A Functional Approach to Posttraumatic Salivary Fistula Treatment: The Use of Botulinum Toxin

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Abstract: This manuscript highlights key aspects regarding the practical use of botulinum toxin for the conservative nonsurgical treatment of a rarely encountered, but significant posttraumatic complication—the parotid salivary fistula. It adds information to the scarce existing literature on the subject. The authors outline the main differences between postoperative and trauma-related parotid injury regarding salivary fistula treatment. A total of 6 patients with trauma-related salivary fistulas have been treated by Abobotulinum toxin A injections over the course of 5 years. The technique is detailed, describing the doses used in the presence of parenchyma and duct injuries, the location and number of injection points in relation to the wound pattern. The results were favorable, leading to the healing of the salivary fistulas in all patients, with 1 injection session, without additional conservative treatment. In our experience, the use of botulinum toxin is of great benefit for treating salivary fistulas in a traumatic context.

Key Words: Botulinum toxin, parotid gland, salivary fistula, trauma

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Botulinum toxin (BT) is a well-known modulator of salivary secretion. Its action on the glandular parasympathetic neurosecretory synapses blocks the release of acetylcholine, resulting in a decrease in salivary production. Although there are many publications describing the use of BT for sialorrhea,[1] there are fewer articles focusing on salivary fistula treatment[2] and even less describing the use of BT for posttraumatic fistulas unrelated to surgery.[3] This is due to the scarcity of patients presenting with salivary gland or duct injury unresponsive to the initial surgical and conservative measures.

Although rare in occurrence, salivary fistulas are a debilitating condition for the patient, affecting the social life, limiting public outings. In a traumatic context, it adds to the unpleasant psychologic outcome determined by the presence of the facial scar. The surgical treatment of the condition implies a prolonged hospital stay and therefore increased costs. An effective nonsurgical management would be more beneficial and BT use offers such an alternative. Due to the small number of posttraumatic patients described in the existing literature, there is no consensus over the selection of the type of BT, the most appropriate dose, location, and number of injection administration.

The purpose of this study is to present the author's experience regarding the management of nonsurgical trauma-related salivary fistulas of the parotid gland by the off-label use of BT injections. We also aim to outline the differences between postoperative and posttraumatic salivary fistulas and their relevance on establishing the treatment plan.

MATERIALS AND METHODS

Patients

We reviewed the medical charts of patients in our institution between January 2013 and December 2017. Over a period of 5 years, 6 patients with posttraumatic parotid fistulas were treated by BT injection. The patients were all male, aged between 18 and 51. They initially presented for trauma-related facial lacerations. The traumatic mechanism involved 2 patients with circular saw injury, 2 grinder wheel injuries, 1 broken glass injury, and a penetrating cow horn injury. An associated lesion of the facial nerve was diagnosed in 2 patients and a mandibular fracture in 1 patient.

Three of the wounds were complex, involving several facial areas, including the parotid-masseteric region (Fig. 1 A-B). Another complex beveled laceration was in the genian region. Two patients presented with relatively small wounds located over the topography of the parotid gland in 1 patient, and at the inferior aspect of the nasal-genian fold in the second patient. Details regarding the patients included in the study and their management are presented in Table 1.

Exploration of the wounds revealed involvement of the parotid glandular tissue in 3 patients with complex facial lacerations. The parotid duct was cannulated using an epidural catheter and methylene blue was injected retrograde, but no injury of the duct was found. A layered closure of the wounds was performed with suturing of the parotid fascia and superficial muscular aponeurotic system layer. A drainage was left in place and was maintained for 3 to 5 days. The external end of the gravitational drainage was placed at the inferior aspect of the wound in 2 patients, and in 1 patient, a suction drain was exteriorized in the lateral cervical region. Conservative measures were introduced for the prevention of salivary fistula formation. Subcutaneous atropine was administrated in doses of 0.5 mg, 30 minutes before each of the 3 main meals. Pressure dressings over the parotid region were performed in all patients for 1 week postoperative during hospital stay.

In the 2 patients presenting with small lacerations and 1 patient with a complex laceration located in the genian region, the initial

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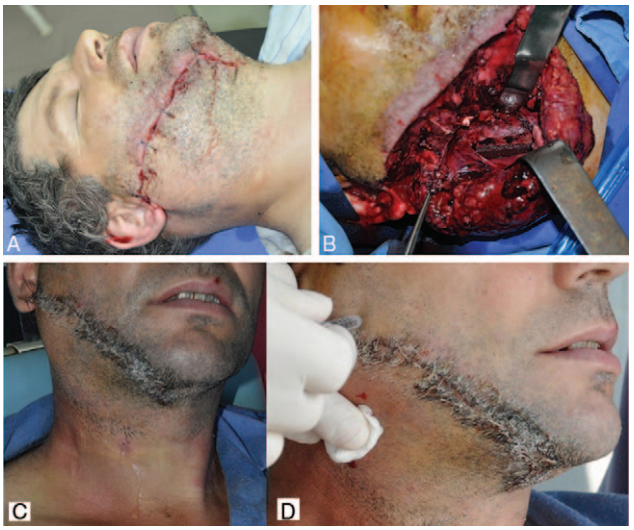

FIGURE 1. (A) Patient with a posttraumatic laceration due to a grinder wheel injury, involving the right parotid-masseteric region, inferior genian region, and the submandibular region. Stay sutures were placed until transfer to the maxillofacial clinic. The patient has an associated right lateral mandibular fracture. (B) Intraoperative view during wound exploration showing the presence of a foreign body (grinder wheel fragment) and the severed parotid tissue. A layered suture with closure of the parotid fascia was performed after the removal of the foreign body. (C) Clinical view 7 days after the suture showing the saliva outflow through the lateral cervical salivary fistula at the previous drainage location. (D) Botulinum toxin injection is performed on both sides of the scar intersecting the parotid area.

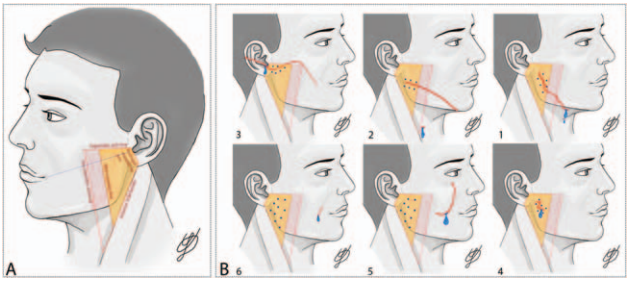

FIGURE 2. (A) Markings of the considered location of the parotid gland (yellow area) and duct projection (in the area located 1.5 cm above and below the blue line from the inferior tragus to the oral commissure). (B) Schematic representation of the facial wounds, salivary fistula location, and botulinum toxin injection points for the patients included in the study.

treatment consisted of immediate suturing of the wound without drainage placement. A parotid parenchyma or duct injury was not initially recognized, and patients were not admitted in the hospital. There were no additional conventional recommendations regarding the prevention of salivary fistula formation.

The cutaneous salivary fistula was diagnosed in between 1 and 2 weeks after the initial wound closure. The location of the fistula was in the submandibular area in 1 patient, in the lateral cervical region in 1 patient (Fig. 1C), in the genian region in 1 patient, at the level of the nasal-genian fold in 1 patient, in the parotid region for 1 patient, and in the external auditory canal for another patient.

In 1 patient with a stabbed nasal-genian wound and 1 patient with a crushed beveled laceration in the genian region, there was reason to suspect a Stensen duct injury, considering the trajectory and character of the laceration. The patients opted for a nonsurgical treatment.

Botulinum toxin injections were performed in all included patients in the same day of the diagnosis of parotid salivary fistula onset (Fig. 1D).

The authors followed the guidelines of the Declaration of Helsinki during the entire investigation process. The study is a clinical review and therefore was exempt from institutional review board approval.

Injection Landmarks

We considered the approximate topography of the parotid gland and duct in an area delineated by the following lines: an anterior superior line tangent to the inferior border of the zygomatic arch, a posterior superior line going from the inferior tragus to the tip of the mastoid, a posterior inferior line following the anterior border of the sternocleidomastoid (SCM) muscle toward the mastoid tip, and an anterior inferior line tangent to the anterior border of the masseter muscle (Fig. 2A).

Palpation was used to determine the bone and muscle landmarks. The masseter anterior border was palpated during forced occlusion. The SCM anterior border was determined with the head rotated to the opposite side and slightly tilted downward, on a line from the medial clavicle to the mastoid. The anterior limit of the parotid tissue was marked approximately at the middle of the distance between the posterior border of the mandible and the anterior

TABLE 1. Patient Description for the Included Patients

Patient	Wound Topography	Etiology	Injury Location	Initial Surgical Treatment	Hospital Admission	Conservative Treatment	Fistula Onset	Fistula Location	Dysport Units, U	Injection Points
1	Parotid-masseteric, genian, submandibular regions	Circular saw	Parotid parenchyma	Layered wound suture	Yes	Yes	PO 7	Submandibular region	100	6
2	Parotid-masseteric, genian, submandibular regions	Grinder wheel	Parotid parenchyma	Layered wound suture	Yes	Yes	PO 7	Lateral cervical area	100	6
3	External ear, external ear canal, parotid-masseteric, genian regions	Circular saw	Parotid parenchyma	Layered wound suture	Yes	Yes	PO 7	External ear canal	100	6
4	Parotid-masseteric region	Broken glass	Not initially recognized	Wound suture	No	No	PO 10	Parotid region	100	6
5	Anterior part of the genian region in the superior two-thirds	Grinder wheel	Not initially recognized	Wound suture	No	No	PO 7	Genian region	150	10
6	Inferior third of the nasal-genian fold region	Cow horn	Not initially recognized	Wound suture	No	No	PO 14	Nasal-genian fold	150	10

PO, postoperative day.

TABLE 2. Salivary Flow Assessment Following BT Injection

Patient	Preinjection	BT, Day 3	BT, Day 7	BT, Day 14	BT, 1 mo	BT, 6 mo	BT, 12 mo
1	+++++	++++	++	–	–	–	–
2	+++++	+++	+	–	–	–	–
3	+++++	++++	++	–	–	–	–
4	+++++	++++	++	–	–	–	–
5	+++++	+++	+	–	–	–	–
6	+++++	+++	+	–	–	–	–

BT, botulinum toxin.

margin of the masseter. Anterior from this line, the parotid duct usually exists the glandular tissue. The height of duct emergence was considered in the area comprising 1.5 cm above and below a line going from the inferior part of the tragus to the oral commissure,[4] in between the mid-masseter and anterior-masseter lines, equivalent to the middle third of the tragus-commissure line.

These landmarks were used to evaluate the location of the parotid gland and duct, and thus to determine the best suited location for the BT injections.

Botulinum Toxin Reconstitution

For the treatment of all salivary fistulas, we used Dysport (Abobotulinum toxin type A, Ipsen Limited, Slough Berkshire, UK). The reconstitution was performed by adding 5 mL of 0.9% sodium chloride solution to the 500 U Dysport vial, reaching a dilution of 100 U/mL, equivalent to 10 U/0.1 mL.

Technique of Botulinum Toxin Injection

Syringes of 1 mL with a detachable 27 G 19-mm long needle were used for the injection. The injections were administered without previous local anesthesia, after skin antisepsis using alcohol in the target area. In the 4 patients with parenchyma injury, the injections were performed aiming for the involved glandular tissue surrounding the scar, over the projection of the gland (Fig. 1C). The dose administered for parenchyma injuries was 100 U (1 mL) of Dysport distributed into 6 injections administered on both sides of the scar in 1 session, at a maximum distance of approximately 1 cm from the wound and ensuring <1.5 cm in between the injection points, considering the diffusion of the BT, attempting to cover most of the surrounding injured glandular tissue. In the 2 patients with possible Stensen duct injury, a total dose of 150 U (1.5 mL) of Dysport was administered into 10 injections spread over the topography of the parotid gland, unrelated to the topography of the wound. The wound patterns, fistula location, and injection points for the included patients are schematically represented in Figure 2B.

The depth of the injection was adapted to the individual build of the patient, delivering the BT into the parotid tissue. The patient was instructed to contract the masseter muscle to better approximate the depth of the injection by muscle palpation. Increased resistance is felt upon needle insertion when the needle reaches the contracted masseter muscle, indicating the need for needle withdrawal by 2 mm to position it into the overlying parotid tissue.

The admitted patients were discharged from the hospital the same day of BT administration with the recommendation of periodic controls at 3 days, 1 week, 2 weeks, 1 month, 6 months, and 12 months. The ambulatory patients had the same indications regarding follow-up visits after BT administration. No additional conservative measures were undertaken.

RESULTS

The subjective salivary flow at the fistula opening was rated in comparison to the preinjection flow at 3 days, 1 week, and 2 weeks after the BT injection (Table 2). The gradual reduction in salivary flow was noticed starting with day 3 and continued, as observed in day 7. Complete resolution of the salivary flow at the fistula orifice was obtained at 2 weeks following the injection in all patients. Controls performed at 1, 6, and 12 months confirmed the healing of the salivary fistula and the maintenance of the results. There were no patients with infection or salivary collections during the interval until complete onset of BT effect.

None of the patients needed additional BT injections or subsequent surgery. There was no need for associated conservative measures such as pressure dressings, antisialogogues or suppression of oral intake. Patients had a normal diet following the injections. No adverse effects were declared by the patients regarding xerostomia, mastication, deglutition, or facial muscle weakness.

DISCUSSION

Controlling the diffusion of the BT is one of the key factors in achieving the desired outcome while minimizing side effects. The balance is maintained when the BT type is purposely selected in knowledge of its characteristics and used in the conditions where it would lead to maximum benefit. The exact diffusion is difficult to quantify and there are differences in opinion regarding the contributing factors. Still, an increased diffusion of the BT has been linked by some studies to a smaller molecular weight, increased volumes of administration and higher doses.[5] For this purpose, we used Dysport (Abobotulinum toxin type A, Ipsen Limited) that has a smaller molecular mass ranging from 300 to 900 kDa, as opposed to Botox (Onabotulinumtoxin type A, Allergan, Inc, Irvine, CA), with a fixed 900 kDa molecular mass. When aiming for "chemical parotidectomy" the increased diffusion of the BT ensures more coverage of the glandular parenchyma with fewer injections and lower quantities of toxin. This desiderate is contrary to cosmetic procedures where precision is key in targeting only certain facial muscles, while sparing others and minimizing side effects. A conversion ratio between Dysport and Botox of 3:1 is stated by most authors to be most accurate in achieving similar effects.[5,6] Although it is very difficult to quantify the exact spread of the toxin from the injection site, most injectors consider that the substance diffuses for approximately 1 cm and use this to protect important anatomic structures during cosmetic injections with good results.[7] We considered the same distance in ensuring uniform spread of the BT in the glandular parenchyma.

The total dose used for parenchyma injuries in our study was similar to the 1 administered for cosmetic procedures—100 U of Dysport, equivalent to approximately 33 U of Botox. Slightly higher doses were administered for Stensen duct injury—150 U of Dysport, equivalent to 50 U of Botox. There is no consensus

among authors regarding the most appropriate dose for achieving salivary blockade. Arnaud et al,[3] in a study concerning posttraumatic salivary fistulas, targeted an aggressive salivary suppression by using 100 U of Botox equivalent to 300 U of Dysport. Guntinas-Lichius and Sittel[8] inject 100 U of Dysport for treating a postparotidectomy fistula. Doses as small as 10 U of Botox equivalent to 30 U of Dysport were described for the treatment of a postparotidectomy salivary fistula by other authors.[9,10] Due to the scarcity of patients presenting with trauma-related salivary fistulas, the diversity of clinical scenarios, and individual differences in the volume of the parotid glands, a statistic study evaluating the most appropriate total dose is not feasible.

In parenchyma lacerations, the location of toxin injections is important because unnecessary injections in the glandular tissue at a greater distance from the actual injury do not benefit fistula closure, but raise the total dose of BT. Some studies using BT for the treatment of postoperative fistulas describe injections around the fistula opening.[10,11] The described postoperative fistulas were overlying the parotid area in all patients and justified the selected injection points. However, the parotid parenchyma fistulas in our study were mostly expressed inferiorly, at the level of the preexisting drainage, in areas not overlying the parotid gland. For this reason, the BT injections were not administered around the fistula opening in all patients, but around the scar overlapping the parotid topography. The thickness of the subcutaneous adipose tissue was considered for establishing the injection depth. An intramuscular injection would lead to the undesirable effect of muscle weakness, volume reduction with facial asymmetry, and to the absence of full effect on the parotid glandular tissue with salivary fistula persistence.

In patients with a salivary fistula unresponsive to BT treatment, the extensions of the parotid glandular tissue outside of the main parotid body should be evaluated for injury and supplementary BT injections should be administered. The tail of the parotid gland is maybe the most exposed extension of parotid tissue vulnerable to injury, because it can stretch for various lengths over the anterior border of the SCM muscle.[12] This is a location commonly overlooked when diagnosing posttraumatic glandular tissue injury, and a common location of injury during neck dissection procedures.

Additional causes for unresponsiveness could be due to a concurrent injury of the submandibular gland tissue or initial insufficient information regarding the trajectory of the laceration. Posttraumatic wounds have an irregular pattern, depth, and beveling. Crushing of the soft tissues is also present, influencing healing. The actual level of the parotid injury may be different from the trajectory of the wound and this influences the injection location. By contrast, when treating postoperative fistulas, the wound is regular, but the difficulty arises from the distorted local anatomy due to the removed or repositioned tissues. Injection patterns and doses of BT must be adapted to the individual patient and ultrasound can be useful for increased precision in postoperative fistulas.

In our study, the injections were performed by an experienced injector, guided by clinical landmarks only.[4,12,13] Due to the effectiveness of the administration, absence for the need of additional or repeated injections, and absence of side effects, we did not consider necessary any imaging guiding for a more exact substance placement. Ultrasound guided injections into the deep lobe have been performed by authors for the treatment of sialorrhea[1,14] and could be a solution for silencing the parapharyngeal glandular tissue in patients with injury with this location. One study found that ultrasound guiding is more useful for injections in the submandibular gland, while anatomic landmarks allow enough accuracy for intraparotid injections.[15] Thus, ultrasound guiding could benefit injections targeting all major salivary glands, performed for the prevention of salivary fistulas in oncologic and reconstructive procedures, including oral cavity reconstruction, neck dissection, and face transplantation procedures.[16,17]

In our experience, 1 session of treatment was enough for the healing of the salivary fistula. Other authors reported patients in which the initial treatment was not followed by a complete resolution of the fistula and reinjections had to be performed to reach the desired outcome. However, the reported patients involved fistulas associated with complex wounds following gunshots or malignant tumor removal and reconstruction.[18,19] In patients unresponsive to the initial treatment, additional doses can be administered, and the precision of the infiltrations can be improved by using ultrasound.[18]

The BT treatment was initiated after considering all available treatment options. Radiotherapy and surgical repair have a high morbidity and imply additional hospitalization time, medication, and monitoring.[20–22] Postoperative radiotherapy performed anyway in most oncologic patients may also benefit fistula closure, but for posttraumatic patients the risks outweigh the benefits. When faced with the surgical alternatives for repair, the patients in our study opted for the nonsurgical approach. This is consistent with the observations of other authors stating that BT treatment has replaced surgical methods for salivary fistula closure in most of patients due to the less invasive character.[21,23]

Due to the diversity of wound patterns as well as the multiple anatomic variations of parotid glandular tissue extension and duct projection, an exact standardization of injection sites and doses is not possible, but an understanding of the physiology of glandular injuries and BT effects, as well as a good knowledge of the regional anatomy, can help the delivering of accurately placed injections and ensure good results.

REFERENCES

1. Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. *Toxins (Basel)* 2013;5:1010–1031
2. Lovato A, Restivo DA, Ottaviano G, et al. Botulinum toxin therapy: functional silencing of salivary disorders. *Acta Otorhinolaryngol Ital* 2017;37:168–171
3. Arnaud S, Batifol D, Goudot P, et al. Non-surgical management of parotid gland and duct injuries: interest of botulinum toxin. *Ann Chir Plast Esthet* 2008;53:36–40
4. Stringer MD, Mirjalili SA, Meredith SJ, et al. Redefining the surface anatomy of the parotid duct: an in vivo ultrasound study. *Plast Reconstr Surg* 2012;130:1032–1037
5. Ravenni R, De Grandis D, Mazza A. Conversion ratio between Dysport and Botox in clinical practice: an overview of available evidence. *Neurol Sci* 2013;34:1043–1048
6. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel)* 2016;8:E65
7. Niamtu J III. Botulinum toxin A: a review of 1,085 oral and maxillofacial patient treatments. *J Oral Maxillofac Surg* 2003;61:317–324
8. Guntinas-Lichius O, Sittel C. Treatment of postparotidectomy salivary fistula with botulinum toxin. *Ann Otol Rhinol Laryngol* 2001;110:1162–1264
9. Marchese-Ragona R, Marioni G, Restivo DA, et al. The role of botulinum toxin in postparotidectomy fistula treatment. A technical note. *Am J Otolaryngol* 2006;27:221–224
10. Lim YC, Choi EC. Treatment of an acute salivary fistula after parotid surgery: botulinum toxin type A injection as primary treatment. *Eur Arch Otorhinolaryngol* 2008;265:243–245
11. Ellies M, Gottstein U, Rohrbach-Volland S, et al. Reduction of salivary flow with botulinum toxin: extended report on 33 patients with drooling, salivary fistulas, and sialadenitis. *Laryngoscope* 2004;114:1856–1860
12. Costan VV. *Management of Extended Parotid Tumors*. Switzerland: Springer International Publishing; 2016
13. Toure G, Foy JP, Vacher C. Surface anatomy of the parotid duct and its clinical relevance. *Clin Anat* 2015;28:455–459

14. Alter KE, Karp BI. Ultrasound guidance for botulinum neurotoxin chemodenervation procedures. *Toxins (Basel)* 2017;10:E18
15. So JI, Song DH, Park JH, et al. Accuracy of ultrasound-guided and non-ultrasound-guided botulinum toxin injection into cadaver salivary glands. *Ann Rehabil Med* 2017;41:51–57
16. Pomahac B, Pribaz J, Eriksson E, et al. Three patients with full facial transplantation. *N Engl J Med* 2012;366:715–722
17. Pribaz JJ, Caterson EJ. Evolution and limitations of conventional autologous reconstruction of the head and neck. *J Craniofac Surg* 2013;24:99–107
18. Gok G, Michl P, Williams MD, et al. Ultrasound-guided botulinum toxin injection to treat a parotid fistula following gunshot injury. *J R Army Med Corps* 2015;161:64–66
19. Ferron C, Cernea SS, Almeida ART, et al. Primary treatment of early fistula of parotid duct with botulinum toxin type A injection. *Ann Bras Dermatol* 2017;92:864–866
20. Christiansen H, Wolff HA, Knauth J, et al. Radiotherapy: an option for refractory salivary fistulas. *HNO* 2009;57:1325–1328
21. Gordin EA, Daniero JJ, Krein H, et al. Parotid gland trauma. *Facial Plast Surg* 2010;26:504–510
22. Bomeli SR, Desai SC, Johnson JT, et al. Management of salivary flow in head and neck cancer patients—a systematic review. *Oral Oncol* 2008;44:1000–1008
23. Arnaud S, Batifol D, Goudot P, et al. Nonsurgical management of traumatic injuries of the parotid gland and duct using type a botulinum toxin. *Plast Reconstr Surg* 2006;117:2426–2430

Joint Statement by the Surgery Journal Editors Group – 2018 of the American College of Surgeons

We, the editors of surgery journals, believe that conducting sex-inclusive biomedical and clinical research is imperative to improving health outcomes of men and women. Recent studies have shown that the majority of biomedical research in the field of surgery and related topics is conducted on male animals and male cells, even when studying diseases prevalent in women.[1] Human clinical research suffers from a lack of sex-based reporting and sex-based analysis of the results.[2,3] Given these findings, the National Institutes of Health (NIH) has now asked that sex be considered as a biologic variable in all NIH-funded research.[4] As such, we support uniform, defined reporting of the sex used for human, animal, tissue, and cell research in all manuscripts published in our journals. If only one sex is reported, authors must include a justification statement as to why only a single-sex study was conducted. We also will require sex-based reporting and analysis of data for all human, animal, tissue, and cell research. As a group, we will require this among all our collective surgery journals.

References

1. Yoon DY, Mansukhani NA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias exists in basic science and translational surgical research. Surgery. 2014;156:508-516
2. U.S. Government Accountability Office. National Institutes of Health: Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research. 2015
3. Mansukhani NA, Yoon DY, Teter KA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Determining if sex bias exists in human surgical clinical research. JAMA Surg. 2016;151:1022-1030
4. National Institutes of Health Office of Extramural Research. Consideration of Sex as a Biological Variable in NIH-funded Research. 2015