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Does the Injection of Botulinum Toxin Improve Symptoms in Patients with
Gastroparesis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selected EBM review is to determine whether or not the injection of botulinum toxin improves symptoms in patients with gastroparesis.

STUDY DESIGN: Review of two published, double blind randomized controlled trials and one published, open label pilot study were used for this review, which were found on PubMed.

OUTCOMES MEASURED: The outcome was the change in gastroparesis-associated symptoms, which was measured using the Gastroparesis Cardinal Scale Index (GCSI) and Gastroparesis Questionnaire. In the two double blind, randomized controlled trials by Arts et al. and Friedenberg et al., symptoms were quantified using the GCSI before and after the injection. Each of the 9 different gastroparesis-associated symptoms (nausea, regurgitation, vomiting, fullness, early satiety, postprandial fullness, loss of appetite, bloating and swollen abdomen) were graded from 0 (none) -5 (very severe), with higher scores indicating higher severity of symptoms. The total GCSI score was calculated by adding all individual symptoms severity scores. In the open-label pilot study conducted by Miller et al., the Gastroparesis Questionnaire was used to grade eight symptoms on a 5-point scale from 0 (none) to 4 (extreme). A total symptom score was determined as the sum of each the eight graded symptoms, with a maximum of 32.

RESULTS: In the study by Arts et al, symptoms improved significantly after the initial injection of saline or botulinum toxin. No additional improvement occurred after the second injection. In the study by Friedenberg et al, the group receiving botulinum toxin showed improvement in symptoms, however, it was not greater than the placebo group. In the study by Miller et al, symptom scores improved with botulinum toxin injection.

CONCLUSION: The results of the two double blind, randomized controlled trials show that the injection of botulinum toxin is not superior to placebo in improving symptoms of gastroparesis. The results of the open-label pilot study indicate that botulinum toxin does improve symptoms.

KEY WORDS: gastroparesis and botulinum toxin

INTRODUCTION

Gastroparesis, or delayed gastric emptying, is a disorder that slows or stops the movement of stomach contents to the small intestine.¹ Normally, muscles of the stomach contract to move food through the gastrointestinal tract.¹ With gastroparesis, however, food is not propelled properly and contents do not empty correctly; food leaves the stomach slowly or does not move at all.¹

This paper evaluates two double blind, randomized controlled trials, which compare the efficacy of the injection of botulinum toxin for improving symptoms of gastroparesis with placebo, and one open-label pilot study, which evaluates the ability of botulinum toxin to mend symptoms. The consideration of improving symptoms of gastroparesis is an important topic to discuss as the disorder is becoming increasingly common; it affects 9.6 per 100,000 men and 38 per 100,000 women and occurs in 80% of patients with dyspepsia.^{2,3} Additionally, over 40% of patients with diabetes have gastroparesis.⁴ As the disorder becomes more prevalent, the cost of medical care for gastroparesis increases as well. Although the cost in recent years is unknown, in 1998 the average cost for hospitalization due to gastroparesis was \$6,972 per patient per month.⁵ Furthermore, diabetic complications including gastroparesis totals \$22.9 billion dollars.⁶ Hospital admissions are also elevated; admissions with gastroparesis as the main diagnosis totaled 10,252 in 2004 and as the secondary diagnosis totaled 134,146 in 2004.⁶

Most cases of gastroparesis are idiopathic and therefore the cause is unknown.¹ When the cause is able to be identified, diabetes is most common.¹ Due to high levels of blood glucose that is often found with diabetic patients, damage can occur to the vagus nerve which leads to paralysis of stomach musculature.¹ Other known causes include

intestinal surgery and nervous system disorders such as Parkinson's disease or multiple sclerosis.¹

Symptoms of gastroparesis include nausea, fullness after a small amount of food, abdominal pain, abdominal bloating, and vomiting undigested food.¹ Severity of the symptoms is highly significant, as it is the basis of how physicians treat the disorder.¹ Change in diet and careful nutrition is often the first attempt at managing gastroparesis.¹ Smaller meals and low-fat, non-fibrous foods are frequently suggested.¹ In addition, medications can be used in management. Anti-emetics such as metoclopramide stimulate stomach muscle contraction and help decrease nausea and vomiting.¹ Antibiotics in low doses, like erythromycin, may also improve gastric emptying.¹ Possible side effects, however, include nausea, vomiting, and abdominal cramps.¹ If symptoms remain uncontrolled, gastric electrical stimulation may be used. With this option, a battery-operated device sends mild electrical pulses to stomach muscles to control nausea and vomiting.¹

Although the treatments listed above have been used to improve symptoms of gastroparesis, no cure exists. The proposed method of botulinum toxin injection has been used as treatment by acting as nerve-blocking agent.¹ The toxin is injected into the pylorus, the sphincter between the stomach and duodenum. Botulinum toxin keeps the pylorus open for longer periods of time which allows food content to be passed more easily to the small intestine and as a result, can lead to improvement of symptoms.¹ Botulinum toxin is shown among the three trials to provide improvement in symptoms but not superior in comparison to placebo.^{7,8,9}

OBJECTIVE

The objective of this systematic review is to determine whether or not the injection of botulinum toxin improves symptoms in patients with gastroparesis.

METHODS

The studies included in this review are one double blind, placebo controlled randomized controlled crossover trial, one double blind, placebo controlled randomized controlled trial, and one open label pilot study. The population studied was men and women with gastroparesis over the age of 18 years. The common intervention used among all studies was botulinum toxin injection. In the study conducted by Arts et al., 100 units (4 mL) of botulinum toxin was injected.⁷ In the second randomized controlled trial, Friedenberg et al. used 200 units (5 mL) of botulinum toxin A.⁸ The open label pilot study used a range of 80-100 units of botulinum toxin.⁹ The comparison intervention in the two double blind, placebo controlled studies was equal volume saline solution.^{7,8} Outcomes measured included change in gastroparesis-associated symptoms and were quantified using the Gastroparesis Cardinal Scale Index (GCSI) and Gastroparesis Questionnaire.^{7,8,9} The GCSI measured nausea, regurgitation, vomiting, fullness, early satiety, postprandial fullness, loss of appetite, bloating and swollen abdomen and the Gastroparesis Questionnaire measured postprandial fullness, early satiety, bloating, epigastric discomfort, epigastric pain, postprandial nausea, belching after meals, and vomiting.^{7,8,9}

Key words used in searches for this systematic review were “gastroparesis” and “botulinum toxin.” All articles were published in English and in peer-reviewed journals, the *American Journal of Gastroenterology* and *Alimentary Pharmacology and*

Therapeutics.^{7,8,9} Articles were selected from PubMed and chosen based on relevance to my clinical question and address of patient-oriented outcomes (POEMS). Inclusion criteria included studies that were randomized controlled trials published after 1996 and subjects that were older than 18 years old with diagnosed, documented gastroparesis. Exclusion criteria consisted of patients under the age of 18 years old and studies specific to one cause of gastroparesis. Summary statistics were reported using: p-values, numbers needed to treat (NNT), and mean change from baseline.^{7,8,9}

OUTCOMES

The outcome measured was change in gastroparesis-associated symptoms using two questionnaires about these symptoms, the GCSI and Gastroparesis Questionnaire. Using the GCSI, each of the nine different gastroparesis-associated symptoms (nausea, regurgitation, vomiting, fullness, early satiety, postprandial fullness, loss of appetite, bloating and swollen abdomen) was graded from 0 (none) to 5 (very severe), with higher scores indicating higher severity of symptoms. The total GCSI score was calculated by adding all individual symptoms severity scores, with a maximum score of 45.

In the crossover study by Arts et al., each patient completed the GCSI questionnaire before the start of the study and one month after each injection of either botulinum toxin or saline.⁷ Improvement in symptoms was based on mean change from the baseline score.⁷ The study conducted by Friedenberget al. also used the GCSI; a total score of ≥ 27 was considered moderate to severe symptoms. A ≥ 9 -point reduction at one month after injection of the study drug was defined as improvement.⁸

In the open-label pilot study by Miller et al., subjects were compared using before and after results of symptom scores based on the Gastroparesis Questionnaire, which

measures eight symptoms on a 5-point scale graded from 0 (none) to 4 (extreme).⁹ A total symptom score was determined as the sum of each the eight graded symptoms, with a maximum of 32.⁹ Improvement in symptoms was based on mean change from baseline score.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Arts (2007)	Double blind RCT crossover	23	>18	Symptoms suggestive of gastroparesis, established delayed gastric emptying for solids and liquids	Presence of esophagitis, gastric atrophy or erosive gastroduodenal lesions on endoscopy, presence of lesions on small bowel x-ray, major abdominal surgery, underlying psychiatric illness, use of NSAIDs, steroids, or drugs affecting gastric acid secretion	0	Pyloric injection of 100 units botulinum toxin A in 4 mL of saline
Friedenberg (2008)	Double blind RCT	32	18 to 75	Age 18-75, diagnosis of gastroparesis within 3 months of study, score of ≥ 27 on GCSI	Pregnancy, unfit to undergo endoscopy, prior abdominal surgery, known allergy to the protein, prior use of botulinum toxin A, unable to stop medications known to exacerbate delayed gastric emptying	2	Pyloric injection of 200 units (5 mL) of Botulinum toxin A
Miller (2002)	Open label pilot study	10	19-70	Idiopathic gastroparesis Symptoms of nausea, vomiting, and/or early satiety, refractory to prokinetic agents	Mechanical cause for delayed gastric emptying, diabetes mellitus, coagulopathy, pregnant or breast-feeding	0	Pyloric injection of 80-100 units of botulinum toxin type A

RESULTS

Two randomized controlled trials (Arts, Friedenber) in this systematic review compared reported symptoms after injection botulinum toxin to placebo, while the open-label plot study trial (Miller) compared symptoms before and after injection of botulinum toxin.^{7,8,9} The study conducted by Arts et al. was a randomized controlled, double-blind crossover study.⁷ All patients were randomized to receive botulinum toxin or saline first and were analyzed in those groups.⁷ Twelve patients received 100 units of botulinum toxin in 4 mL of saline and 11 patients received equal volume saline as the first injection.⁷ Prior to the start of the study and four weeks after each treatment, subjects completed the GCSI.⁷ In the group receiving botulinum toxin injections initially, the GCSI decreased significantly and had a mean change from baseline of -5.6 (21.3 to 15.7).⁷ Four weeks later, after saline injection, no additional improvement occurred (13.4).⁷ Subjects receiving initial saline injections showed significant improvement and had a mean change from baseline of -5.8 (32.1 to 26.3).⁷ Further improvement followed with botulinum toxin injections which had a mean change from baseline of -4.9 (26.3 to 21.4).⁷ All p-values were significant and ≤ 0.05 ; for initial botulinum toxin injection, the p-value was < 0.05 and for initial saline injections followed by botulinum toxin injections, $p = 0.002$.⁷

Table 2. GCSI Scores Before and After Initial Saline Treatment

Baseline	4 weeks after initial saline injection	4 weeks after botulinum toxin injection
32.1	26.3	21.4

Table 3. GCSI Scores Before and After Initial Botulinum Toxin Treatment

Baseline	4 weeks after initial botulinum toxin injection	4 weeks after saline injection
21.3	15.7	13.4

The study performed by Friedenberget al. included 32 patients who were assigned to a randomized group to receive botulinum toxin or placebo injections.⁸ Sixteen patients received botulinum toxin injections and the remaining 16 received saline injections.⁸ The GCSI scores were calculated before injection and one month later.⁸ At the one month follow up, six of 16 (37.5%) patients randomized to botulinum toxin and nine of 16 (56.3%) patients randomized to placebo had improvement in symptoms.⁸ The relative risk benefit (RBI) was calculated to -33.3% and absolute benefit increase (ABI) was -18.75%. Number needed to treat (NNT) was -5, meaning for every five people treated with botulinum toxin, one person fewer will have the expected benefit. The p-value was 0.01 in both the experimental and control group.⁸ Although the group receiving botulinum toxin showed improvement in symptoms, it was not greater than the placebo group.

Table 4. Summary of Effects of Botulinum Toxin and Placebo, One Month Post-Injection

	Botulinum Toxin	P-value	Placebo	P-value
Improved % *	37.5		56.3	
GCSI	-6.8 ± 9.2	0.01	-10.1 ± 12.7	0.01

* Improvement defined as a >9-point reduction in the score of the Gastroparesis Cardinal Symptom Index.

Table 5. Benefit of botulinum toxin on improvement of gastroparesis symptoms

Placebo control event rate (CER)	Botulinum toxin experimental event rate (EER)	RBI	ABI	NNT
56.25%	37.5%	-33.3%	-18.75%	-5

In the third and final study, by Miller et al., 10 patients received 80-100 units of

botulinum toxin injections.⁹ Subjects completed the Gastroparesis Questionnaire before treatment and at two- and four-week intervals post-injection.⁹ Overall, nine of the 10 patients had improvement in the total symptom score.⁹ The total symptom score had a mean change from baseline of -5 and -6.3 at two and four weeks, respectively (15.3 to 10.3 and 9.0).⁹ All p-values were less than 0.05., with p=0.034 at two weeks and p=0.006 at four weeks. As seen in Table 6, there were also significant improvements in specific symptoms: postprandial fullness ($p = 0.009$), bloating ($p = 0.017$), and abdominal discomfort ($p=0.042$).⁹

Table 6. Change in symptoms to botulinum toxin injection

Symptom	Before	4 weeks after injection	<i>P</i>
Post-prandial fullness	2.8	1.6	0.009
Post-prandial bloating	2.6	1.5	0.017
Post-prandial abdominal discomfort	2.1	1.1	0.042
Early satiety	1.9	1.5	0.104
Post-prandial epigastric pain	1.7	1.0	0.111
Post-prandial nausea	2.2	1.3	0.068
Belching after meals	1.3	0.8	0.177
Vomiting	0.8	0.6	0.168
Total symptom score	15.3	9.1	0.006

DISCUSSION

This systematic review investigated two randomized controlled trials and one open label pilot study to determine if botulinum toxin improves symptoms in patients with gastroparesis. Although all of the studies demonstrated that botulinum toxin does

improve symptoms of gastroparesis, the study by Arts et al. and Friedenberg et al. showed that botulinum toxin was not superior to placebo.^{7,8} The open label pilot study by Miller et al. revealed significant improvement in symptoms, however, there was no placebo group for comparison.⁹ In addition, only patients with idiopathic gastroparesis participated in the trial.⁹

As the likelihood is high that more patients will develop gastroparesis in the future, botulinum toxin represents a possible alternative management.⁸ Botulinum toxin cleaves SNAP-25, which blocks the exocytosis of acetylcholine in cholinergic nerve endings.⁷ As a result, botulinum toxin can inhibit an amplified barrier function at the pylorus and keep the pylorus open for a longer amount of time.^{1,7} The injection is simple and has local nerve-blocking effects, as opposed to prokinetic agents, the current mainstay of treatment, which have marginal benefit and significant toxicities.⁸

Additionally, researchers have used botulinum toxin to treat spastic disorders of striated and smooth muscles by local injection into the muscle.⁸ For example, botulinum toxin has been injected into the lower esophageal sphincter for treatment of achalasia.⁹ Symptoms improved temporarily for approximately three months.⁹

Limitations exist among the studies presented in this review. Sample sizes were narrow; the largest number of subjects was 32, in the study by Friedenberg et al., and the smallest number was 10, in the study by Miller et al.^{8,9} Future studies with a greater population may be necessary for further evaluation. In addition, in the study by Arts et al. and Miller et al., patients were evaluated one month after injection; a longer follow-up period may be required to adequately assess improvement in symptoms.^{7,9} Another limitation was the amount of botulinum toxin injection. In all three studies, the dose

ranged from 80-200 units of botulinum toxin.^{7,8,9} Future investigations may use higher doses to determine efficacy. Also, the open label pilot was not a blinded study, which may have obstructed patients' expectations and the improvement of symptoms may represent a placebo response.

CONCLUSION

Significant improvement in symptoms of gastroparesis with botulinum toxin injection was demonstrated in all three studies, however, in the two double blind, randomized controlled trials, botulinum toxin did not have greater results compared to placebo.^{7,8,9} Therefore, botulinum toxin does improve symptoms in patients with gastroparesis, but the evidence does not show superiority to placebo.^{7,8} Future studies should focus on adding more participants to increase the integrity and decrease limitations of the study. Researchers may also investigate different amounts of botulinum toxin needed to improve symptoms. Designs of future studies may use numerous botulinum toxin injections given over several months. Improvement of symptoms can then be better evaluated, as botulinum toxin is only a temporary nerve blocking agent and several injections may be required to achieve maximal improvement in symptoms. Continued research on botulinum toxin injections for the improvement of gastroparesis symptoms is necessary to benefit patients who do not have adequate control of symptoms with other treatment.

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