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Effectiveness of senna vs polyethylene glycol as laxative therapy in children with constipation related to anorectal malformation

Karla Alejandra Santos-Jasso [a,*,1,2,3,4,5], José Luis Arredondo-García [b,1,5], Jorge Maza-Vallejos [a,1,5], Pablo Lezama-Del Valle [c,1,3,4,5]

[a] Department of General Pediatric Surgery, Instituto Nacional de Pediatría, Ciudad de México, Mexico 04530
[b] Department of Medical Research, Instituto Nacional de Pediatría, Ciudad de México, Mexico 04530
[c] Department of General Pediatric Surgery, and Cochrane Center, Hospital Infantil de México Federico Gómez, Mexico

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ABSTRACT

Purpose: Constipation is present in 80% of children with corrected anorectal malformations, usually associated to rectal dilation and hypomotility. Osmotic laxatives are routinely used for idiopathic constipation. Senna is a stimulant laxative that produces contractions improving colonic motility without affecting the stool consistency. We designed this trial to study the effectiveness of Senna versus polyethylene glycol for the treatment of constipation in children with anorectal malformation.

Methods: A randomized controlled crossover design clinical trial, including a washout period, was conducted, including children with corrected anorectal malformations with fecal continence and constipation. The sample size was calculated for proportions (n = 28) according to available data for Senna. Effectiveness of laxative therapy was measured with a three variable construct: 1) daily bowel movement, 2) fecal soiling, 3) a "clean" abdominal x-ray. Data analysis included descriptive statistics and a Fisher's exact test for the outcome variable (effectiveness).

Results: The study was terminated early because the interim analysis showed a clear benefit toward Senna ($p = 0.026$). The sample showed a normal statistical distribution for the variables age and presence of megarectum. The maximum daily dose of Senna (sennosides A and B) was 38.7 mg and 17 g for polyethylene glycol. No adverse effects were identified.

Conclusion: Therapy with Senna should be the laxative treatment of choice as part of a bowel management program in children with repaired anorectal malformations and constipation, since the stimulation of colonic propulsion waves could lead to stool evacuation without modification of its consistency which can affect fecal continence.

Level of Evidence: I – randomized controlled trial with adequate statistical power.

The patients with anorectal malformations tend to experience constipation and fecal incontinence [1,2]. Successful bowel management programs significantly improve the quality of life [2].

Patients with constipation have decreased frequency in bowel movements and have difficulty passing hardened feces. In some cases, these patients are unable to pass stool, causing fecal retention [3,4]. Morbidities include fecal impaction, megarectum, dilation of the sigmoid colon and pseudoincontinence. These can necessitate remediation through procedures such as sigmoidectomy or sigmoid plasty or anterograde enemas, which otherwise might have been avoided with a bowel management program.

We observed that the use of osmotic laxatives (polyethylene glycol and lactulose) in patients with corrected anorectal malformations can help with colonic emptying. However, these laxatives cause liquid stool and increase the frequency of fecal accidents, or soiling, and thereby affecting the patient's quality of life.

At the Colorectal Center for Children of Mexico and Latin America, and the National Institute of Pediatrics, since 2010 and 2012 respectively, we have used Senna as the laxative of choice in patients with repaired anorectal malformations and constipation. Given that the physiopathology of constipation in this group of patients is mainly due to impaired colonic motility, the stimulation of colonic propulsion waves would lead to stool evacuation without affecting the fecal continence, since there is no modification of the stool consistency. We reviewed our results and found that 89% of patients had a good response. Mild colicky

* Corresponding author. Tel.: +52 551084 0900x1244.
E-mail address: santosjasso@hotmail.com (K.A. Santos-Jasso).
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pain or cramping was the only transient secondary effect in 5.8%, which usually resolved after adaptation [5].

The purpose of this study was to conduct a trial designed with proper methodology to evaluate both effectiveness and safety of Senna versus polyethylene glycol for the treatment of constipation in patients with repaired anorectal malformations. Our goal is to assess which laxative therapy is more effective without an increased occurrence of soiling.

1. Material and methods

This was a randomized controlled crossover design clinical trial, with a washout period (a period during which subjects received no laxative treatment, and the effects of the previously administered drug are eliminated), comparing two different laxative regimens (Senna versus polyethylene glycol) used for the treatment of constipation in patients with repaired anorectal malformations at the National Institute of Pediatrics in Mexico City, from January 2014 through January 2015. Recruitment was originally planned to continue until December 2015, but the study was terminated early. The participants and care providers were not blinded, but the researcher analyzing the data did not know the medication used for each treatment period. Randomization was done by blocks of three. Partial randomization was performed this way because we received the supply of medications for every six patients. One of the researchers generated the allocation sequence with the sealed envelope method, and this was hidden until the patient was recruited by the principal investigator at the clinic.

We included boys and girls with anal sphincter control who had an anorectal malformation repaired with a posterior sagittal approach, who were seen in the clinic with a complaint of constipation or those with fecal impaction.

Patency of the anoplasty was verified with adequate passage of the appropriate Hegar dilator. In all patients, pathology specimens were obtained from the distal rectum at the time of the posterior sagittal anorectoplasty, and all showed ganglion cells. Informed consent was granted by the parents. In patients aged 12 years or older, we also obtained informed assent. Patients with an unfavorable perineal physical examination, specifically if the anus was located outside the muscle complex, were excluded.

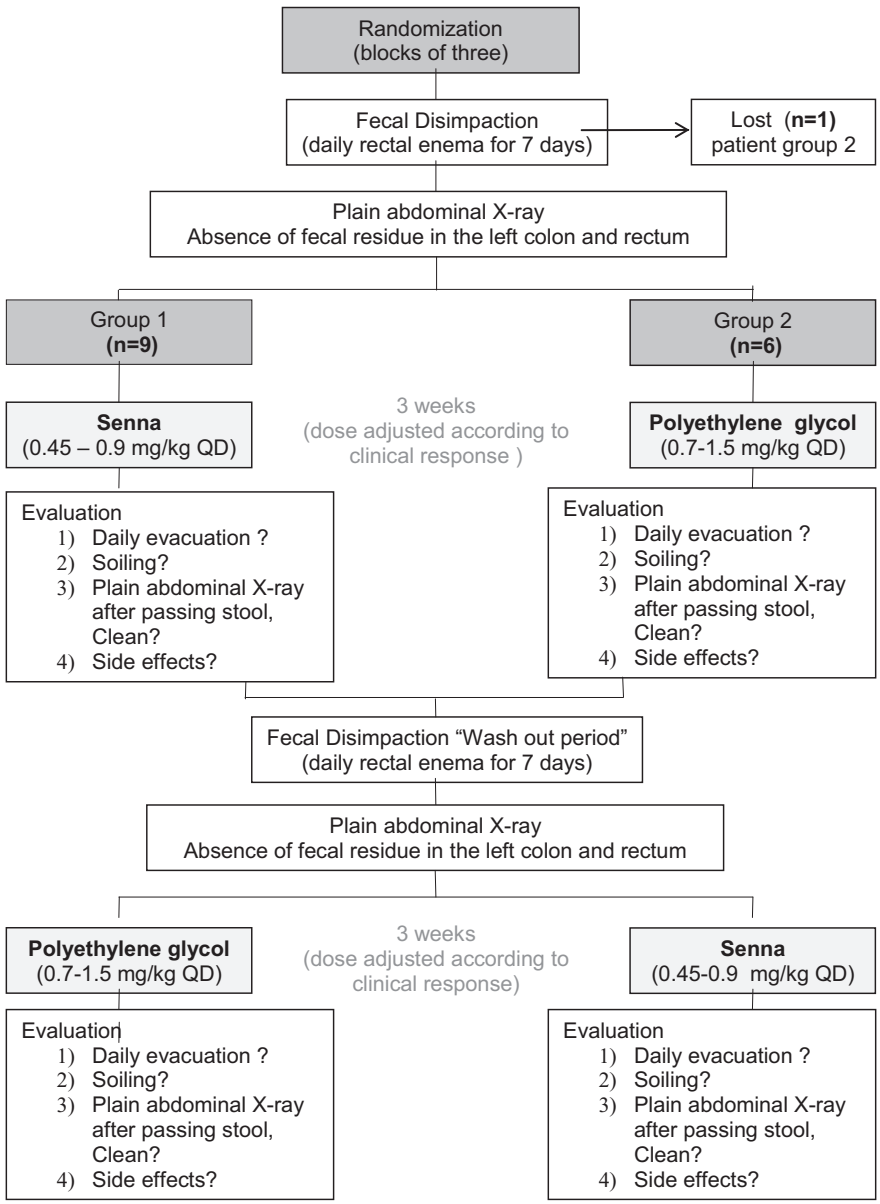

Fig. A.1. Flow chart for the study.

The outcome variable was effectiveness and was evaluated by means of a construct that included three components: 1) the presence of daily bowel movements, 2) absence of fecal soiling, and 3) a "clean" plain abdominal x-ray obtained after passing stool, defined by the absence of fecal residue in the left colon and rectum. To score the treatment regimen as effective, all three components must be present.

The principal investigator could not be blinded because she would perform dose adjustments for the medications according to patients' response at weekly clinic visits. Given the physicochemical nature and presentation of each medication and budget constraints, we could not blind the participants and their care givers.

Sample size was calculated using a proportional formula, favoring Senna, with an effectiveness of approximately 80% [5]. The size obtained was n = 28 patients. This protocol was authorized by the institutional review board with the number 0020/2013.

When a patient met inclusion criteria, a period of fecal disimpaction was done with rectal enemas with normal saline solution, 20 ml/kg, given once a day for one week. Then a plain abdominal x-ray was obtained to assess the absence of fecal residue in the left colon and rectum. Once this was assured, the patient was allocated to one of two treatment groups by means of a sealed envelope. Every weekly visit to the clinic included a review of the patient's log for stooling and soiling, clinical assessment and a plain abdominal x-ray obtained after passing stool.

The doses for Senna (sennosides A and B) and polyethylene glycol were the same for both groups, as follows: Senna laxative (sennosides A and B, Senokot®) was initiated at recommended dosage (0.45–0.9 mg/kg QD), and this was adjusted weekly according to response without surpassing 38.7 mg/day (four and a half 8.6 mg tablets) [6]. The initial polyethylene glycol (Contumax®) dose was 0.7–1.5 mg/kg QD, and it was adjusted weekly according to response without surpassing 17 g/day. The sequence for the laxative therapy differs for both groups, as explained below.

Group 1. Patients in this group were started on a Senna laxative (sennosides A and B, Senokot®) and were seen at the clinic on a weekly basis, adjusting dose according to response. After three weeks, final evaluations were performed for this treatment period, and the washout period of one week was initiated. During this period, patients received no laxative medication and were given a daily rectal enema with normal saline. After this, the patient was evaluated again at the clinic and was started on polyethylene glycol, with weekly assessment and dose adjustments. On the third week, patients visited the clinic for a final evaluation for this treatment period (Fig. A.1).

Group 2. Patients in this group were started on polyethylene glycol and were seen at the clinic weekly, with dose adjustments according to response. After three weeks, the final evaluation for this treatment period was done and the washout period of one week was then initiated. During this period patients received no laxative medication and were given a daily rectal enema with normal saline After this, the patients were started on a Senna laxative and assessed weekly in the clinic, with dose adjustments being made as required. On the third week, patients visited the clinic for a final evaluation (Fig. A.1).

An interim analysis was done after completion of 50% of the calculated sample size. The categorical variables were analyzed with descriptive statistics. Fisher's exact test was used for the outcome variable of effectiveness (the construct including all three of daily bowel movements, absence of fecal soiling and a "clean" abdominal x-ray obtained after passing stool) and for the side effects of the medications. The previously reported side effects of PEG include abdominal distention, colicky pain, flatulence and nausea. For Senna, reported side effects are colicky abdominal pain, nausea, vomiting, perianal irritation, and electrolyte disturbance. SPSS version 20.0 was the software used for this analysis.

2. Results

Even though the trial was open on January 2014, actual recruitment started on April 2014. The trial was planned to continue recruitment until December 2015, but the interim analysis done in January 2015 after 50% of the calculated sample size was completed. The interim analysis showed marked difference in favor of the Senna laxative, and for ethical reasons the study was terminated early, as will be explained below.

One patient met the inclusion criteria and consented for the trial, but after the initial disimpaction period declined to participate due to impossibility to attend the clinic weekly for six more occasions. The type of anorectal malformation in the remaining 15 patients was as follows: 9 with rectovestibular fistula, 4 with rectoperineal fistula and 2 with rectobulbar-urethral fistula. There were 4 males and 11 females, and the age range was from 2 to 14 years old. The weight range was from 10 to 63 kg (Table B.1).

Group 1 (Senna as the first treatment and polyethylene glycol as the second treatment) included 9 patients, and in 8 of them there was a better response to one of the medications; in 7 of them to the first one (Senna). There was one patient in this group that did not have a good response to either laxative at the dosages used in this protocol, and therefore was excluded from the crossover design analysis. Group 2 (polyethylene glycol as the first treatment and Senna as the second treatment) included 6 patients and all of them had a better response to one of the two laxatives, 5 of them to Senna. The total of patients analyzed were 14, and the results are summarized in Table B.2. The sample showed a normal statistical distribution for the variables age and presence of megarectum.

Twelve patients had a better response to Senna in terms of effectiveness, meanwhile only 2 had a better response to polyethylene glycol. Effectiveness is determined by the previously defined construct on day 21 of the treatment period.

The Fisher's exact test for the two treatment groups showed a significant difference in favor of the effectiveness of Senna over polyethylene glycol ($p = 0.026$) for the treatment of constipation in patients with repaired anorectal malformations. Due to these findings, the study was terminated early for ethical reasons.

The main cause for failure of polyethylene glycol was that patients reported liquid stools with frequent soiling (12 out of 15 participants). None of the patients included in this study reported any side effects for either medication.

The three patients that failed for the Senna laxative as a better medication were because of incomplete emptying of the left colon and rectum in the x-ray (Table B.3).

Table B.1
Demographic data.

Participant number	Gender	Age	Type of anorectal malformation	Weight (kg)
1	Female	2 y	RPF	12.1
2	Female	8 y	RVF	25.5
3	Female	14 y	RVF	63
4	Female	2 y	RPF	10
5	Male	10 y	RPF	36
6	Female	9 y	RVF	20
7	Male	9 y	RBUF	36
8	Male	14 y	RPF	45
9[a]	Female	7 y	RVF	25
10	Female	3 y	RVF	14
11	Female	8 y	RVF	26
12	Female	10 y	RVF	21
13	Female	10 y	RVF	27
14	Female	2 y	RVF	11
15	Male	12 y	RBUF	50
16	Female	11 y	RVF	45

RPF: rectoperineal fistula.
RVF: rectovestibular fistula.
RBUF: rectobulbar urethral fistula.
[a] Declined to participate.

Table B.2
Crossover statistical analysis (Fisher's exact test).

		Results		
		First medication better	Second medication better	Total
Group 1	Senna – polyethylene glycol	7	1	8
Group 2	Polyethylene glycol – Senna	1	5	6
Total		8	6	14

3. Discussion

Up to 90% of patients with surgically corrected anorectal malformations can achieve fecal continence. However, 75% to 80% of them suffer from constipation. This should be identified early and aggressively treated to avoid dilatation of the sigmoid colon and rectum. Dilatation leads to a vicious cycle of more dilation and less colonic motility, worsening constipation with fecal impaction, pseudoincontinence, soiling, and psychological and social repercussions [2].

Since 1998, the need to rehabilitate all patients operated on for anorectal malformations was recognized. The Bowel Management Program was then designed to restitute the fecal functionality of these children, with the goal of identifying the postoperative sequelae followed by rehabilitation treatment. There are two phases in this program: 1) fecal disimpaction, and 2) maintenance treatment [7]. The lack of long term follow up of these patients by committed surgeons is a very frequent situation that has a negative impact on them. If the patients are referred to the pediatric gastroenterologist for the treatment of constipation, they will be treated with osmotic laxatives, such as polyethylene glycol of lactulose, that are the first line of treatment for functional constipation [8–15]. Nevertheless, the continence in patients with repaired anorectal malformations is borderline due to the abnormality of the erigent nerves and parasympathetic pelvic nerves, poor muscle complex, decreased resting pressure of the anorectal barrier due to a decreased density of the external anal sphincter, with a decreased sensitivity of the rectum with a limited discrimination between gas and liquid or solid stool [16]. The osmotic laxative is not a good treatment option for many of these patients, and in some cases out of frustration they will be sent to a surgeon or interventional radiologist for an antegrade enema procedure, or to a surgeon for sigmoid surgery.

We have seen in our practice that a stimulant laxative that does not modify the stool consistency is the best option for our patients with anorectal malformations that suffer constipation. However, this had not been validated before in a clinical trial. In our extensive literature review prior to this study, we could not find relevant toxicity reports for Senna laxatives [17–19]. We decided to use a randomized controlled crossover design clinical trial because the patients are their own control group. Given the complexity of continence and sensitive mechanisms, we thought that this was the best option. Finding a reliable control group with another design would have been a very difficult task. We should make clear that a limitation of this study is that the "clean abdominal x-ray" or without fecal residue in the left colon as a part of the construct of effectiveness could be subjective, but in terms of day to day clinical work is useful. The types of anorectal malformations included in our trial correspond with those reported in the literature with best prognosis for continence.

It has been theorized that patients with anorectal malformation respond better to Senna because they have decreased cells of Cajal, and that results in poor colonic motility [16]. The findings in our study may be used as the basis for a trial with higher doses of Senna in those patients that fail to respond to the standard dosage.

4. Conclusions

Laxative therapy with Senna should be treatment of choice as a part of a bowel management program in children with repaired anorectal malformations and constipation. This is because of the pathophysiology of constipation in this group of patients, that require a stimulant laxative that do not modify the consistency of the stool and therefore is not associated with an increased risk of fecal accidents and soiling. Although some patients may fail to respond with the standard doses, this trial may provide grounds for investigating the safety of higher doses in selected patients.

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Table B.3
Effectiveness of laxative therapy.

Participant number	Group	Senna dose (mg/kg)	Effectiveness[a] of Senna	Cause of failure of Senna	PEG dose (mg/kg)	Effectiveness[a] of PEG	Cause of failure of PEG
1	1	0.15	Yes		1.4	No	Soiling/x-ray
2	2	1.34	Yes		0.7	No	Soiling
3	2	0.41	No	X-ray	0.3	Yes	
4	1	0.45	No	X-ray	1.7	Yes	
5	1	1.08	No	X-ray	0.5	No	Soiling/x-ray
6	1	0.86	Yes		0.9	No	Soiling/x-ray
7	2	0.48	Yes		0.5	No	Soiling
8	1	0.48	Yes		0.4	No	Soiling/x-ray
9	2	Declined to participate					
10	2	0.1	Yes		1.2	No	Soiling
11	1	1.32	Yes		0.7	No	No daily BM/soiling/x-ray
12	1	1.23	Yes		0.8	No	No daily BM/soiling/x-ray
13	2	0.96	Yes		0.6	No	Soiling
14	1	0.22	Yes		1.5	No	Soiling/x-ray
15	2	0.35	Yes		0.3	No	No daily BM/soiling/x-ray
16	1	0.76	Yes		0.4	No	X-ray

BM: bowel movement.
[a] Effectiveness 1) the presence of daily BM, 2) absence of fecal soiling, and 3) a "clean" plain abdominal x-ray obtained after passing stool, defined by the absence of fecal residue in the left colon and rectum.

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