, salivary glands

1. Introduction

Sialorrhea consists in excessive drooling. It can induce skin irritation, halitosis and hygiene problems, and has negative social impact. Pharyngeal salivary congestion can cause inhalation accidents and iterative bronchopulmonary infection, aggravating disease burden [1,2]. Sialorrhea is frequent in cerebral palsy [3], where the underlying mechanisms are multiple: increased production of saliva, but more often defective oral and pharyngeal muscular control, with labial closure and control defect, lingual propulsion disorder, dental malocclusion, pharyngeal sensory deficit, and/or impaired central command of swallowing reflexes [2,3]. Extrinsic factors may also be involved: antiepileptic medication, repeated airway infection, dental decay, and gastroesophageal reflux [4]. Over and above controlling these factors, several treatments are available, often in association, for sialorrhea in children, based on oral motor rehabilitation and anticholinergic drugs, but often with systemic impact [5,6]. In the event of failure, intraglandular injection of botulinum toxin A (BtA) offers an alternative to salivary gland surgery. The effect of BtA in application on the neuromuscular junction has been widely described, but more recent studies also showed an effect in application on the neuroglandular junction, broadening indications to palmar and axillary hyperhidrosis and, more recently, to adult sialorrhea [3,7]. In France, Xeomin® has market authorization in adult sialorrhea, but not as yet in children, despite extensive literature [2, 4, 6, 8–10]. However, pediatric salivary gland injection is most often performed under general anesthesia, making the technique invasive; moreover, injection needs to be repeated, at variable intervals. The few studies using local anesthesia included little data on tolerance, which was never a main endpoint [5, 11–13].

The main aim of the present study was to assess tolerance for salivary gland BtA injection under local anesthesia and nitrous oxide in children with sialorrhea and/or pharyngeal salivary congestion. Secondary endpoints comprised efficacy and side-effects.

2. Materials and methods

A retrospective observational study included all children receiving salivary gland BtA injection between January 2013 and March 2020. All had previously undergone sialorrhea treatment associating speech therapy and anticholinergics. Injection was indicated due to failure, poor tolerance or contraindications to non-invasive treatment.

Injections were to the submaxillary and/or parotid glands. In patients with conserved exclusive oral feeding associated with sialorrhea with only moderate impact, only the submandibular glands were treated, with parotid injection in a subsequent session in case of deficient efficacy. Bilateral submandibulectomy and resection of the sublingual glands was proposed if BtA injection proved ineffective. In case of persistence or recurrence of sialorrhea, parotid gland injection was performed. The interval between injection sessions was according to individual need, with a minimum of 3 months. The BtA product was Xeomin® 100 IU powder for injectable solution. Injection location was determined clinically. Submandibular injection was performed 2 cm forward of and under the mandibular angle, and parotid injection 2 cm under the tragus. The injected dose was 100 IU, and not more than 10 IU/kg in children weighing less than 10 kg, with a volume of 0.3 ml in each submandibular gland and 0.2ml in each parotid gland. Dose could be increased, to a maximum 150 IU, in case of inefficacy of the preceding injection. Injection was under local anesthesia by EMLA patch positioned 1 or 2 hours in advance, associated to nitrous oxide inhalation delivered by a competent person.

The study was registered with the CNIL data protection commission (DEC20-088). Data were epidemiological (age, gender) and clinical (principal pathology, feeding, weight, dose per kg). Sixty patient files were analyzed. Patients aged over 18 years at first injection (2 cases),

receiving all injections under general anesthesia (1 case) or without tolerance assessment (2 cases) were excluded. Thus 55 patients were included, for 162 injection sessions: 140 in all 4 glands, 10 (in 3 patients) in submandibular glands only, and 12 (in 5 patients) in parotid glands only. Seven patients underwent bilateral submandibulectomy associated to resection of both sublingual glands, 5 requiring subsequent parotid gland injection. Table 1 presents demographic data.

The main endpoint was assessed on the validated French version of the Face-Legs-Activity-Cry-Consolability (FLACC) hetero-assessment pain scale. At each session, the operator noted dose, type of anesthesia and FLACC score per gland. Pain was considered absent for a score of 0, mild for 1-3, moderate for 4-5 and intense for >5. Treatment response was assessed by the parents on a global clinical impression question with binary response: effective, ineffective. All side-effects were noted.

Continuous variables were reported as mean, standard deviation and median, and categoric variables as number and percentage. Comparison of means for independent samples used the Wilcoxon test, and comparison of means for matched samples used the matched Wilcoxon test. Analyses used Excel (Microsoft, USA) and SPSS software version 19 (IBM, USA). The significance threshold was set at $p<0.005$ [14, 15].

3. Results

3.1 Immediate tolerance

In submandibular glands, 81 injections (54%) caused no pain, 64 (42.6%) mild pain, 4 (2.7%) moderate pain, and 1 (0.7%) intense pain, in a patient with severe pharmacoresistant epileptic encephalopathy in whom the rate of convulsions increased with the injections. Mean FLACC

score in submandibular injections was 0.92, for a median of 0; mean score for the first injection was 0.87, for a median of 0.

In parotid glands, 45 injections (29.6%) caused no pain, 89 (58.6%) mild pain, 17 (11.2%) moderate pain, and 1 (0.6%) intense pain, in the same patient with severe pharmacoresistant epileptic encephalopathy. Mean FLACC score was 1.71, for a median of 2, and 1.77 for the first injection, for a median of 2.

Comparison of mean values disclosed a significant difference in tolerance between glands ($p<0.005$), with poorer tolerance in parotid glands (Figure 1).

Tolerance progression is shown in figure 2. Excluding the one patient with more than 7 injections, there was no significant correlation between FLACC score and number of injections in parotid or submandibular glands ($p>0.005$).

3.2 Efficacy

125 injection sessions (77.2%) were effective and 37 (22.8%) ineffective against sialorrhea. Forty-three patients (78.2%) patients experienced at least 1 effective injection. Mean dose per kg in case of efficacy was 3.9 IU/kg, compared to 4.7 IU/kg in case of inefficacy, the difference being non-significant ($p = 0.027$).

3.3 Side-effects

Side-effects were found in 15 patients (9.2%). Six patients showed transient aggravation of swallowing disorder, due to xerostomia in 4 cases and to very thick saliva in 2; none required extra medical treatment. One patient experienced residual injection site pain. One presented a small submandibular hematoma at the injection site. One presented transient odynophagia, without impact on swallowing. One presented 8 hours' decompensation of his epileptic

encephalopathy. Five reported paradoxical hypersialorrhea during the first 5 days. Mean BtA dose per kg was 4.5±2 in case of side-effects and 4.1±1.8 without, there being no significant difference ($p = 0.44$) (Figure 3).

Table 2 shows the main study findings.

4. Discussion

In most pediatric studies, intraglandular BtA injection is performed under general anesthesia [6, 9, 16, 17]. This is invasive, especially as injection is repeated and the children have serious comorbidities liable to complicate anesthesia. Data are sparse for tolerance of injection under local anesthesia, which was not a main endpoint in any studies. Bothwell et al. reported parotid injection under local anesthesia in 9 children, with no adverse effects during the procedure [5]. Hassin Baer et al. reported that some of their 9 patients experienced anxiety and discomfort during parotid injection under local anesthesia [11]. Ellies et al. reported very good tolerance of salivary gland injection without anesthesia in all 5 of their patients [13]. In the present series, tolerance was good under EMLA patch with nitrous oxide. EMLA is known to be locally effective, but the success rate is not known and efficacy factors are difficult to assess, although success is related to type of procedure, application time and anxiety [18]. The efficacy of associating cutaneous analgesia to nitrous oxide sedation varies according to number and type of procedure [19,20]. Collado et al., in a review of the literature, found adverse effects of nitrous oxide in 1 in 1,000 cases, most often concerning nausea and vomiting [21]; they highlighted the fact that the patient is conscious and therefore needs accompanying for analgesia to be effective [21]. As pointed out by Montgomery et al., injection under local instead of general anesthesia enables easier and quicker treatment [12].

There are a number of solutions to combat sialorrhea in children, but none are without side-effects, and efficacy is limited [6]. Scopolamine is effective, but side-effects and drug

interactions limit use in children [6,16]. Salivary gland surgery is effective but invasive and often difficult to accept for patients and parents [16,22]. The efficacy of surgery depends on the technique. Reed et al., in a meta-analysis, showed that bilateral submandibular gland resection and parotid duct ligation is the most effective procedure (87.8%) and ligation of the 4 salivary ducts is the least (64.1%) [23]. Maximalist surgery should be indicated only with caution, due to the risk of xerostomia and its consequences [24,25]. Also, persistent sialorrhea after bilateral submandibulectomy is due not only to increased parotid activity but also, especially in children with cerebral palsy, to permanent oro-labial malocclusion, causing drooling [26]. In our center, bilateral submandibulectomy associated to bilateral sublingual gland resection is proposed in case of failure of less invasive treatment and of favorable risk/benefit ratio. In this context, salivary gland BtA injection offers a useful alternative. Many studies assessed the efficacy of salivary gland BtA injection for sialorrhea and/or pharyngeal salivary congestion [6, 8, 27]; many were prospective, one was a randomized controlled trial and two were controlled clinical studies [2, 3, 5, 6, 8,11, 27]. Although efficacy was reported, with success rates between 30% and 75%, there is no consensus regarding injection modalities [16]. In the present study, efficacy was slightly greater than reported elsewhere, but to the wide variety of assessment instruments makes comparison difficult. Some studies used objective measurement of quantitative change in saliva, calculating weight using bibs; others used subjective measures, with estimation by the parents of sialorrhea before and after injection on severity and frequency scores or global clinical impression scales, with various possible responses [5,11]. Reid et al. advocated the Drooling Impact Scale to assess interventions to control salivation in intellectually deficient children [28]. Also, most patients in the present series had continued multidisciplinary management of their sialorrhea; combined to assessment of the impact of sialorrhea, this approach is a key step in treatment decision-making [29]. Twenty-nine patients continued transdermal

scopolamine treatment, 7 of whom were able to reduce the dose; 17 interrupted it due to adverse effects, 1 due to cost and 9 due to the adequate efficacy of the injections. The present study found a paradoxical inverse relation with injected dose, although this was not actually significant; we have no explanation for this apparent trend, and it has not been reported elsewhere. Montgomery et al. suggested that male gender and cerebral palsy are factors for better outcome, but this was not confirmed by Scheffer et al. [2, 12]. Several studies, in adults and in children, recommended ultrasound guidance of injection [16,17,29,30]; those performed in children used general anesthesia and found neither greater efficacy nor fewer side-effects [16,17]. As Montgomery et al. pointed out, ultrasound-guided injection is a longer procedure, leading to poorer tolerance under local anesthesia, and should therefore be reserved for anatomically complex situations [12].

Most studies of BtA injection in children reported few side-effects [2,3], but the most frequent was dysphagia due to xerostomia or to aggravated congestion caused by thickened saliva [2,12]. In the present study, the most frequent side-effect was transient aggravation of swallowing disorder, although this did not impact weight gain as these children had a gastrostomy. According to We et al., enteral feeding compensates for the impact of the dysphagia induced by the BtA injection [10]. The present study also highlighted the phenomenon of initial paradoxical hypersialorrhea in some cases, which has been little described but needs to be made known to the parents [3, 5].

The weak point of the present study lay in its retrospective design, based on subjective assessment of several operators, relativizing the significance of the results. Moreover, the binary score assessing efficacy was highly subjective, thus lacking precision. A validated score assessing drooling severity would provide better evaluation of this secondary endpoint.

Another bias may have been introduced by the open follow-up of varying duration, hindering assessment of long-term benefit.

5. Conclusion

Salivary gland BtA injection should be seen as an integral part of the management of sialorrhea and/or pharyngeal salivary congestion in children. It is safe and effective, and often better tolerated than other options. The present study showed that it can be performed under local anesthesia in children, with good tolerance. This avoids resort to iterative general anesthesia in children who are often frail, allowing the procedure to be repeated without organizational problems, so as to meet individual needs.

Disclosure of interest

The authors have no conflicts of interest to disclose in relation to the present article.

References

[1]. Van der Burg JJW, Jongerius PH, van Limbeek J, van Hulst K, Rotteveel JJ. Social interaction and self-esteem of children with cerebral palsy after treatment for severe drooling. *Eur J Pediatr* 2006;165(1):37-41.

[2]. Scheffer ART, Erasmus C, van Hulst K, van Limbeek J, Jongerius PH, van den Hoogen FJA. Efficacy and duration of botulinum toxin treatment for drooling in 131 children. *Arch Otolaryngol Head Neck Surg* 2010;136(9):873-7.

[3]. Suskind DL, Tilton A. Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. *The Laryngoscope* 2002;112(1):73-81.

[4]. Porte M, Chaléat-Valayer E, Patte K, D'Anjou M-C, Boulay C, Laffont I. Relevance of intraglandular injections of Botulinum toxin for the treatment of sialorrhea in children with cerebral palsy: a review. *Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc* nov 2014;18(6):649-57.

[5]. Bothwell JE, Clarke K, Dooley JM, et al. Botulinum toxin A as a treatment for excessive drooling in children. *Pediatr Neurol* 2002;27(1):18-22.

[6]. Jongerius PH, van den Hoogen FJA, van Limbeek J, Gabreëls FJ, van Hulst K, Rotteveel JJ. Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. *Pediatrics* 2004;114(3):620-7.

[7]. Jost WH, Friedman A, Michel O, et al. SIAXI: Placebo-controlled, randomized, double-blind study of incobotulinumtoxinA for sialorrhea. *Neurology* 2019;92(17):e1982-91.

[8]. Alrefai AH, Aburahma SK, Khader YS. Treatment of sialorrhea in children with cerebral palsy: a double-blind placebo controlled trial. *Clin Neurol Neurosurg* 2009;111(1):79-82.

[9]. Alvarenga A, Campos M, Dias M, Melão L, Estevão-Costa J. BOTOX-A injection of salivary glands for drooling. *J Pediatr Surg* 2017;52(8):1283-6.

[10]. Wu KP-H, Ke J-Y, Chen C-Y, Chen C-L, Chou M-Y, Pei Y-C. Botulinum toxin type A on oral health in treating sialorrhea in children with cerebral palsy: a randomized, double-blind, placebo-controlled study. *J Child Neurol* 2011;26(7):838-43.

[11]. Hassin-Baer S, Scheuer E, Buchman AS, Jacobson I, Ben-Zeev B. Botulinum toxin injections for children with excessive drooling. *J Child Neurol* 2005;20(2):120-3.

[12]. Montgomery J, McCusker S, Hendry J, Lumley E, Kubba H. Botulinum toxin A for children with salivary control problems. *Int J Pediatr Otorhinolaryngol* 2014;78(11):1970-3.

[13]. Ellies M, Rohrbach-Volland S, Arglebe C, Wilken B, Laskawi R, Hanefeld F. Successful management of drooling with botulinum toxin A in neurologically disabled children. *Neuropediatrics* 2002;33(6):327-30.

[14]. Laccourreye O, Fakhry N, Franco-Vidal L, et al. Statistics in scientific articles published in the European Annals of Otorhinolaryngology Head & Neck Diseases. *Eur Ann Otorhinolaryngol Head Neck Dis* 2020. Sous presse.

[15]. Ioannidis JPA. The Proposal to Lower P Value Thresholds to .005. *JAMA* 2018;319(14):1429-30.

[16]. Lungren MP, Halula S, Coyne S, Sidell D, Racadio JM, Patel MN. Ultrasound-Guided Botulinum Toxin Type A Salivary Gland Injection in Children for Refractory Sialorrhea: 10-Year Experience at a Large Tertiary Children's Hospital. *Pediatr Neurol* 2016;54:70-5.

[17]. Breheret R, Bizon A, Jeufroy C, Laccourreye L. Ultrasound-guided botulinum toxin injections for treatment of drooling. *Eur Ann Otorhinolaryngol Head Neck Dis* 2011;128(5):224-9.

[18]. Lander J, Hodgins M, Nazarali S, McTavish J, Ouellette J, Friesen E. Determinants of success and failure of EMLA. *Pain* 1996;64(1):89-97.

[19]. Ekbom K, Jakobsson J, Marcus C. Nitrous oxide inhalation is a safe and effective way to facilitate procedures in paediatric outpatient departments. *Arch Dis Child* 2005;90(10):1073-6.

[20]. Gambart G, Mette F, Pellot A-S, Richard I. Evaluation of analgesic protocol with nitrous oxide and EMLA cream during botulinum toxin injections in children. *Ann Readaptation Med Phys Rev Sci Soc Francaise Reeducation Fonct Readaptation Med Phys* 2007;50(5):275-9.

[21]. Collado V, Nicolas E, Faulks D, Hennequin M. A review of the safety of 50% nitrous oxide/oxygen in conscious sedation. *Expert Opin Drug Saf* 2007;6(5):559-71.

[22]. Kok SE, Erasmus CE, Scheffer ART, van Hulst K, Rovers MM, van den Hoogen FJA. Effectiveness of submandibular duct relocation in 91 children with excessive drooling: A prospective cohort study. *Clin Otolaryngol Off J ENT-UK Off J Neth Soc Oto-Rhino-Laryngol Cervico-Facial Surg* 2018;43(6):1471-7.

[23]. Reed J, Mans CK, Brietzke SE. Surgical management of drooling: a meta-analysis. *Arch Otolaryngol Head Neck Surg* 2009;135(9):924-31.

[24]. Stern Y, Feinmesser R, Collins M, Shott SR, Cotton RT. Bilateral submandibular gland excision with parotid duct ligation for treatment of sialorrhea in children: long-term results. *Arch Otolaryngol Head Neck Surg* 2002;128(7):801-3.

[25]. Gallagher TQ, Hartnick CJ. Bilateral submandibular gland excision and parotid duct ligation. *Adv Otorhinolaryngol* 2012;73:70-5.

[26]. Delsing CPA, Bekkers S, van Hulst K, Erasmus CE, van den Hoogen FJA. Unsuccessful submandibular duct surgery for anterior drooling: Surgical failure or parotid gland salivation ? *Int J Pediatr Otorhinolaryngol* 2019;123:132-7.

[27]. Reid SM, Johnstone BR, Westbury C, Rawicki B, Reddihough DS. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling in children with neurological disorders. *Dev Med Child Neurol* 2008;50(2):123-8.

[28]. Reid SM, Johnson HM, Reddihough DS. The Drooling Impact Scale: a measure of the impact of drooling in children with developmental disabilities. *Dev Med Child Neurol* 2010;52(2):e23-28.

[29]. Reddihough D, Erasmus CE, Johnson H, McKellar GMW, Jongerius PH, Cereral Palsy Institute. Botulinum toxin assessment, intervention and aftercare for paediatric and adult drooling: international consensus statement. *Eur J Neurol* 2010;17 Suppl 2:109-21.

[30]. Dogu O, Apaydin D, Sevim S, Talas DU, Aral M. Ultrasound-guided versus « blind » intraparotid injections of botulinum toxin-A for the treatment of sialorrhoea in patients with Parkinson’s disease. *Clin Neurol Neurosurg* 2004;106(2):93-6.

Clinical and epidemiological data N= 55	Values
Age at first injection (years): range Mean±standard deviation Median	1-17 10±4 8
Gender: n (%) Female Male	 22 (40) 33 (60)
Weight range (kg) Mean Median	11-55 27.1±10.5 27
Dose range (IU/k Mean Median	1.3 - 9.1 4.1±1.9 3.7
Range of number of injections Mean Median	1-10 2.9±1.9 2
Mean interval between injections (months) Median	9.1±6.5 7
Cases at diagnosis: n (%) Exclusively oral feeding Exclusively enteral feeding Mixed	 14 (25.4) 26 (47.3) 15 (27.3)

Main comorbidities: n (%)	
Myopathy	2 (3.6)
Psychomotor retardation	6 (10.9)
Mixed nerve palsy	1 (1.8)
Cerebral palsy	9 (16.4)
Encephalopathy	37 (67.3)

Table 1: Clinical and demographic data for the 55 patients.

Results	Values
Tolerance of submandibular (sm) gland injection (N=152) FLACC sm = 0 (%) FLACC sm = 1-3 (%) FLACC sm = 4-5 (%) FLACC sm > 5 (%) Mean FLACC sm Median FLACC sm	 81 (54) 64 (42.6) 4 (2.7) 1 (0.7) 0.92±1.2 0
Mean FLACC sm at first injection (N=53) Median	0.87±1.3 0
Tolerance of parotid (p) gland injection (N=150) FLACC p = 0 (%) FLACC p = 1-3 (%) FLACC p = 4-5 (%) FLACC p > 5 (%) Mean FLACC p Median	 45 (29.6) 89 (58.6) 17 (11.2) 1 (0.6) 1.71±1.5 2
Mean FLACC p at first injection (N=52) Median	1.77±1.4 2

Injection efficacy (N=162) (%)	
Number of effective injections (%)	125 (77.2)
Number of ineffective injections (%)	37 (22.8)
Number of patients with at least 1 effective injection (N=55) (%)	43 (78.2)
Side-effects (N=162)	
Number of injection side-effects (%)	15 (9.2)
Transient aggravation of swallowing disorder	6 (3.7)
Residual injection-site pain	1 (0.6)
Submandibular hematoma	1 (0.6)
Transient odynophagia	1 (0.6)
Transient decompensation of epileptic encephalopathy	1 (0.6)
Transient paradoxical hypersialorrhea	5 (3.1)

Table 2: Main results.

Figure 1: FLACC score according to gland

Boxplot comparing FLACC scores for submandibular gland (FLACC sm) and parotid gland (FLACC p) injections.

Figure 2: Tolerance progression.

Progression of mean FLACC score for submandibular gland (FLACC sm) and parotid gland (FLACC p) injections.

Figure 3: Relation between injected dose and side-effects

Boxplot comparing dose (IU/kg) in children with (1) and without (0) side-effects.

Figure 1

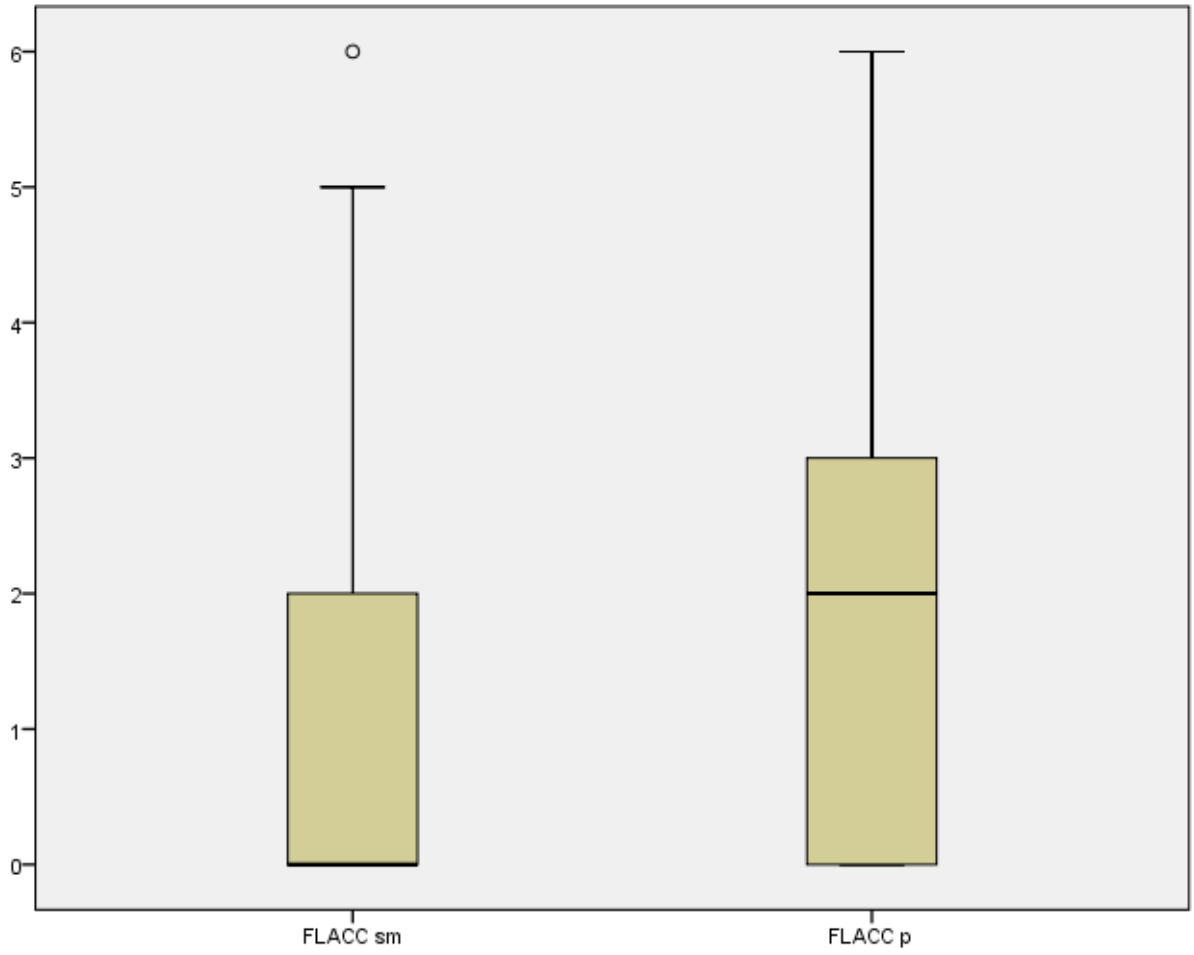

Figure 2

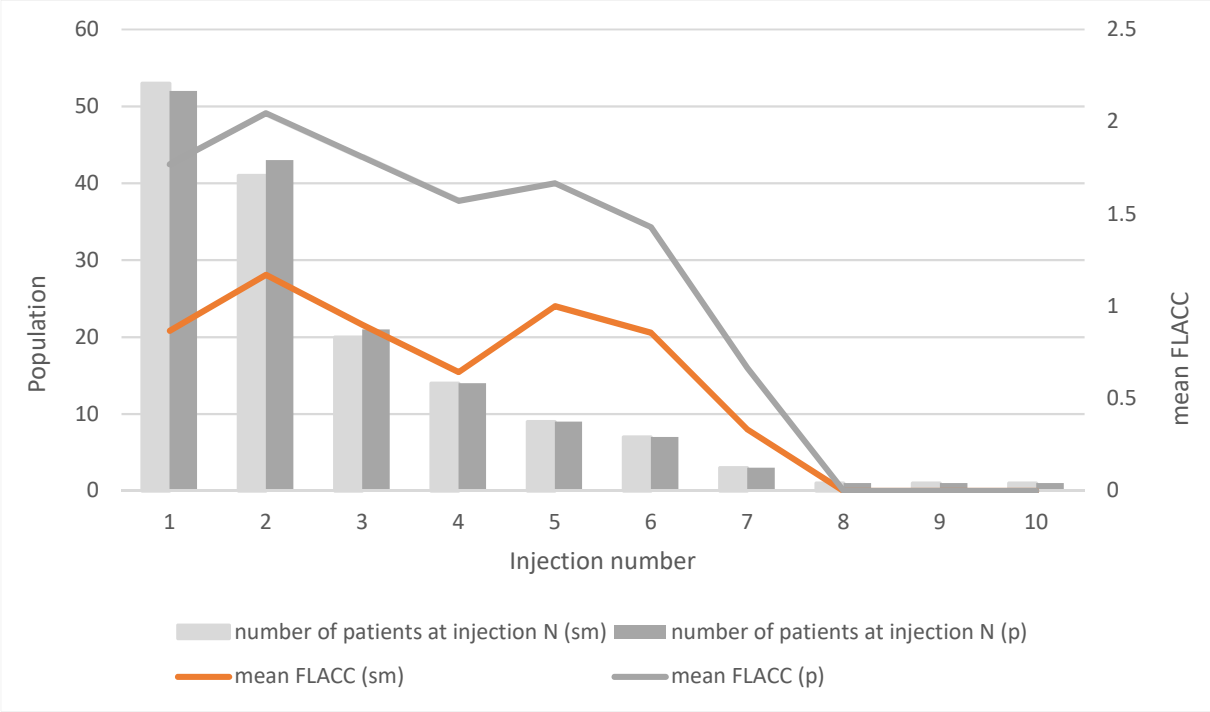
60
50
40
30
20
10
0
Population
2.5
2
1.5
1
0.5
0
mean FLACC
1
2
3
4
5
6
7
8
9
10
Injection number
number of patients at injection N (sm)
number of patients at injection N (p)
mean FLACC (sm)
mean FLACC (p)

Figure 3