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A prospective, double-blind, randomized, placebo-controlled trial comparing the efficacy of polyethylene glycol versus polyethylene glycol combined with topical diltiazem for treating anal fissure in children

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ABSTRACT

Background: Anal fissure (AF) in children is usually treated with laxatives and/or topical agents such as calcium channel blockers. We hypothesize that owing to the superior efficacy of Polyethylene glycol (PEG) in treating constipation in children, adding diltiazem (DTZ) might not improve healing of AF.
Methods: Children ≤14 years with anal fissure presented to the pediatric surgery clinic between November 2014 and March 2016 were recruited. Randomization was performed to either PEG with DTZ or PEG with placebo. Study personnel, patients, and their families were blinded. Primary outcome was resolution of symptoms. Secondary outcomes were constipation and treatment complications at 12-week follow up.
Results: 48 patients were randomized: 24 to PEG + DTZ and 24 to PEG + placebo. Both groups were similar in their baseline characteristics. At week 12, majority of patients' symptoms have improved without significant difference between groups; painful defecation at week 12: 20.8% and 8.3% (p-value 0.41), blood per rectum at week 12: 4.2% and 8.3% (p value 0.58) in the DTZ and placebo groups, respectively. Additionally, there was similar improvement in constipation in both groups.
Conclusion: PEG alone was associated with similar improvement in anal fissure symptoms in children compared to PEG and topical diltiazem combined.
Level of evidence: I

Anal fissure (AF) is a relatively common problem in children presenting to pediatric surgery clinics. It usually presents with painful defecation, bloody stool, and stool withholding behavior that often cause significant distress to the child and the caregivers. The pathogenesis of this linear tear in the mucosa of the anal canal has not been clearly established. However, several factors seem to be involved including constipation causing microtrauma, anal sphincter hypertonia, and reduced anal blood flow [1–3]. Improving constipation is an essential step in the treatment of AF using dietary modification and stool softeners. Compared to different laxatives, polyethylene glycol (PEG) has shown superior effectiveness in treating constipation in multiple randomized trials [4–9]. On the other hand, several topical medications have been used in order to enhance AF healing through reducing the internal anal sphincter basal tone [10,11]. There have been many recent randomized trials describing the effectiveness of glyceryl trinitrate (GTN), botulinum toxin injection or the topical calcium channel blockers such as diltiazem (DTZ) and nifedipine in adult and children [12–23]. A systematic review of the available randomized trials has shown that topical agents are marginally better than placebo [11,24]. Furthermore, in most trials that have demonstrated effectiveness of topical agents in children, laxatives usage was either not well controlled or lactulose was the main agent used [13,15,17,21,23]. Most adults and pediatric trials that have shown effectiveness of topical agents in AF healing have focused on comparing various topical agents to placebo; however, the effectiveness in comparison to placebo has never been demonstrated in patients simultaneously being treated with a more effective laxative such as PEG. We hypothesize that treating AF with PEG, as a sole agent, is not inferior to PEG and topical DTZ together.

1. Methods

1.1. Study design

We conducted a prospective, randomized, double-blind, noninferiority clinical trial of patients diagnosed with anal fissure in two tertiary

Abbreviations: AF, anal fissure; PEG, polyethylene glycol; DTZ, diltiazem; GTN, glyceryl trinitrate.

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hospitals in Riyadh, Saudi Arabia. Patients were randomized to receive either oral PEG with topical DTZ ointment or PEG with topical placebo as treatment of anal fissure. Patients, their families, and physicians were blinded to the study group until the time of data analysis. The study was approved by the institutional review board and registered at ClinicalTrials.gov (identifier: NCT02419534).

1.2. Patient selection and enrollment

Patients were recruited consecutively from pediatric surgery clinics at two tertiary hospitals. Once the children were diagnosed with anal fissure by a single and fully trained pediatric surgeon, the research team confirmed their eligibility. Written informed consent was obtained from the parents at time of enrollment. Withdrawal from the study was possible at any time. Printed instructions were handed to the parents.

1.3. Inclusion criteria

- Children aged 0–14 years
- Painful defection with clinical diagnosis of anal fissure
- Symptoms for at least 2-week duration

1.4. Exclusion criteria

- Chronic illness affecting the anorectal region
- Previous surgery in the anorectal region
- Refusal to participate

1.5. Randomization

Eligible participants were randomized to either DTZ or placebo group using web-based randomization (https://randomizer.org). The website generated 2 sets of unique numbers ranging from 1 to 48. Our pharmacy personnel, who are not participating in the study, prepared containers of DTZ or placebo ointment and numbered them from 1 to 48. Each participant was randomized to a number that will indicate which container they will be given. The patients, their family, and research team were blinded to the patients' assignment. Containers identification numbers were kept concealed from the research team with the pharmacist during the study period.

1.6. Intervention

1.6.1. Oral polyethylene glycol (PEG)

PEG is a nontoxic, water-soluble, osmotic laxative that is not absorbed in the gastrointestinal tract. It was given to all participants in both groups to treat underlying constipation and enhance AF healing. The starting dose was 1 g/kg/day for children younger than 1 year and 2 g/kg/day in divided doses for older children with maximum dose of 17 g/day. The dose was titrated every 2 days until the child is able to pass soft stool at least once a day without distress.

1.6.2. Diltiazem and placebo

2% Diltiazem (DTZ) ointment was prepared in petroleum jelly by our pharmacist. Placebo was also prepared using petroleum jelly in similar containers. The physical properties of DTZ and placebo ointments were identical with regards to color, smell, and texture. All containers were numbered 1–48. Parents were instructed to apply 5 ml of ointment on a fingertip or a cotton applicator to the anal region twice daily.

1.7. Outcomes

Baseline characteristics were collected included age, sex, and presenting symptoms. Primary outcomes included complete healing of the anal fissure as documented by physical examination or resolution of symptoms i.e. painful defecation or rectal bleeding. Secondary outcomes included constipation symptoms and medication-related adverse events. We have decided to analyze the outcomes at the 6th and 12th week of the study period.

1.8. Follow-up

Phone follow-up assessment was conducted in week 1, 2, 4, 6 and 12 of the study period. During each phone conversation, standardized questions were discussed with the parents. A follow-up clinic visit was arranged at the end of the follow-up period.

1.9. Power calculation

In order to anticipate effect size, we have reviewed several studies that examined efficacy of treating constipation with PEG. Gremse et al. compared PEG versus lactulose and showed 38% difference in favor of PEG [4]. Others have shown that PEG is significantly superior to lactulose with a 26% difference [25].

Several studies have prospectively investigated treatment of anal fissure in children with topical agents. Cevik et al. showed anal fissure healing rate of 82% after 8 weeks of treatment with topical DTZ compared to 39% and 25% in GTN and lidocaine groups, respectively [17]. In another trial, GTN was more effective in treating 84% of patients compared to 50% in lidocaine and 35% in placebo groups [12].

Based on previous studies, we chose effect size of at least 40% difference in outcomes. Using α of 5% and power of 80%, our calculated sample size was 24 patients in each arm.

1.10. Statistical analysis

Data were analyzed using SPSS (version 23, IBM, NY, USA). Categorical variables were compared using Chi-Square and Fisher Exact tests, while continuous variables were compared using Mann–Whitney U test. All data were analyzed using intention-to-treat analysis. P-value <0.05 was considered statistically significant.

2. Results

2.1. Study cohort

Participants were enrolled between October 2014 and April 2016. In total, 50 patients were assessed for eligibility. One participant was excluded owing to symptoms suggestive of inflammatory bowel disease and one patient's parents refused to participate. A total of 48 patients were consented and randomized to receive either DTZ or placebo. During the study, two patients discontinued the ointment owing to (local irritation $n = 1$, no clear benefit $n = 1$). One patient was lost to follow-up owing to travel. All 3 patients were in the placebo group. All 48 patients were included in the final analysis. Consort flow diagram of the trial is shown in Fig. 1.

2.2. Baseline characteristics

As shown in Table 1, median age in the placebo and DTZ groups was 32 and 26.5 months, respectively ($p = 0.48$). 58.3% of the placebo group and 33.3% of the DTZ group were males ($p = 0.082$). The patients in the DTZ group had relatively longer median duration of symptoms (360 vs. 165 days, $p = 0.054$). All patients in both groups had at least a single visible anal fissure. Location of the fissure was anterior (45.8%), posterior (25%), multiple (29.2%) in the placebo group and anterior (37.5%), posterior (29.2%), multiple (33.3%) in the DTZ group. Among patients in the placebo group, the presenting symptoms were straining (100%), painful defecation (95.8%), constipation (87.5%), and blood per rectum (66.7%). On the other hand, patients in the DTZ group presented with painful defecation (95.8%), constipation (91.7%), straining (91.7%), and blood

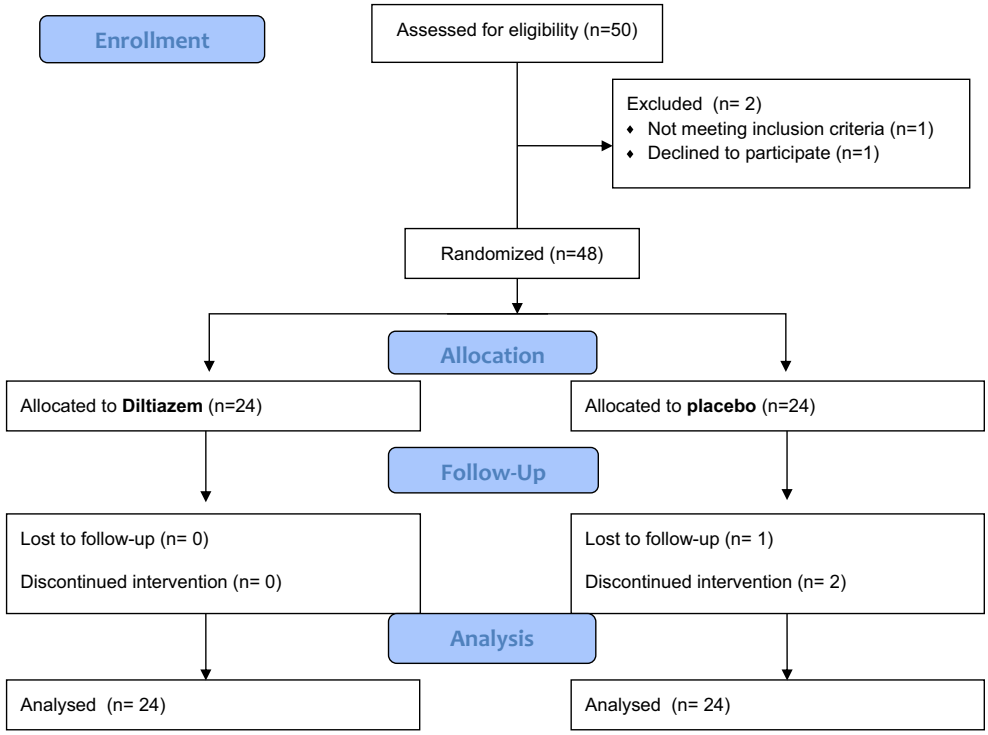

Fig. 1. Consort flow diagram of the trial.

per rectum (58.3%). There was no statistically significant difference in the presenting symptoms between both groups.

2.3. Outcomes at 6 weeks

By the end of 6 weeks of treatment, only 11/24 (45.8%) and 17/24 (70.8%) were still taking PEG in the placebo and DTZ groups, respectively ($p = 0.48$). In addition, 13/24 (54.2%) and 10/24 (41.7%) were still applying the placebo and DTZ ointments, respectively ($P = 0.51$). All symptoms showed improvement after 6 weeks of treatment; however, the degree of improvement was similar in both groups. Particularly, only 6/24 (25%) and 8/24 (33.3%) continued to have painful defection in the placebo and DTZ groups, respectively ($p = 0.95$). Blood per rectum was reported in 1/24 (4.2%) and 2/24 (8.3%) in the placebo and DTZ groups, respectively ($p = 1.0$). On the other hand, 7/24 (29.2%) and 10/24 (41.7%) reported constipation in the placebo and DTZ groups, respectively ($p = 0.79$). Details of the 6-week outcomes are shown in Table 2.

Table 1
Patients' characteristics.

	Placebo group	Diltiazem group	P-value
Age in months (median, IQR)	32 (35)	26.5 (38)	0.48
Duration of symptoms in days (median, IQR)	165 (225)	360 (315)	0.054
Male gender (*n*, %)	14 (58.3%)	8 (33.3%)	0.082
At initial presentation:			
Anal fissure (*n*, %)	24 (100%)	24 (100%)	
Anterior	11 (45.8%)	9 (37.5%)	
Posterior	6 (25%)	7 (29.2%)	0.84
Multiple	7 (29.2%)	8 (33.3%)	
Constipation (*n*, %)	21 (87.5%)	22 (91.7%)	1.0
Painful defecation (*n*, %)	23 (95.8%)	23 (95.8%)	1.0
Straining (*n*, %)	24 (100%)	22 (91.7%)	0.49
Dry stool (*n*, %)	19 (79.2%)	16 (66.7%)	0.33
Stool pellets (*n*, %)	19 (79.2%)	20 (83.3%)	1.0
Blood per rectum (*n*, %)	16 (66.7%)	14 (58.3%)	0.55

2.4. Outcomes at 12 weeks

As shown in Table 3, only 9/24 (37.5%) and 11/24 (45.8%) were still taking PEG in the placebo and DTZ groups, respectively ($p = 0.77$). By 12 weeks, 7/24 (29.2%) were still applying the prescribed ointment similarly in both groups ($P = 0.8$). Further improvement of the symptoms was reported as well. Particularly, only 2/24 (8.3%) and 5/24 (20.8%) continued to have painful defection in the placebo and DTZ groups, respectively ($p = 0.41$). Blood per rectum was reported in 2/24 (8.3%) and 1/24 (4.2%) in the placebo and DTZ groups, respectively ($p = 0.58$). On the other hand, 4/24 (16.7%) and 8/24 (33.3%) reported constipation in the placebo and DTZ groups, respectively ($p = 0.24$). Fig. 2 depicts the proportion of patients with painful defection in both groups during the study period.

2.5. Follow-up and medication-related adverse events

Within the placebo group, two patients discontinued the prescribed ointment owing to (local irritation $n = 1$, no clear benefit $n = 1$) and one patient lost to follow-up owing to travel. The remaining 45 patients had completed phone follow-up. No patient returned to the 12-week clinic visit. A part from local irritation in the placebo phone group ($n = 1$), there were no reported adverse events.

Table 2
Outcomes at 6 weeks of treatment.

	Placebo group	Diltiazem group	P-value
Taking PEG (*n*, %)	11 (45.8%)	17 (70.8%)	0.48
Applying ointment (*n*, %)	13 (54.2%)	10 (41.7%)	0.51
Constipation (*n*, %)	7 (29.2%)	10 (41.7%)	0.79
Painful defecation (*n*, %)	6 (25%)	8 (33.3%)	0.95
Straining (*n*, %)	9 (37.5%)	8 (33.3%)	0.3
Dry stool (*n*, %)	3 (12.5%)	7 (29.2%)	0.47
Stool pellets (*n*, %)	7 (29.2%)	6 (25%)	0.34
Blood per rectum (*n*, %)	1 (4.2%)	2 (8.3%)	1.0

Table 3
Outcomes at 12 weeks of treatment.

	Placebo group	Diltiazem group	P-value
Taking PEG (*n*, %)	9 (37.5%)	11 (45.8%)	0.77
Applying ointment (*n*, %)	7 (29.2%)	7 (29.2%)	0.8
Constipation (*n*, %)	4 (16.7%)	8 (33.3%)	0.24
Painful defecation (*n*, %)	2 (8.3%)	5 (20.8%)	0.41
Straining (*n*, %)	4 (16.7%)	7 (29.2%)	0.39
Dry stool (*n*, %)	2 (8.3%)	4 (16.7%)	0.67
Stool pellets (*n*, %)	4 (16.7%)	5 (20.8%)	1.0
Blood per rectum (*n*, %)	2 (8.3%)	1 (4.2%)	0.58

3. Discussion

This study was conducted in order to comparatively examine the effect of topical DTZ on AF healing in children receiving effective laxative i.e. PEG. To our knowledge, this has not been investigated using a similar design. We hypothesized that effective management of constipation is all that is required to treat most AF in children. Despite potential benefit of topical agents in adult population, their efficacy in children is still questionable. Cevik et al. have demonstrated superiority of DTZ compared to GTN and lidocaine in the healing of AF in children [17]. Topical GTN with lactulose was also found to be superior to lactulose alone in a randomized trial by Joda et al. [20]. Without the use of laxatives, GTN was superior to lidocaine and placebo with regards to AF healing and relief of symptoms [12]. In contrast, there was no difference between GTN and EMLA cream after 8 weeks of treatment on healing of AF [13]. Additionally, another randomized controlled trial has shown no benefit of GTN compared to placebo with the use of lactulose and senna which highlights the importance of more effective management of constipation in children with AF [21]. A systematic review of seven published RCTs has concluded that topical DTZ and GTN were equally effective in treating AF in adults; however, DTZ was associated with a lower incidence of headache and AF recurrence. Therefore, we chose to use DTZ as a topical agent in our study.

Appropriate management of associated constipation is the mainstay of the treatment of anal fissure starting with high fiber diet and increased daily water intake to different types of laxatives. Oral lactulose is a very commonly used osmotic laxative in children; however, it may not be very effective in severe form of constipation. On the other hand, PEG is a nontoxic and water soluble osmotic laxative with a large molecular weight. When PEG is orally administered, it results in hydration of the colonic content to facilitate passage of stool in a linear dose-dependent fashion. PEG is minimally absorbed in the gastrointestinal tract and is not associated with major adverse events [8]. Several comparative studies have demonstrated superior efficacy of PEG in managing constipation compared to other laxative such as lactulose and milk of magnesia [4–7,25,26]. Therefore, PEG was used in this study as the laxative of choice.

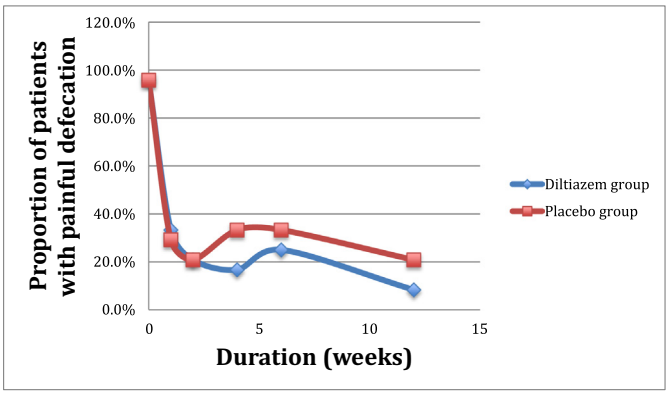

Fig. 2. Proportion of patients with painful defection in both groups during the study period.

In our study, we have shown that painful defection has decreased from 95.8% to 8.3% and 20.8% in the placebo and DTZ group, respectively, after 12 weeks of treatment. The lack of statistically significant difference between both groups indicates that DTZ did not have added value in the observed symptomatic improvement. Additionally, passage of bloody stool has improved from 58.3% in the DTZ group to 4.2%, and from 66.7% in the placebo group to 8.3%. Constipation also improved during the study period with no difference between both groups. Interestingly, only 37.5% were still taking PEG and 29.2% were applying ointment in the placebo group at 12 weeks. Similarly, 45.8% were still taking PEG and 29.2% were applying ointment in the DTZ group. This was likely owing to the observed improvement of the patients' symptoms. During the study period, no adverse events were observed apart from local irritation reported in the placebo group ($n = 1$).

Our study had several limitations. First, there was no documented healing of the fissure. Despite our best effort to arrange follow-up visits, parents did not feel the need to attend given the significant improvement in the patient's symptoms. Second, recurrence of AF was not captured beyond 12-week study period. Third, only one topical agent (DTZ) was used in the study; therefore, other agents may need to be investigated.

4. Conclusion

The results of our study indicate that 2% topical DTZ ointment does not result in any added value with regards to symptomatic improvement of children with AF treated with PEG compared to those treated with PEG and placebo ointment over 12-week period.

Acknowledgments

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