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ORIGINAL ARTICLE

Chemical components separation with botulinum toxin A: a novel technique to improve primary fascial closure rates of the open abdomen

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Abstract
Introduction Failure to definitively close the open abdomen (OA) after damage control laparotomy leads to considerable morbidity and mortality. We have developed a novel technique, the "chemical components separation," which incorporates injection of botulinum toxin A (BTX), a long-term flaccid paralytic, into the lateral abdominal wall musculature.
Methods This is a retrospective review of all OA patients (age ≥18) from December 2009–June 2010 who underwent BTX injection. Under ultrasound guidance, a total of 300 units of BTX were injected into the external oblique, internal oblique and transversus abdominus.
Results A total of 18 patients were injected with a median age of 66 years (56 % male). Indications for OA treatment included questionable bowel viability (39 %), shock (33 %), loss of abdominal domain (6 %) and feculent contamination (17 %). Median ASA score was 3 with an APACHE 3 score of 85. Patients underwent a median of 4 serial abdominal explorations. The primary fascial closure rate was 83 % with a partial fascial closure rate of 6 % and planned ventral hernia rate of 11 %. Of the 9 patients injected within 24 h of their initial OA procedure, 89 % achieved primary fascial closure. Mortality was 11 %; death was unrelated to BTX injection. The overall complication rate was 67 %; specific complications rates included fascial dehiscence (11 %), enterocutaneous fistula development (0 %), intra-abdominal abscess (44 %) and deep surgical site infection (33 %).
Conclusion The "chemical components separation" technique described is safe and avoids the extensive dissection necessary for mechanical components separation in critically ill patients with infected/contaminated abdominal domains. While further evaluation is required, the described technique provides potential to improve delayed primary fascial closure rates in the OA setting.

Keywords Components separation · Open abdomen · Damage control · Laparotomy · Hernia

Introduction

Open abdomen management (OA) after damage control and second look laparotomies is a technique utilized by acute care surgeons in the most critically ill trauma and acute general surgery patients. This maneuver, while potentially life saving, has significant short- and long-term ramifications. Complications including wound infection, intra-abdominal abscess, enterocutaneous fistula and ventral hernia formation are common [1, 2]. The only way to reduce the rate of these morbidities is to perform delayed primary fascial closure. Proven methods for decreasing the rate of planned ventral hernia provide tension in the midline to counter the effects of lateral abdominal wall muscular retraction [3–5]. Despite these improvements, however, the planned ventral hernia rate continues to be substantial [6–8].

Botulinum toxin A (BTX, Botox®, Allergan, Inc. Irvine, CA 92612) is a FDA-approved neuromodulating agent that has been used extensively in motor, pain and cosmetic disorders over the past 20 years [9, 10]. This toxin

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functions by blocking the release of acetylcholine and pain modulators (calcitonin gene–related peptide and substance P) from the pre-synaptic cholinergic nerve terminal, resulting in flaccid paralysis and pain modulation. We have developed a "chemical components separation" technique that takes advantage of the flaccid paralysis created after BTX injection. If this flaccid paralysis can provide decreased midline abdominal wall tension, then, theoretically, the rate of primary fascial closure will increase. We had 2 aims: (1) to describe and analyze the BTX injection technique and (2) to determine the effects that BTX has on the abdominal wall after OA.

Methods

Authorization by the Institutional Review Board was obtained to analyze retrospectively patients that underwent BTX injection after OA from December 2009 through June 2010. Patients aged less than 18 years old were excluded. Data in relation to demographics, comorbidities, American Society of Anesthesiologists (ASA) and Acute Physiology and Chronic Health Evaluation III (APACHE 3) scoring models, vital signs, serial laboratory data and outcomes including complications and in-hospital mortality were recorded. The indications for OA management were defined upon review of the operative report and were defined as "shock" (hypotension with evidence for end organ damage), "bowel viability" (need for second look laparotomy in the face of bowel ischemia without signs of shock), "loss of abdominal domain" (inability to primarily close the fascia after laparotomy) and "feculent contamination" (septic contamination within the abdominal cavity requiring repeat operative abdominal washout). The type of abdominal closure was defined using modifications of the Open Abdomen Advisory Panel definitions of abbreviated celiotomy; "planned ventral hernia" was expanded to include any abdominal wall defect closed with polyglactin 910 mesh, and therefore, "partial fascial closure" was defined as closure with permanent or bioprosthetic protheses [7, 11]. Serial abdominal exploration was defined as abdominal re-exploration in the operating room after the initial OA procedure. Post-operative acute renal failure (ARF) was defined by the RIFLE criteria [12]. Mortality was defined as death by post-operative day 30 or prior to hospital dismissal.

Data are presented as medians and percents or ranges, as appropriate.

Chemical components separation technique

Due to the associated severity of illness secondary to severe sepsis and/or hemorrhagic shock universally present within this patient population, focus on treatment of the underlying clinical problem is paramount. We do not recommend performing the BTX injection procedure in the operating room (OR) during the initial laparotomy. DCL mandates speedy performance of life saving procedures. Only once the patient's hemodynamic status has stabilized and aggressive resuscitation has been completed, generally within 12–24 h, should the surgeon consider proceeding. Management of the DCL patient should follow descriptions previously published [8, 11]. We recommend either a negative pressure dressing or a Wittman patch as a TAC device to ensure midline tension, based on surgeon preference and experience. A surgical intensive care unit (SICU) comfortable with the management of DCL should have the equipment and experience necessary for the procedure. Alternatively, the procedure can be performed during a return trip to the OR.

After obtaining informed consent, and ensuring no contraindications exist (Table 1), the abdomen is widely prepped and draped, a surgical pause confirming the patient and procedure is performed. Depending on the type of TAC utilized, this may need to be removed or altered to allow for sufficient space for ultrasound (US)-guided BTX injection. Three-hundred units of BTX are reconstituted in 150 cc of injectable normal saline (NS; final concentration = 2 units/cc). Two separate syringes are labeled and loaded onto a 3-way stopcock, one with the BTX solution and the other with injectable NS. There are 6 separate injection sites on the patient's abdominal wall: right/left subcostal; right/left anterior axillary; right/left lower quadrants (Fig. 1). An 18-gauge spinal needle attached to a 3-way stopcock via a 9-inch extension tubing is advanced under US guidance into the external oblique, internal oblique and transversus abdominus muscles at each of the 6 injection sites (Fig. 2a, b). For ease of tissue layer identification, the initial injection is into the transversus abdominus layer first with subsequent injections into the remaining muscle bellies as the needle is withdrawn. One to two milliliters of injectable NS is injected in each layer to ensure appropriate needle placement—when the appropriate fascial planes bulge on US view, then the correct plane has been entered (Fig. 2a, b). Injection of 8.3 cc (16.6 units) of the BTX solution for each muscle is then performed at each of the 6 injection sites (25 cc/50 units per injection site). The goal, after completion of the procedure, is diffuse spread and saturation of the BTX solution in all 6 lateral abdominal wall muscles bellies (right/left transversus abdominus; right/left internal oblique; right/left external oblique).

Results

A total of 18 patients underwent chemical components separation with a median age of 66 years (56 % male). Questionable bowel viability was the most common

Table 1 Indications and contraindications for botulinum toxin type A injection after damage control laparotomy

Indications
1. Patient <18 years of age with an open abdomen after damage control laparotomy likely require temporary abdominal closure for >24 h
Contraindications
1. Pregnancy/breast feeding
2. Pre-existing pareses:
a. Amyotrophic lateral sclerosis
b. Myopathy
c. Motor polyneuropathies
3. Impaired neuromuscular transmission
a. Myasthenia gravis
b. Lambert–Eaton syndrome
4. Concurrent or potential likelihood for aminoglycoside use (i.e., Gentamicin)
5. Abdominal wall necrosis
6. Hemodynamic instability

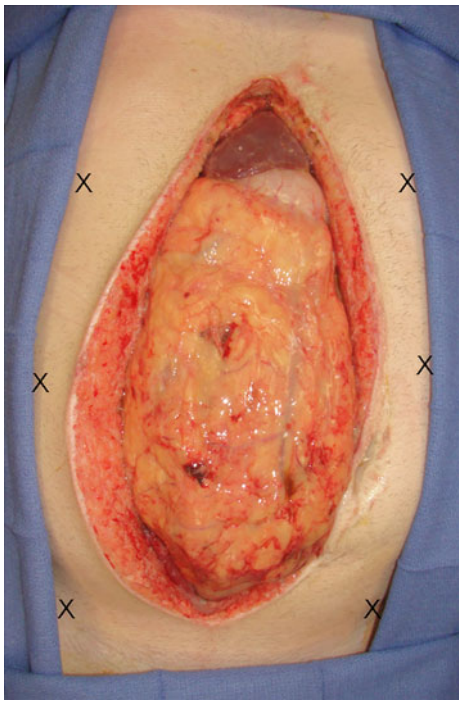

Fig. 1 Botulinum toxin type A injection sites—right/left subcostal; right/left anterior axillary; right/left lower quadrants

Table 2 Indications for open abdomen management

Indication	*N* (%)
Bowel viability	9 (39 %)
Shock	6 (33 %)
Loss of abdominal domain	1 (6 %)
Feculent contamination	3 (17 %)

Table 3 Patient demographic, pre-operative and intra-operative characteristics

	BTX ($n = 18$)
Comorbidities	
CAD	7 (39 %)
Arrhythmia	4 (22 %)
PVD	4 (22 %)
Malignancy	4 (22 %)
Prior ventral hernia repair	4 (22 %)
PUD	3 (17 %)
Diabetes mellitus	3 (17 %)
Steroid use	3 (17 %)
CHF	2 (11 %)
CRF	2 (11 %)
COPD	2 (11 %)
CVA	1 (6 %)
Dialysis	1 (6 %)
Connective tissue disorder	1 (6 %)
ASA score	3 (2–4)
APACHE 3	85 (30–133)

OA open abdomen, *SBP* systolic blood pressure, *CHF* congestive heart failure, *CAD* coronary artery disease, *CRF* chronic renal failure, *COPD* chronic obstructive pulmonary disease, *PVD* peripheral vascular disease, *PUD* peptic ulcer disease, *CVA* cerebral vascular disease, *ASA* American Society of Anesthesiologists, *APACHE* Acute Physiology and Chronic Health Evaluation

indication for OA (Table 2). The etiologies of shock included septic (67 %), hemorrhagic (28 %) and cardiogenic (4 %). All temporary abdominal closures were negative pressure dressings. Patient characteristics are presented in Table 3 and demonstrate a patient population with substantial comorbid conditions. Total fluid balance was 10,302 cc (3,509–22,283 cc) for the first 24-h after the initial DCL and 5878 cc (2,300–28,359 cc) for the second 24-h period. There was 11 % mortality rate with substantial complications rates (Table 4). There were a median of 3 serial abdominal explorations (1–8) after the initial OA procedure. The primary fascial closure rate was 83 % with a partial fascial closure rate of 6 % and planned ventral hernia rate of 11 %.

Nine patients underwent chemical components separation within 24 h of their initial OA procedure. Of these, 89 % (8/9) achieved primary fascial closure with one partial fascial closure (11 %). There were no complications related to BTX.

Discussion

OA management is an increasingly adapted technique used in critically ill surgical patients. Although it has been

Table 4 Patient outcomes

Outcome	BTX $n = 18$ (range)
Mortality	11 %
Overall morbidity	67 %
Intra-abdominal abscess	44 %
Superficial wound infection	33 %
Deep surgical site infection	33 %
ARF	17 %
Re-operation after closure	17 %
Fascial dehiscence	11 %
Tracheostomy	11 %
Fascial necrosis	6 %
Enterocutaneous fistula	0 %
ICU days, median	9 (3–57)
Ventilator days	7 (2–10)
Days with OA	5 (2–9)
Hospital days, median	23 (8–108)

OA open abdomen, *ARF* acute renal failure, *IQR* interquartile range, *BTX* botulinum toxin A

shown that OA has a survival advantage, there is a price associated with this success [12]. Failure to achieve primary fascial closure costs the patient a higher rate of overall morbidity, enterocutaneous fistulae and ventral herniae as well as lower quality of life [13, 14]. Therefore, primary fascial closure is a key goal of any patient with an OA. The "mechanical components separation" as originally described by Ramirez [11, 15] will facilitate fascial closure but should be avoided in the acute phase; it requires large subcutaneous and muscular flap dissection in a contaminated or grossly infected field and eliminates its use for long-term reconstruction of the abdominal wall. To avoid these, we developed the "chemical components separation," a minimally invasive technique that provides flaccid paralysis of the lateral abdominal wall muscles.

The presence of an open abdomen allows for biomechanical forces to develop that ordinarily are counteracted from normal anatomical structure of the abdominal wall [16]. The lateral abdominal wall musculature (external oblique, internal oblique and transversus abdominus) creates a lateral retraction force that is opposed centrally at the linea alba. Save for the systemic paralysis present during

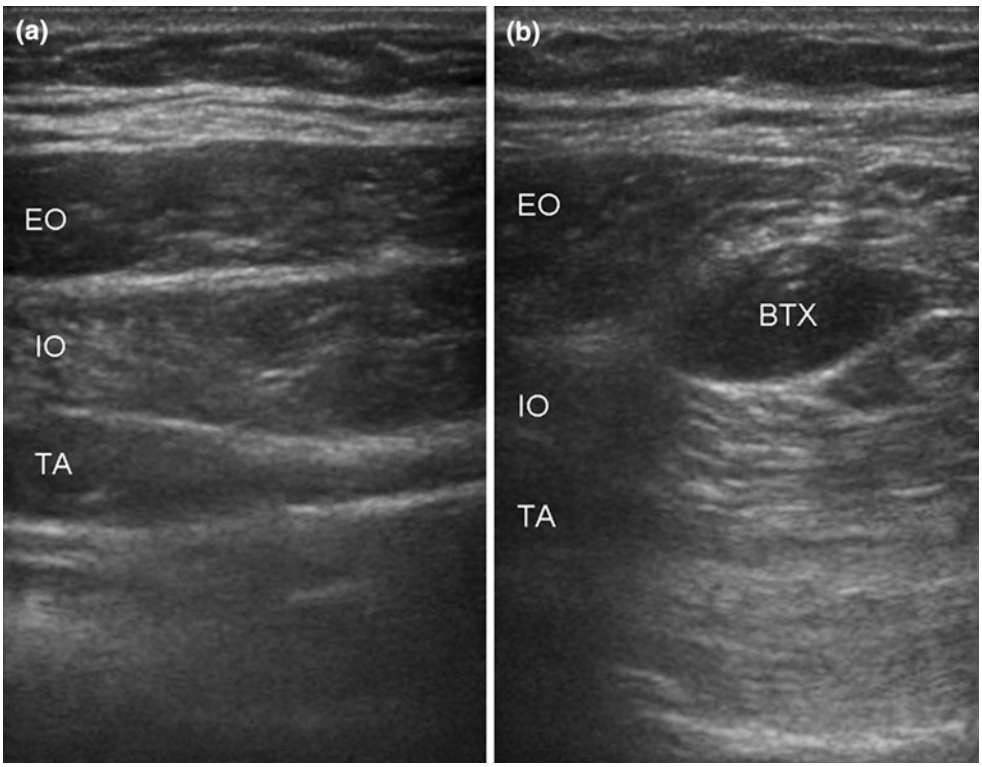

Fig. 2 Ultrasound-guided injection of the botulinum toxin into the lateral abdominal wall musculature. **a** Anatomy of the abdominal wall muscles prior to injection. **b** Anatomy of the abdominal wall muscles after injection. *EO* external oblique, *IO* internal oblique, *TA* transversus abdominus, *BTX* botulinum toxin

general anesthesia, these muscles will contract from voluntary movements and involuntary spasms. With the obliteration of the linea alba that results from midline laparotomy and OA management, there is an unopposed lateral abdominal wall retraction [17]. The success of negative pressure dressings and the Wittmann patch in enhancing the ability to perform primary fascial closure is likely related to the opposition of this lateral wall abdominal retraction [18, 19]. Logically, therefore, if a safe method of decreasing the lateral abdominal wall retraction can be developed, the ability to perform primary fascial closure could improve.

BTX is a potent neurotoxin produced by the anaerobic gram positive rod, *Clostridium botulinum* [9]. Seven serotypes exist (a–g) with variable efficacy and duration of action, two of which are commercially available within the United States, namely serotypes A and B. BTX functions via cleavage of cytosolic-soluble proteins present at the motor nerve terminus. This reaction blocks the exocytosis of acetylcholine-rich exosomes creating flaccid paralysis. The clinical effect of this paralysis can be demonstrated as early as day 3 after intramuscular injection with maximum effect reached at 2 weeks [9]. The effect is temporary with full nerve recovery by 3–6 months.

The biomechanical forces of the abdominal wall under the influence of BTX have been studied, but are not well defined, particularly after DCL. The toxin injection into the abdominal wall musculature is known to decrease intra-abdominal pressure, increase intra-abdominal volume and decrease the motor unit potential of the abdominal muscles in rats [20]. Additionally, a porcine model has been developed that demonstrates the beneficial effects of BTX injection of the abdominal wall. In this model, 79 % of the tension of a mechanical components separation was achieved [21]. The only extant human study is a case series of 10 patients who underwent BTX injection during elective ventral hernia repair after healing from OA [22]. This technique reduced the hernia diameter by more than 5 cm on average. They then performed elective operative hernia repair. At 9 months, there were no known hernia recurrences.

The most significant drawback to our technique is the limitations of BTX's mechanism of action. The protein cleavage necessary to prevent endosome release takes several days to realize. A subjective clinical effect will not be noticed for 48 h; maximum effect is reached at 2 weeks, with duration of effect lasting 6–9 months [9]. Given the higher rate of fascial closure if the chemical components separation is performed within 24 h, we therefore recommend injection as soon as possible, after appropriate hemodynamic stabilization. This will maximize BTX's effects. Promisingly, the long duration of effect may be beneficial by providing reduced lateral tension on the healing midline wound for several months.

BTX uses are widespread throughout the body to safely treat disorders associated with muscular spasm in all age groups [23, 24]. The doses used vary and are based on muscle size and location of the motor end plate [25]. The lateral abdominal wall muscles are broad-based and flat, limiting the ability to anatomically identify the motor end plates associated with each muscle [26]. Instead, we utilized toxin diffusion to ensure appropriate spread of the medication throughout the muscle belly. Low concentrations and high volumes of injection through large bore needles have been shown to improve the outcomes of patients with spasticity in similar shaped muscles [27]. One must be careful, however, as the chance for systemic spread increases with larger volumes [13]. In addition, there has been concern over systemic spread with doses over 400 units; therefore, we chose a dose believed to have appropriate efficacy as well as safety in the setting of the desired diffusion (300 units) [28]. We chose 6 separate injection sites (3 per side) as it has been suggested that 50 units per site is the practical upper limit dose [29].

Our protocol utilizes US rather than EMG to localize the injections. We found that US-guided injection is an easy-to-master technique that allows for accurate placement of BTX into the appropriate muscle layers. Similar to introduction of a central venous catheter, use of US greatly assists with identification and localization of the 3 muscle layers to be injected (Fig. 2a, b). One can be sure they are not within the peritoneal cavity by following the needle to the correct layer. Injection of 1–2 cc of NS assists in ensuring correct needle placement by real time visualization of the associated engorgement of the appropriate fascial plane. In addition, the diffusion of the BTX can be seen on live US imaging, ensuring that the large surface area of these muscles is covered.

Paralysis of the abdominal wall for abdominal wall defects is not novel. Systemic paralysis to facilitate closure of gastroschisis defects has been described, but not accepted by the pediatric surgery community [30]. More recently, De laet et al. Hg [31] described the effects of systemic paralysis in patients with intra-abdominal hypertension by showing a reduction in intra-abdominal pressure from 18 mm Hg to 14 mm. In addition, some members of the Open Abdomen Advisory Committee will systemically paralyze their patients to "prevent evisceration and fascial retraction" in the setting of an OA [11]. There are severe drawbacks to any approach that utilizes systemic paralysis. Patients require ventilatory support and are at significant risk for decubitus ulcers, venous thromboembolism as well as infectious complications. These risks are obviated by the selective paralysis provided for by BTX.

An additional advantage to BTX use in the open abdomen is its ability to modulate pain. In addition to the paralytic effects, BTX inhibits the release of substance P and

calcitonin gene related peptide, powerful molecules that are involved in inflammation and pain sensation [32]. Decreased release of these factors may lead to lower narcotic and sedation requirements, potentially lessening delirium and ileus rates in this critically ill population. BTX has been shown to be successful in pain relief in clinical trials in other pain disorders [33, 34]. In addition, The BTX injection technique presented here has ben shown to be beneficial in myofascial pain after ventral hernia repair [19].

There are important drawbacks to the presented technique. Firstly, patients undergoing OA by their vary nature are critically ill. They must stabilize prior to performing this technique. Secondly, although there is substantial data that prove the safety BTX, systemic absorption is a possibility. While our protocol prescribes a large dose of BTX relative to most cosmetic procedures, BTX has a broad therapeutic window [9]. Systemic absorption is relevant only at doses significantly higher than those used within our protocol. The local, desired effects of abdominal wall muscles, however, can diminish the function of accessory respiratory muscles. Therefore, chronic obstructive pulmonary disease is a contraindication to the procedure until further study is complete. Thirdly, as a neuromodulator, there are potential interactions with pre-existing pareses and impaired neuromuscular transmission syndromes (Table 1) Patients with these rare conditions have a contraindication to BTX.

The chemical components separation technique described was safe and feasible. We believe that BTX provided for a relaxation of the lateral abdominal wall musculature creats less tension at the midline throughout the duration of the OA. When used in conjunction with techniques that oppose lateral wall retraction such as negative pressure dressings or the Wittmann patch, we feel a reduction in tension at the time of attempted closure results, facilitating primary facial closure. Further experience in the form of a clinical trial is necessary prior to widespread implementation of this novel technique.

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