

Research Article



Evaluation the Efficacy and Outcome of Intersphincteric Injection of Botulinum Toxin in the Treatment of Children with Chronic Idiopathic Constipation in Iraqi Hospital

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ABSTRACT

Injection of botulinum toxin into the anal sphincter is an innovative, most safe and first-hand treatment of chronic idiopathic constipation and anal fissure in children. The purpose of this study was to determine the utility of intra-sphincteric injection of botox in the treatment of children with refractory constipation. All children who suffered from chronic constipation for more than three months, and who had not responded to medical treatment, were referred to pediatrics surgical clinic for surgical intervention by pediatric gastroenterologist. The patients were randomly divided into cases and control group. The control group received no injection and was only treated with stool softeners. While the case group received stool softeners in addition to botulinum injection. Next to the botox injection step, the patients were questioned about the presence or not for any signs of constipation that include painful defecation, vomiting, stool consistence, soiling and defecation interval. Defecation of painful stool existed in 88% of patients before botox injection and it was reduced to 15% after botox injection. In the control group, 90% of patients had painful defecation, which reduced to 86% after medical treatment ($P=0.0001$). Stool was hard in 80% of patients before was reduced to 28% after botox injection. In the control group, it existed in 81% of children and reduced to 78% after medical treatment ($P=0.0001$). Soiling existed in 62% of patients before and was reduced to 8% after botox injection, but in the control group it reduced from 62% to 42.5% after medical treatment ($P=0.0001$). In the control group, 98% of the patients had defecation intervals more than 3 days and it was the same after medical treatment. In case group, this index before botox injection was 9.1 days, and after botox injection was reduced to 2.6 days ($P=0.0001$). The present study results showed that injection of botulinum toxin into anal sphincter is an effective and safe new treatment of chronic idiopathic constipation in children.

Keywords: Botulinum toxin, chronic functional constipation, Internal anal sphincter, Pelvic floor dysfunction, Slow colon transit time.

INTRODUCTION

Chronic Constipation

Chronic functional constipation (CFC) is defined as a delay in defecation with < 3 times /week standing for > than 2 weeks and it accompanying with stool withholding behavior and painful defecation (without underlying anatomic or medical etiologies). Thus, CFC is also known as Idiopathic. The treatment contains primary stool evacuation, toilet training, high fiber diet and laxative administration, on the other hand insistent constipation does not quickly react with the dietary management or simple laxative treatment which can be called as chronic. A child with chronic constipation usually presents with fecal soiling. Also the organic causes should be contained into account in the diagnostic checkup for chronic¹.

The most common chronic disorders of childhood is constipation, that affecting 1- 30% of children all over the world. Constipation is in charge for 3% of all primary care visits for children and 10% - 25% of pediatric gastroenterology visits².

Anatomy and Physiology of anal continence in pediatric

The smooth muscle of the internal anal sphincter (IAS) has continuousness with the inner circular muscle of the rectum that is considered as the most common one in the lower part of the anal canal. IAS is attaching to voluntary external sphincter and perianal skin by muscular strands. It could give at least 85% of the resting anal canal pressure since it is involuntarily in a tonic state of contraction that saves the anal canal locked normally. The relaxation of IAS takes place completely by reflex response to rectal distention. This reflex is intrinsic and consequently it remains independent from extrinsic innervations and mediated by the myenteric plexus

The normal construction of external anal sphincter is a striated muscle but is partially under voluntary control. The muscle surrounds the anus below the dentate line and is attached posteriorly to the anococcygeal raphe and anteriorly to the perineal body. The external anal sphincter provides part (10 –15%) of the resting anal sphincter tone. Unlike the IAS, the tonic contraction of the external sphincter depends on extrinsic efferent innervation. The phasic contractions are born voluntary and involuntary.³⁻⁵



Fecal continence depends on the adaptive compliance of the colon with the retentive mechanism of the anorectum. Factors that affect the continence are:

1. The angulations in the sigmoid colon and the valves of Houston in the rectum impede the caudal movement of fecal contents.
2. The 80-degree anorectal angle.
3. The longitudinal mucosal folds in the anus also related with the continence of semisolid or fluid feces by the way they fold together, even when the internal sphincter partially relaxes.
4. The anal sphincters show an important role in preserving continence, and both the voluntary external sphincter and the involuntary internal sphincter have a resting tone. The fecal continence may require a normally functioning IAS, external sphincter complex, and levator funnel, as well as intact sensory input from the rectum and anal canal⁴.

Etiology of Chronic Constipation

The main factors included in which they all are said to contribute to the main etiology of chronic constipation are:

A-Extrinsic Factors e.g.

- Little fiber intake
- Insufficient hydration,
- In case of decreasing mobility or immobility of the patient ,
- Electrolyte disturbances (e.g.hypercalcemia)
- Endocrine and metabolic disorders (e.g. DM, chronic renal failure),
- Neurological disorders (e.g. spinal cord injuries)
- And co-existing medications (e.g.acetaminophen and NSAIDs).

Amongst them, the broadly recognized factors were lacking of alimentary fibers, fluids, and exercise, but the evidence behind these 3 factors is unpredictable⁽⁶⁾.

B-Intrinsic Factors:

Usually the normal defecation needs a series of orchestrated actions, starting with relaxation of the puborectalis muscles, descent of the pelvic floor with straightening of the anorectal angle, inhibition of segmental colonic peristalsis, contraction of the abdominal wall muscles, and finally, relaxation of the external anal sphincter with expulsion of feces.

Intrinsic factors leading to chronic constipation can be broadly classified into 2 categories:

- Pelvic floor dysfunction (PFD)
- And slow colon transit time (STC) based on physiologic tests.

Yet, a perfect peculiarity between the two still unfeasible and overlapped frequently by percent of 55%. Anorectal PFD includes laxity of the muscles of pelvic floor, impaired sensation of rectum, and decreased pressure in the lumen of anal canal and has been recorded as causes for chronic constipation in the elderly, especially in women. On the opposing, paradoxical contraction of the puborectalis and external anal sphincter during defecation can lead to incomplete emptying or even functional outlet obstruction. Finally, anatomic variations (such as rectal wall prolapsed) or trauma to perineal region (from childbirth or injury to sacral nerve). STC is a poorly understood situation believed to be a cause of intractable constipation in children. It is characterized by altered an colonic propagated contraction which leads to decreased transmission of feces, gas bloating, abdominal cramps, and incomplete defecation. The prolonged time in the colon resulting in hard and small fecal mass, and fails to reach adequate rectal pressure to trigger the defecation reflex. Often, the pressure essential is established to be higher than in subjects with normal colonic transit.

Various physiologic and histo-biochemical outcomes have been assumed to explain the phenomenon of slow colonic transit:

- diminished cholinergic and elevated adrenergic responses ;
- alleviated gastrocolic reflex ;
- incoordination of rectosigmoid colonic activities ;
- neurodegeneration of both the enteric myenteric plexus ganglia and the interstitial cells of Cajal ;
- And irregularities of enteric neurotransmitters such as substance P, vasoactive intestinal peptides, and nitric oxide⁵⁻⁷.

Clinical features and the diagnosis

Using the Rome III Diagnostic Criteria for Diagnosing Functional Constipation in Children; At least two of the following in a child with a developmental age younger than four years may present:-

- i. Two or fewer bowel movements per week
- ii. At least one episode of incontinence per week after the acquisition of toileting skills
- iii. History of excessive stool retention
- iv. History of painful or hard bowel movement
- v. Presence of a large fecal mass in the rectum
- vi. History of large diameter stools that may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety, and they may disappear immediately following passage of a large stool^{5, 7, 8}.



Organic causes of chronic constipation should be kept in mind and lined out. The organic causes of constipation are summarized as shown below in table (1) ⁵

Table 1: The organic causes of constipation.

anatomic	neurogenic	intestinal neuromuscular disorders	endocrine and metabolic disorders	Drugs
anal fissure	Spina pifida	hirschsprung's disease	Hypothyroidism ,hyper parathyroidism	anticholinergics
anal stenosis	myelomeningocele	chronic intestinal pseudo-obstruction	hypercalcemia	Opiates
imperforate anus	cerebral palsy	intestinal neuronal dysplasia	celiac disease	antidepressant
anterior displaced anus			cystic fibrosis	Antacids
			DM, diabetic insipidus	Iron

Treatment

Because most children continue to have the same problem even after treatment that carries the treatment into non fixed steps. The absence of response is multifactorial, but in most likely cases it related to the pathophysiology of constipation in children is still indefinite⁹. Part of treatment of child's constipation including daily changes in their diet such as increasing the child's consumption of fluids and carbohydrates¹⁰.

In several randomized trials, laxatives have been shown to be advantageous for treatment of chronic childhood constipation . Other studies have also demonstrate the employment of that polyethylene glycol, mineral oil, magnesium hydroxide, and lactulose to be used for in treatment of constipation prolonged time periods without an obvious risk. Nevertheless, these approaches does not cure patient's constipation with less satisfied significant results. The need for eliminating any pain associated with the passage of bowel movements in children is the important keystone. Until now, the common treatment of internal sphincter anal ashalasia was internal sphincter myectomy. When this method was used , the symptoms of the patient improved, but complications such as fecal incontinency due to permanent damage to the sphincter become very common and worrisome . The use of Intraspinal botulinum toxin injection is regarded as a valuable replacement therapy and many of the current studies indicate that it is equally effective as myectomy with fewer complications owing to the absence of permanent damage to the sphincter¹¹.

Complications of Chronic Constipation

- (1) Fecal incontinence:
- (2) Anal fissure:
- (3) Organ prolapses
- (4) Fecal impaction and bowel obstruction
- (5) Hemorrhoids
- (6) Bowel perforation and stercoral peritonitis¹².

Background about the role of Botulinum toxin A

In the previous, Botox injection into the anal sphincter in children was first accomplished in patients with recalcitrant Hirschsprung disease, as described by Langer JC, Birnbaum E (1997). Preliminary experience with intraspinal botulinum toxin for persistent constipation after pull-through for Hirschsprung's disease, and then applied to anal achalasia¹³.

This discovery was made by Burgen *et al* in 1949 that botulinum toxin blocks neuromuscular transmission provided theoretical basis for the development of the toxin as an influential therapeutic tool later. The clinical use of purified botulinum toxin (BTX) represented one of the most remarkable role reversals in modern medicine and it transformed into a health benefit agent which is now-a day used widely in an expanding scope of a lot of human conditions¹⁴.

Botulinum toxin

It is a neurotoxin that inhibits pre-synaptic re-uptake of acetylcholine. Injection results in sustained relaxation of the internal sphincter, treating both the painful sphincter spasm and the vascular component and promoting healing of the fissure.

Two commercial formulations exist: Botox and Dysport. There is no consensus as to the dose, the site or the number of injections; usually 30—50 units of botulinum toxin are injected into the internal anal sphincter in the posterior commissure and same dose on either side. Numerous reviews and meta-analyses have evaluated botulinum toxin¹⁵.

Botox has proven more effective than placebo in one study with a healing rate of 73% and of similar efficacy . Lateral internal sphincterotomy is more effective with greater chance of healing and a recurrence rate six times less frequent than with Botox treatment. However, the risk of anal incontinence for gas is nine times more common with sphincterotomy. Overall, botulinum toxin results in an



average healing rate of 67.5%. The healing rate appears to be better for higher doses. Few side effects are reported. The most common is transient anal incontinence of gas and stool in 10–18% and 5% of cases, respectively ¹².

Mechanism of action for Botulinum toxin

Botulinum toxin has a unique muscular activity and its effect at the neuromuscular junction and muscle spindle, BTX acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. BTX encourages weakness of striated muscles through inhibiting transmission of α -motor neurons at the neuromuscular junction. This makes the use of BTX important in conditions with muscular over activity, such as dystonia. Transmission is also inhibited at gamma neurons in muscle spindles, which may alter reflex over activity. Recovery occurs through proximal axonal sprouting and muscle re-innervations by formation of new neuromuscular junction ¹⁵.

Using of botulinum toxin injection causes temporary paralysis to anal sphincter leading to alter the bowel habit of the patient with a good symptomatic improvement. This was first used in adults with a chronic anal fissure resulting in rapid healing of the fissure. Further studies were undertaken to a randomized control trial showing a clear benefit of BTX over placebo use of BTX ¹⁶.

The threesome safety, effectiveness, and specificity along with reversibility of BTX make it a powerful and versatile tool in a wide variety of neurological disorders, and it is likely that the applications of BTX therapy will continue to expand far along ⁽¹⁷⁾.

MATERIALS AND METHODS

This was a prospective case control study which was done in The Pediatric Surgery Center in The Central Child's Teaching Hospital, Baghdad. The study was carried out over a period of 6 months from the 1st of April to the last of October 2015. A 50 patient (32 male & 18 female) was randomly selected from the outpatient clinic in our hospital. Children aged between 2 years–8 years who suffered from chronic constipation for more than three months, and who had not responded to medical treatment and were referred to pediatric surgical clinic for interventions by pediatric gastroenterologist, were included in our study. A (data collection form) was designed regarding the history and physical examination. A full history—including frequency of defecation and soiling, pain during defecation, duration of symptoms and that of laxative treatment, types of laxatives and enema, general health, and behavior with regard to the bowel problem was taken; in addition, assessment of stool detected on abdominal examination was conducted. Perineal examination in the first step provided that they did not have macroscopic anatomical abnormalities. In case of accompanying diseases or abnormal anus and perineum, and children with transition zone in barium

enema were excluded from the study (exclusion criteria). The patients were randomly divided into cases and control group. The control group (30 of the 50) received no injection and was treated exclusively with stool softeners. The case group (20 of the 50) received botulinum toxin injection in addition to this therapy. Botox injection was carried out under general anesthesia in three regions of the anal sphincter in lithotomy position with use of rectal speculum to aid in the visualization of the Dentate line and locating the anal sphincter. The botulinum toxin was injected in sphincter in 3, 6 and 9 o'clock. It was not injected in 12 o'clock to avoid the possibility of urinary incontinence. Total dose was 100 units, half of it (i.e. 50 units) was injected in 6 o'clock and one-fourth (i.e. 25 units) in 3 o'clock and one-fourth in 9 o'clock. Injection was done simultaneously in both internal and external anal sphincters. A written informed consent was obtained from all parents. In the first month after injection, all patients were evaluated once a week and were investigated regarding the improvement or recurrence of symptoms and followed up monthly in the first six months. The response to Botox injection six months after injection was compared with the control group.

For evaluation of the patients' condition after the Botox injection, patients were asked questions about the presence of the signs of constipation including painful defecation, vomiting, stool's consistency, and soiling and defecation intervals.

Statistical analysis

The sample size based on statistical calculations is 50 patients (20 cases and 30 controls). Continuous variables are expressed in the form of mean and standard deviation. For comparing proportions, chi 2 test and for comparing quantitative variables, t-test was used.

RESULTS

The symptoms of chronic constipation before and after Botox injection.

Painful defecation existed in 85% of patients (cases) before botox injection and it was reduced to 20% after botox injection. In the control group, 90% of patients had painful defecation, which reduced to 80% after medical treatment and the difference was statistically significant ($P=0.0001$). Stool condensation existed in 80% of patients (cases) before botox injection, and it was reduced to 25% after botox injection. In the control group, it existed in 83.3% of children and reduced to 73.3% after medical treatment and the difference was statistically significant ($P=0.0001$). Soiling existed in 65% of patients before botox injection and was reduced to 10% after botox injection. In the control group it reduced from 66.6% to 43.3 % after medical treatment and the difference was statistically significant ($P=0.0001$).

Defecation interval more than 3 days existed in 100% of patients before botox injection and it was reduced to



15% after botox which was also statistically significant ($P=0.0001$). In the control group, 100% of the patients had defecation intervals more than 3 days and it was reduced to 90% after medical treatment. In average,

defecation interval before botox injection was 8.3 days, and after botox injection was reduced to 2.3 days, which is statistically significant ($P=0.0001$).

Table 2: The symptoms of chronic constipation before and after Botox injection

Symptoms	Before botox injection	After botox injection	p. value
painful defecation	85% (17)	20% (4)	0.0001
Stool condensation	80% (16)	25% (5)	0.0001
Soiling	65% (13)	10% (2)	0.0001
Defecation interval more than 3 days	100% (20)	15% (3)	0.0001

In botox injection group there were 12 boys and 8 girls, the difference was not statistically significant between the two genders. The table (1) shows the symptoms of chronic constipation in the case group before and after the botox injection are expressed as percentages.

The signs and symptoms of chronic constipation before and after botulinum toxin injection based on the sex of patients.

The table(2) shows the percentage of decrease in signs has been brought based on the sex of patients in which there was no significant difference between girls and boys, therefore, the effect of botox injection did not have any relation with the sex of patient with chronic idiopathic constipation where ($P=0.0001$).

Parameters	Gender	Before injection	After injection	P. value	P. value male/female
Painful defecation	Male	91.6%(11)	25%(3)	0.0001	0.2
	Female	75%(6)	12.5%(1)		
Stool condensation	Male	91.6%(11)	33.3%(4)	0.0001	0.1
	Female	62.5%(5)	12.5%(1)		
Soiling	Male	66.6%(8)	16.5%(2)	0.0001	0.1
	Female	62.5%(5)	0%(0)		
Defecation interval more than 3 days	Male	100%(12)	16.6%(2)	0.0001	0.4
	Female	100%(8)	12.5%(1)		

Signs and symptoms of chronic constipation in two above and below 5 year olds, before and after botulinum toxin injection

In this study, the minimum age of the patients was 2 years and the maximum 8 years, the most frequent age group was 4 years. In table(3) which shows that the decrease of signs is compared between two groups of above and below 5 year olds, in which a significant

difference is not evident; Therefore, the effect of botox injection has no relationship with the age of patients with chronic idiopathic constipation. The Table (3) also shows that the decrease of signs has been compared between the two groups of above and below 5 year olds, in which a significant difference was also not observed. Therefore, the effect of botox injection has no relationship with the age of patients with chronic idiopathic constipation.

Table 3: The signs and symptoms of chronic constipation in two above and below 5 year olds, before and after botulinum toxin injection

Symptom	Age	Before Botox injection	After Botox injection	P. value	Ratio
Pain full defecation	5yr. >	90%	10%	0.0001	6%
	5yr. ≤	80%	10%	0.0001	
Stool Condensation	5yr. >	80%	10%	0.0001	4%
	5yr. ≤	60%	15%	0.002	
Soiling	5yr. >	70%	5%	0.0001	8%
	5yr. ≤	60%	5%	0.001	
Defecation interval more than 3 days	5yr. >	100%	5%	0.0001	5%
	5yr. ≤	100%	10%	0.0001	



The symptoms and signs and the numbers of patients of chronic constipation before and after botulinum toxin injection for the cases and control groups.

The table (4) shows the percentage of symptoms and signs and the numbers of patients of chronic constipation before and after botulinum toxin injection for the cases and control groups.

Table 4: The percentage of symptoms and signs and the numbers of patients of chronic constipation before and after botulinum toxin injection for the cases and control groups.

Parameters	Percentage of patients before treatment %	Percentage of patients after treatment %	No. of patients before treatment	No. of patients after treatment
Painful defecation(case)	85%	20%	17	4
Painful defecation(control)	90%	80%	27	24
Stool condensation (case)	80%	25%	16	5
Stool condensation(control)	83%	73%	23	22
Soiling(case)	65%	10%	13	2
Soiling(control)	66.6%	43.3%	20	13
Defecation interval more than 3 days(case)	100%	15	20	3
Defecation interval more than 3 days(control)	100%	90%	30	27

DISCUSSION

Constipation is a common problem in children. The incidence of constipation is estimated to be from 0.3% to 8% in childhood¹⁸. When constipation becomes chronic and refractory it produces much distress and problems for the patient and family¹⁹. The exact cause of chronic constipation is not identified in most children; therefore it is diagnosed as idiopathic or functional²⁰. Anal achalasia can be seen and cause constipation in otherwise healthy children¹⁸. Anal dilatation might have a role in management of chronic refractory functional constipation in children in preschool age²¹. The traditional treatment of IASA is myectomy or myotomy²². An alternative approach to treat IASA in patients without HD is botulinum toxin injection in anal sphincter^{18, 22}. Botulinum Toxin interferes with acetylcholine release at the neuromuscular junction in anal sphincter after injection²².

By this mechanism, it produces a chemical denervation or paralysis of sphincter²³. Therefore; intra sphincteric botulinum toxin injection, by inhibition of nerve stimulation to sphincter can induce a chemical myectomy and it could be useful in treatment of IASA^{13, 18, 22} and chronic idiopathic constipation¹⁸.

In one study, Botox injection has proven more effective than placebo with a healing rate of 73% and of similar efficacy. Lateral internal sphincterotomy is more effective with greater chance of healing and a recurrence rate six times less frequent than with Botox treatment. However, the risk of anal in continence for gas is nine times more common with sphincterotomy. Overall, botulinum toxin results in an average healing rate of 67.5%. The healing

rate appears to be better for higher doses. Few side effects are reported. The most common is transient anal incontinence of gas and stool in 10-18% and 5% of cases respectively¹⁵.

A lot of studies was done in this field like: a new study which done by Keshtgar AS *et. al.*, presented that the Botox injection in internal anal sphincter had definite effect in improvement of patients who had obstruction or constipation after pull-through for treatment of Hirschsprung's disease²⁴. In those patients, residual a ganglionic segment and anastomotic stricture were ruled out by rectal biopsy and barium enema and physical examination²⁴.

In another study by Chao NSY *et. al.*, confirmed that the injection of Botox had a transient effect in treatment of most children with anismus and in some patients it showed a long term effect of botulinum toxin in treatment of refractory constipation associated with anal sphincter hyper-tonicity and it agreed with prospective study in Chinese children²⁵.

The study of Ahmadi Javad *et. al.*, showed that the injection of botulinum toxin into anal sphincter is an effective, safe and new treatment of chronic idiopathic constipation in children and there was a statistically significant improving in the symptoms of children with refractory constipation²⁶.

The present study demonstrate that the painful defecation existed in 85% of patients before Botox injection and it was reduced to 20% after Botox injection and the difference was statistically significant ($P=0.0001$), this is compatible with the study with the Ahmadi Javad *et. al.*, which found that painful defecation existed in 88%



of patients before botulinum toxin injection and it was reduced to 15% after toxin botulinum toxin injection and the differences was also statistically significant ($P=0.0001$).

Moreover the current study showed that stool condensation existed in 80% of those patients before Botox injection then it was reduced to 25% after botulinum toxin injection, with a high statistical difference ($P=0.0001$) and it is matched with Ahmadi Javad *et. al.*, study, which found that stool condensation existed in 80% of those patients before botulinum toxin injection, it was reduced to 28% after botulinum toxin injection with a greatly significant difference ($P=0.0001$).

Also the present-day study results showed that soiling existed in 65% of patients before Botox injection and was reduced to 10% after Botox injection and the difference was statistically significant ($P=0.0001$), and it is matched with Ahmadi Javad *et. al.*, study, which found that soiling existed in 62% of patients before Botox injection and was reduced to 8% after Botox injection with significant statistical difference ($P=0.0001$).

The defecation interval >3 days which be present in 100% of patients before Botox injection and it was reduced to 15% after Botox which is also statistically significant ($P=0.0001$), and it is compatible with the study with the Ahmadi Javad *et. al.*, which found that defecation interval more than 3 days existed in 100% of patients before Botox injection and it was reduced to 15% after Botox which is also statistically significant ($P=0.0001$).

In the control group, 100% had defecation intervals >3 days and it and it reduced to 90% after medical treatment. In average defecation interval before Botox injection was 8.3 days and after Botox injection was reduced to 2.3 days which is also statistically significant ($P=0.0001$)²⁶.

In the present study the patient who received a botulinum toxin injection showed no evidence of adverse effect after the period of treatment, and there was no fecal incontinence from our knowledge. These results are encouraging to the next steps for the use of botulinum toxin as a new therapeutic agent in the treatment of chronic idiopathic constipation and fecal incontinence in children.

CONCLUSION

Injection of botulinum toxin into the internal anal sphincter is a new and safe modality for the treatment of chronic idiopathic constipation in children. Also the use of botulinum toxin is effective method in the management of chronic idiopathic constipation in children as compared with other modalities of treatment.

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