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BOTULINUM TOXIN A INDUCED PARALYSIS OF THE LATERAL ABDOMINAL WALL AFTER DAMAGE CONTROL LAPAROTOMY: A MULTIINSTITUTIONAL, PROSPECTIVE, RANDOMIZED, PLACEBO CONTROLLED PILOT STUDY

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Abstract

INTRODUCTION—Damage control laparotomy (DCL) is a life-saving operation used in critically ill patients; however, interval primary fascial closure remains a challenge. We hypothesized that flaccid paralysis of the lateral abdominal wall musculature induced by Botulinum Toxin A (BTX), would improve of rates of primary fascial closure, decrease duration of hospital stay (LOS), and enhance pain control.

METHODS—Consenting adults who had undergone a DCL at two institutions were prospectively randomized to receive ultrasound-guided injections of their external oblique, internal oblique, and

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Study Type: Therapeutic/Care Management Study

Disclosure: Off-label use of Botulinum Toxin A

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transversus abdominus muscles with either BTX (150cc, 2units/cc) or placebo (150cc 0.9%NaCl). Patients were excluded if they had a BMI>50, remained unstable or coagulopathic, were home O_2 dependent or had an existing neuromuscular disorder. Outcomes were assessed in a double-blinded manner. Univariate and Kaplan Meier estimates of cumulative probability of abdominal closure were performed.

RESULTS—We randomized 46 patients (24 BTX, 22 placebo). There were no significant differences in demographics, comorbidities, and physiological status. Injections were performed on average 1.8 ± 2.8 days after DCL (range 0-14). The 10-day cumulative probability of primary fascial closure was similar between groups: 96% for BTX (95% CI 72%-99%) and 93% for placebo (95% CI 61%-99%); HR =1.0 (95% CI 0.5-1.8). No difference between BTX and placebo groups was observed for LOS (37 vs 26 days, p=0.30) or intensive care unit stay (17 vs 11 days, p=0.27). There was no difference in median morphine equivalents following DCL. The overall complication rate was similar (63% vs 68%, p=0.69), with 2 deaths in the placebo group and 0 in the BTX group. No BTX or injection procedure complications were observed.

CONCLUSION—Use of BTX after DCL was safe but did not appear to affect primary fascial closure, LOS, or pain modulation after DCL. Given higher than expected rates of primary fascial closure, type II error may have occurred.

Keywords

Open Abdomen; Damage Control Laparotomy; Trauma; Emergency Surgery

Introduction

Damage control laparotomy (DCL) is a lifesaving maneuver used successfully in critically ill trauma and emergency general surgery patients.[1,2] This technique utilizes source control of hemorrhage and sepsis via an abbreviated laparotomy with temporary abdominal closure (TAC). Subsequent resuscitation in the surgical intensive care unit using Surviving Sepsis and damage control resuscitation techniques are performed until re-exploration once stabilized.[3,4] At this point, injuries are definitively repaired and abdominal fascial re-approximation is attempted.[5] Unfortunately, only 43% of patients will be closed at the first attempt with decreasing rates of closure thereafter. [6] In fact, 10-50% of patients will leave the hospital with a hernia. [9,7,8]

For those patients in whom fascial closure is not achieved, complications including wound infections, enterocutaneous fistulae, and intra-abdominal abscesses occur at alarmingly high rates.[9,10] Additionally, extensive abdominal wall reconstruction will likely be required in the long term. The key for preventing these complications is definitive closure of the abdominal fascia. The application of midline tension from temporary abdominal closure devices such as negative pressure dressings have been shown to improve rates of primary fascial closure; despite these advances, planned ventral hernia rates remain substantial. [11,12,13,14]

The Food and Drug Administration has approved the clinical use of botulinum toxin a (BTX; Botox; Allergan, Inc.; Irvine, CA) for myriad conditions including cosmetic, motor and pain disorders.[15,16] As a neuromodulating agent, BTX temporarily blocks the release of

peptide-rich endosomes at the pre-synaptic cholinergic nerve terminal. These endosomes primarily contain acetylcholine in addition to pain and inflammatory mediators such as calcitonin gene related peptide and substance P. When the synaptic transmission of these agents is prevented, the injected skeletal muscle becomes flaccidly paralyzed with diminished pain sensation.[17,18] Injection of BTX, therefore, into the lateral abdominal wall muscles should result in reduced lateral tension. When used in combination with known techniques that provide midline tension, a theoretical synergistic effect may improve the rates of primary fascial closure after TAC. In fact, we have previously published our retrospective results in a separate patient population with encouraging results.[19] We aimed to determine the actual effect of BTX on the abdominal wall after DCL. We hypothesized that patients injected with BTX would have greater rates of primary fascial closure, lesser rates of complications, and correspondingly lower pain medication requirements.

Methods

Institutional Review Board approval at Mayo Clinic (Rochester, MN) and the University of Minnesota - Regions Hospital (St. Paul, MN) was obtained to perform a randomized, double blinded, placebo controlled, multi-institutional pilot study comparing the injection of BTX versus placebo (0.9% injectable normal saline) into the lateral abdominal wall muscles of patients who underwent TAC for trauma and emergency general surgery. Given the novelty of the intervention and lack of comparative data, the study was run as a pilot study to accrue data for potential further BTX studies in open abdomen (OA) patients. The study began in November 2011 and was completed May 2014. Patients were excluded if they were younger than 18 years of age, had a body mass index greater than 50, failed to achieve hemodynamic stability prior to injection (stable/decreasing lactate, base deficit, or vasopressor use), pregnancy, prisoners, pre-existing pareses (Amyotrophic Lateral Sclerosis, myopathies, motor polyneuropathies), impaired neuromuscular transmission (Myasthenia Gravis, Lambert-Eaton Syndrome), concurrent aminoglycoside use, complicated Chronic Obstructive Pulmonary Disease (COPD; chronic oxygen dependence, chronic hypercarbia 50 mm Hg or greater or steroid dependent), known metastatic malignancy, necrotizing fasciitis of the trunk, or International Normalized Ratio greater than 1.5. Data was collected in a prospective fashion and managed using REDCap electronic data capture tools hosted at Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[20] Informed consent was obtained from the patient or their legal authorized representative using trained study coordinators and/or the site Principal Investigators.

A DCL protocol was followed at both institutions to ensure standardization of DCL management. The treating surgeon’s discretion was used to determine the need for DCL. The ABThera system was used (KCI, Inc. San Antonio, TX) for TAC purposes in concert with fascial retention sutures. Planned re-exploration occurred at least every 48 hours to attempt fascial re-approximation. Patients who had uncontrolled sources of sepsis or hemorrhage were returned to the operating room as dictated by their clinical course.

The primary endpoint of interest was the rate of primary fascial closure by hospital dismissal. Secondary endpoints of interest included in-hospital mortality, complications (wound infection, fascial dehiscence, enterocutaneous fistula, acute renal failure, pneumonia), ventilator days, ICU LOS, hospital LOS, and narcotic pain medication utilization.

Injection Procedure

Mayo Clinic provided the blocked randomization scheme for 6 patients to Regions Hospital. BTX was prepared at each institution. Patients randomized to the BTX group underwent injection of 150 units BTX diluted 2:1 in 300 cc of 0.9% normal saline while patients randomized to the placebo arm had 300 cc of 0.9% normal saline injected. Both the clinicians and patients were blinded to the group assigned; both injection fluids are clear. Our technique of BTX injection has been previously published.[19,21] Briefly, ultrasound guidance is used to identify the lateral abdominal wall muscles (external oblique, internal oblique, and transversus abdominus) to guide an 18 gauge needle into their respective muscular planes. All three muscles are injected bilaterally (6 muscles total) with a total of 50 cc per muscle. Each muscle had 3 separate injections points; right/left subcostal; right/left anterior axillary; right/left lower quadrants to ensure adequate distribution of the injected fluid.

Statistics

As a pilot study, a power analysis was not performed. A blocked randomization code was assigned to each patient to help ensure a relatively equal distribution of patients who received BTX or placebo. The statisticians were blinded to group allocation until the point of study completion and data analysis. Associations of primary fascial closure, morbidity, mortality, and duration of hospital and ICU stay were compared using the chi-square, Fisher exact, and Wilcoxon rank sum tests. The magnitude of the association of each feature studied was evaluated with logistic regression and summarized with an odds ratio and 95% confidence interval. All tests were two-sided with p-values <0.05 considered statistically significant.

Results

A total of 155 patients underwent DCL during the study period and were screened for eligibility, of whom 46 were enrolled (24 BTX, 22 placebo; **Figure 1**). Six patients were injected at Regions Hospital (3 BTX, 3 placebo) and 39 (21 BTX, 19 placebo) were injected at Mayo Clinic. All patients received the intended treatment and were therefore included in analysis of the primary endpoint. As expected from randomization, no differences were noted in baseline clinical characteristics or demographics save for an elevated BMI in the placebo group (**Table 1**).

The primary endpoint of primary fascial closure was equivalent whether patients received BTX or placebo (96%; 95% CI 72%-99% vs. 93%; 95% CI 61%-99%; HR =1.0 95% CI 0.5-1.8). The average post-DCL day of injection was 1.8 ± 2.8 days (range 0-14). There was no difference in outcomes in regards to durations of hospital (LOS; 37 vs 26 days, p=0.30)

or intensive care unit stay (17 vs 11 days, p=0.27; **Table 2**). The overall complication rate was similar (63% vs 68%, p=0.69), with 2 deaths in the placebo group and 0 in the BTX group. No difference was noted in the amount of morphine equivalents throughout the first 5 days following DCL (**Table 3**). No BTX or injection procedure complications were observed.

Discussion

The ability to close the OA remains a significant limitation to the use of DCL. Despite the historically low rates of primary fascial closure in the literature, our study demonstrated a very high rate no matter if BTX or placebo was injected. Additionally, there was no difference in the other secondary endpoints under study.

BTX, as a neuromodulating agent, decreases intra-abdominal pressure thereby increasing intra-abdominal volume in rats.[22] The "chemical component separation" provided by BTX has also been shown to achieve 79% of the tension of a mechanical components separation in pigs.[23] Whether this translates into a beneficial clinical effect in humans, however, is uncertain. In the only previously existing study of BTX in the OA, we were able to demonstrate a significant rate of improvement in primary fascial closure from 66% to 83% after BTX; however, while BTX injection into the abdominal wall in the OA setting was demonstrated, it was the inherent limitations from this flawed retrospective study which prompted us to perform the current clinical trial.[19] We did not, however, expect such a dramatic improvement in the rate primary fascial closure in the new study which was a significant limitation. Previous reports show a rate of primary fascial closure ranging from 52% to 83%.[2,7,19] Even a recent multi-institutional, prospective study of Level I trauma centers had a primary fascial closure rate of 66%.[14] The reasons for the improvement we documented are unclear but likely multifactorial. With the advent of damage control resuscitation for hemorrhage, significantly less crystalloid is administered, likely improving the pliability of the abdominal wall.[24] In addition, the recognition of the short- and long-term complications associated with planned ventral hernia has resulted in our increased aggressiveness in pursuing primary fascial closure. Another potential bias to the study are the inclusion criteria we utilized. Given the novelty of the procedure and the need to ensure safety, we incorporated multiple exclusion criteria. It is entirely possible that the patients who were excluded may be the very ones that could have benefited from BTX the most (e.g. obesity, COPD, anticoagulation, and hemodynamic instability requiring increased fluid for resuscitation). Lastly, in anticipation of this study, we protocolized OA management inclusive of re-exploration every 48 hours as well as the use of abdominal retention sutures.[8] The combination of these factors likely improved the rate of primary fascial closure thereby diminishing our ability to statistically discern a difference when perhaps a true difference existed.

The use of BTX injection has better studied for ventral hernias. Similar to DCL, lateral tension against the hernia repair is a risk factor for recurrence.[25] Minimization of this tension in the short term, perhaps through the injection of BTX, may lead to decreased rates of recurrence in the long term.[26,27] In addition, given the analgesic effects of BTX, there

may be a benefit to injection in terms of pain control and limited use of narcotic medications.[21] This analgesic benefit, however, was not demonstrated in our study.

Despite the theoretical benefits to reduction of lateral abdominal wall tension for OA patients, no benefit was noted. While there are many potential reasons for this, we believe the primary reason may be due to the mechanism of action of BTX. By blocking neurotransmitter release into the synaptic cleft, flaccid paralysis of the injected muscle will result. This effect, however, takes at least 2-3 days to demonstrate any effect and up to three weeks to reach maximum effect. While this can be anticipated for elective repairs of ventral hernias, the unpredictability of trauma does not provide the luxury of injection prior to DCL. As a result, only the initial effects of BTX were present for the majority of the patients included in this study. Knowing the limitations to the mechanism of action of BTX, persistence in closure of the abdominal wall after injection may have biased the study towards a higher rate of primary fascial closure in both arms. This detriment in the short term, however, may prove to be a benefit in the long term as flaccid paralysis can last up to 6 months. During this time, the midline fascial closure is healing. Reduced lateral abdominal wall tension at this stage may limit rates of long term incisional ventral hernias.

The ability to perform primary fascial closure after DCL seems to be improving; nevertheless, significant complications endure. While long term follow-up is required, BTX injection during the setting of DCL did not have any appreciable clinical benefits in the short term in this pilot study. Nevertheless, its use appears to be safe as the observed outcomes and complications were similar whether BTX or placebo was injected. Aggressive pursuit of primary fascial closure should continue in order to reach 100% primary fascial closure.

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NIH Registration #NCT01495962. The Biomechanical Effects of Flaccid Paralysis Induced by Botulinum Toxin a After Damage Control Laparotomy. Accessible at clinicaltrials.gov. Funded by the Eastern Association for the Surgery of Trauma.

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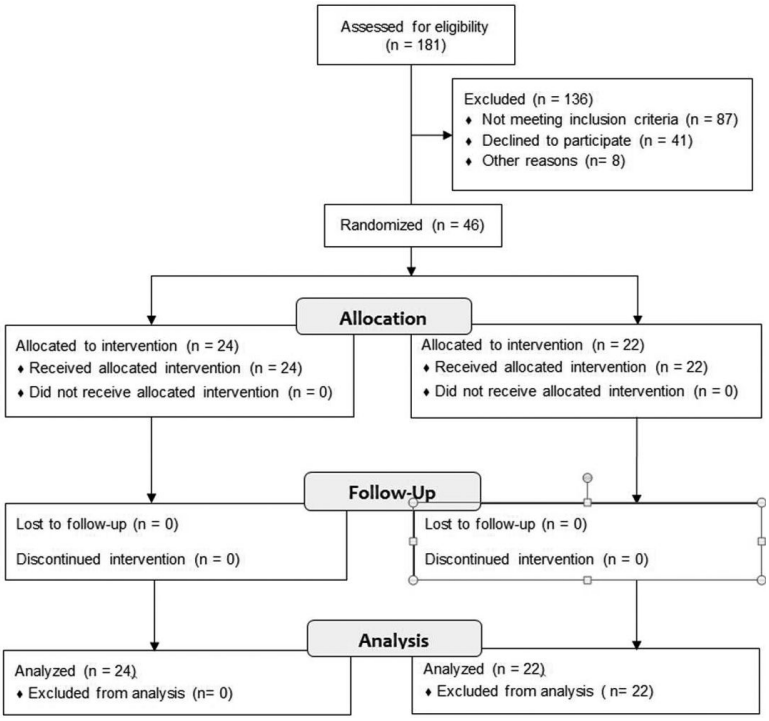

Figure 1.
CONSORT Flow Diagram for screening and eligibility criteria.

Table 1

Baseline Preoperative and Intraoperative Patient Characteristics. Continuous variables are presented as median (interquartile range) while nominal variables are presented as *n* (percentages).

Patient Characteristic/Comorbidity	**BTX (*n* = 24)**	**Placebo (*n* = 22)**	***P* value**
Age	58.3 (52.6-67.9)	61.9 (48.4-67.3)	.88
Male gender	13% (54%)	17 (77%)	.13
BMI	26.3 (19.9-30.7)	30.0 (26.9-32.9)	.032
Lowest systolic blood pressure	81 (67-91)	76 (70-87)	.71
Highest heart rate	114 (104-129)	130 (100-147)	.45
Highest temperature (C)	38.1 (37.3-39.2)	37.8 (37.0-38.7)	.36
Greatest base deficit	⁻6 (⁻10—4)	⁻5 (⁻14—2)	>.99
Highest lactate (mmol/L)	3.5 (1.8-4.2)	4.4 (2.1-7.0)	.93
Highest white blood cell count	15.4 (12.0-23.5)	15.3 (11.9-20.6)	.53
Lowest pre-op hemoglobin	9.2 (7.9-11.2)	9.3 (7.9-13.2)	>.99
Highest pre-op INR	1.3 (1.1-1.5)	1.4 (1.3-2.0)	.18
CAD or CHF	7 (29)	9 (41)	.54
Diabetes mellitus	5 (21)	3 (14)	.70
Hypertension	13 (54)	12 (55)	>.99
Chronic Renal Insufficiency	5 (21)	4 (18)	>.99
Tobacco use within 30 days	6 (26)	7 (35)	.74
Anticoagulated*	6 (25)	8 (40)	.34
Prior Abdominal Operation	14 (61)	10 (48)	.55
History of steroid use	3 (13)	2 (9)	>.99
ASA score ≥ 3	21 (88)	19 (86)	.43
Intra-op packed Red Blood Cells (units)	8.0 (1.0-16.9)	4.8 (0-4.3)	.18
Emergency laparotomy	20 (83)	16 (76)	.71
Bowel viable	10 (42)	11 (50)	.77
Contamination	6 (25)	4 (18)	.73
Septic shock	2 (8)	1 (5)	>.99
Hemorrhagic shock	8 (33)	8 (36)	>.99
Abdominal compartment syndrome	6 (25)	1 (5)	.10
Bowel resection	13 (57)	15 (68)	.54
Prior Abdominal Operation	14 (61)	10 (48)	.55

BMI – body mass index; INR – International Normalized Ratio; ASA – American Society of Anesthesiologists; CAD – coronary artery disease; CHF – congestive heart failure; INR – international normalized ratio

*Anticoagulated with clopidogrel, warfarin, or heparin

Table 2

Comparison of outcomes between groups. Continuous variables are presented as median (interquartile range) while nominal variables are presented as *n* (percentages).

Outcomes and Complications	**BTX (*n* = 24)**	**Placebo (*n* = 22)**	***P* value**
Number of index abdominal procedures	2 (1-3)	2.0 (1-3)	.14
Number of days of open abdomen	5.0 (2.0-6.5)	2.0 (2.0-5.0)	.15
Duration of hospital stay	23.5 (13.5-36.5)	19.0 (11.0-23.0)	.19
ICU Duration of stay (median)	8.0 (4.0-25.0)	6.0 (3.0-13.5)	.32
Ventilator days	3.0 (1.0-9.0)	4.0 (1.0-9.0)	.44
30 day mortality	0 (0)	2 (9)	.22
Wound infection	2 (8)	0(0)	>.99
Intraabdominal abscess	1 (4)	1 (5)	>.99
Anastomotic leak	1 (4)	0 (0)	>.99
Dehiscence	2 (8)	0 (0)	.49
Enterocutaneous fistula	1 (4)	1 (5)	>0.99
Bleeding	5 (21)	4 (18)	>.99
Reoperation after closure	0 (0)	1 (5)	.48
Acute renal failure	6 (25)	7 (32)	.75

ICU – intensive care unit

Table 3

Postoperative morphine equivalents of BTX vs Placebo groups. Results are presented as median (interquartile ranges).

Day	BTX (MSO4 mg)	Placebo (MSO4 mg)	P
1	112 (63.4-147.3)	90.8 (44.6-144.8)	.13
2	105 (67.3-157.8)	86.2 (40-155.5)	.21
3	88.9 (52.3-153.6)	95.3 (38.8-120.1)	.37
4	55.5 (30.7-148.7)	80.9 (33.8-99.4)	.40
5	53.8 (23.0-136.2)	45.5 (25.6-64.5)	.19