Randomized Controlled Clinical Trial on Value of Domperidone in Functional Abdominal Pain in Children

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ABSTRACT

Objectives: The aim of the study was to evaluate the therapeutic effect of domperidone on children with abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs).

Methods: One hundred children (aged 5–12 years) fulfilling Rome III criteria for AP-FGIDs were randomized into 8 weeks of domperidone or placebo treatment. Primary outcomes defined were cure and patient-reported general improvement. Secondary outcomes were reduction in the severity of abdominal pain and increase in gastric motility. Patients were followed up for 6 months.

Results: Eighty-nine (42 in placebo group, 47 in domperidone group) completed the trial at 8 weeks. Seventy-nine completed the 6-month follow-up. When primary outcomes were assessed at 8 weeks, 37 (74%) in the domperidone group and 25 (50%) in the placebo group showed patient-reported general improvement ($P = 0.013$), whereas no significant difference was observed in cure (22 [44%] vs 14 [28%] $P = 0.09$). At 6-month follow-up 30 (60%) in the domperidone group and 19 (38%) in the placebo group reported cure ($P = 0.028$), whereas 44 (88%) in the domperidone group and 33 (66%) in the placebo group showed patient-reported general improvement ($P = 0.009$). When assessing secondary outcomes at 8 weeks, the domperidone group reported significant reduction in the severity of abdominal pain (54.1% vs 24.7%, $P = 0.008$) and an increase in the antral motility index (27.5% vs 7.2%, $P = 0.029$). None of the patients reported intervention-related adverse effects.

Conclusions: Domperidone may be a safe and effective therapeutic modality to achieve a lasting remission of symptoms in children with AP-FGIDs.

Key Words: functional abdominal pain, functional dyspepsia, gastric motility, gastroprokinetics, irritable bowel syndrome

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What Is Known

- Functional abdominal pain is a common problem in children.
- As a group, they lead to a great deal of suffering.
- There are only limited therapeutic options for treating children with this group of disorders.

What Is New

- Domperidone is an effective therapeutic modality to achieve remission of symptoms.
- Approximately, 90% of children treated with domperidone for 8 weeks were able to sustain the clinical improvement and 60% achieved cure at 6 months.
- The therapeutic effects are unrelated to the gastroprokinetic action of domperidone.

Abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) are common in children, with a worldwide prevalence of 13.5% (1). There are 4 main AP-FGIDs types; irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD), and abdominal migraine. AP-FGIDs have a significant negative impact on the health-related quality of life and school performances of affected children (2–4).

AP-FGIDs in children are difficult to manage due to a lack of well-defined treatment modalities. Although hypnotherapy and yoga therapy have been shown to be effective in research settings, it is difficult to implement them in day-to-day clinical practice (5). A systematic review has shown that most of the previous studies on pharmacological interventions lack adequate power and are suboptimal in methodological quality (6). The drugs such as amitriptyline has failed to demonstrate a significant therapeutic benefit when compared to a placebo (7).

The etiology of AP-FGIDs is multifactorial (8). We have shown children with AP-FGIDs to have delayed gastric emptying and decreased antral motility (9–12). Domperidone is a butyrophenone derivative with antidopaminergic properties at peripheral dopamine 2 receptors. Domperidone enhances antroduodenal contractions, improves coordinated peristalsis across the pylorus, and accelerates gastric emptying (13,14). It is reported to augment gastric emptying of both solids and liquids in healthy subjects and patients with impaired gastric emptying (15,16). Several adult studies have demonstrated beneficial effects of domperidone in FD and IBS (17–21). In addition, 2 meta-analyses, which summarized adult studies, have shown the positive effects of gastroprokinetic

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agents in the treatment of FD (22,23). In a randomized, placebo controlled trial on the effects of domperidone on FD and gastric emptying, Sarin et al (24) found a decrease in gastric emptying time and an improvement of symptoms with domperidone. Another study assessing the effects of a 7-day treatment schedule of domperidone has shown that the subgroup with delayed gastric emptying had higher improvements of gastric emptying and symptom relief when compared to the placebo (25).

Therefore, we hypothesized that children with AP-FGIDs can perhaps be effectively treated with domperidone to improve symptoms and gastric emptying. The objective of the present study was to determine the efficacy of domperidone as a treatment modality for AP-FGIDs and its effects on gastric motility in children.

METHODS

Study Design

A randomized, double-blind, placebo-controlled trial was conducted from October 2012 to October 2014. Domperidone or a placebo was administered for 8 weeks to children with AP-FGIDs and they were followed up for 6 months.

Study Population and Selection of Participants

Consecutive patients ages 5 to 12 years, who were eligible according to the inclusion criteria, were recruited from pediatric clinics at North Colombo Teaching Hospital, Ragama, Sri Lanka and investigated in the Gastroenterology Research Laboratory, Faculty of Medicine of the University of Kelaniya, Sri Lanka.

Inclusion Criteria

1. Children with an AP-FGIDs according to Rome III criteria (26).
   AND
2. Children with abdominal pain at least once per week for at least 2 months before diagnosis.
   AND
3. Pain severity >25% (25 mm) on a 100 mm visual analogue scale (VAS) and pain interrupting activities of the child (eg, sleep, play, schooling).
   AND
4. Securing informed consent from parents or guardians.

Exclusion Criteria

1. Clinical or laboratory evidence suggestive of an organic pathology.
2. Medical or surgical diseases other than FGIDs
3. Long-term medication for any illness.
4. Previous abdominal surgery except for an appendectomy.
5. Subjects who has received drugs that can alter gastrointestinal motility and prolong QT, within 30 days before diagnosis.

Initial Assessment

Details of the sociodemographic features and pain characteristics were obtained using an interviewer administered questionnaire. AP-FGIDs were diagnosed using the Rome III Questionnaire for Paediatric Functional Gastrointestinal Disorders (27).

Patients were screened for organic diseases with clinical evaluation, stool microscopy, urine microscopy and culture, full blood count, C-reactive protein, liver and renal function tests, and ultrasound scan of the abdomen. A baseline electrocardiogram was also performed to rule out cardiac conduction abnormalities. Serum electrolytes (sodium, potassium, and chloride) were also checked before starting therapy. Patients were not screened for coeliac disease because it is extremely rare in Sri Lanka.

Recruitment and Randomization

One hundred children were recruited and randomized into 2 groups (50 in a group) using computer generated random numbers, irrespective of the baseline symptom severity and gastric motility status. Recruited children were asked to stop all treatment from the time of the initial evaluation. The time lag between the initial assessment and the beginning of the trial was 14 days (washout period). Parents were instructed not to change the diet or lifestyle of the child after recruitment.

The random allocation sequence was generated using the Ralloc procedure in STATA version 12 (28) and participant were assigned to intervention and placebo groups by an independent statistician who is not an investigator of the present study.

Administration of the Drug and the Placebo

The intervention group received domperidone, 10 mg 3 times per day, and the placebo group received the placebo, 30 minutes before meals for 8 weeks. The placebo was identical to domperidone tablet in physical appearance, color, taste, and packing. One hundred sixty-eight identical tablets (an 8-week supply) of the drug or the placebo were provided to all children who were included in the study. A symptom diary was provided to document adherence to treatment, severity, frequency, and duration of symptoms and interruption of activities.

After completion of the trial, parents were requested to use only a simple analgesic (acetaminophen) for pain and not to use any other therapy for AP-FGIDs for 6 months. They were requested to record the drugs used, any diseases or symptoms developed and complications encountered in the diary provided, and to report during weekly telephone inquiries.

Patients were reviewed at 8th week and 6th month with regards to primary and secondary outcomes.

Adherence to the Protocol

All subjects were contacted weekly by telephone by the first author throughout the study. The first telephone call was made on 3rd day and was used to give an opportunity to verify any doubts, assess compliance, and assure completion of the symptom diary.

In addition, parents were provided with a dedicated help telephone line which was answered by the first author during the whole period of the trial. They were requested to contact the first author to clarify any doubts or to report possible adverse reactions.

Blinding

Patients recruited, their parents, and the investigators who assessed the primary and secondary outcomes were blind to the exact intervention administered.

An identical custom-designed specific packaging with 168 small recesses numbered from 1 to 168 was used to repack the drug and placebo. Each pack had 56 rows and each row had 3 recesses containing 3 tablets to be administered per day. The parents were requested to administer the drug in order and only according to the day. When a drug dose is missed, the parents were instructed to

allow the tablet to remain in the sealed recess. Parents were requested to bring the packing at the end of the 8 weeks and the remaining tablets were counted. If the remaining pills were 20% or more from the original 168, they were considered to be noncompliant.

Outcome Assessment

Primary outcomes were measured at the completion of treatment (8 weeks) and at 6 months. Secondary outcomes were measured at the end of 8 weeks.

Primary Outcomes

1. Cure
   Cure was defined when a patient fulfilled all of the following 3 criteria
   - Abdominal pain <4 episodes per month.
   - Average severity of abdominal pain <25 mm in the VAS.
   - None of the pain episodes being severe enough to disrupt the daily activities of the child (eg, sleep, play, schooling).
2. Patient-reported General Improvement
   Patient-reported general improvement was defined as overall satisfaction and satisfactory relief of pain following treatment. This was assessed by using 2 questions (7).
   When he/she indicates positive result for both of the following questions, he/she was considered to have general improvement of AP-FGIDs.
   - Overall how do you feel your problem is?
     Answer was better, same or worse. ''Better'' was regarded as positive result. ''Same'' or ''worse'' was regarded as a negative result.
   - How did the medication relieve your pain?

   Sense of improvement was expressed as excellent, good, fair, and poor. Excellent and good were considered as positive result. Fair and poor were considered as negative results.

Secondary Outcomes

Decrease in Pain Severity

The percentage of pain improvement was assessed as the difference of mean pain severity reported on a validated 100 mm VAS (29,30) before and after the treatment.

Increase in Gastric Motility

Main gastric motility parameters used as outcomes were gastric emptying rate (GER) and antral motility index. The percentage increase in GER and antral motility index at post-treatment period compared to pretreatment assessment was calculated to determine the improvement of gastric motility.

Measurements

Gastric Motility Studies

Pre- and post-treatment gastric motility was assessed according to a validated protocol (31), using a high-resolution real-time scanner (Siemens ACUSON X300) with a 1.8 to 6.4 MHz curved linear transducers with record and playback facilities. The main gastric motility parameters assessed were GER and antral motility index. All motility assessments were performed between 8.30 and 9.30 AM. The method had previously been used to assess gastric motility in children with FGIDs (9–12).

Gastric emptying was calculated as follows:

Gastric emptying = (antral area at 1 minute − antral area at 15 minutes)/antral area at 1 minute × 100

Antral motility index was calculated as follows:

Antral motility index = (amplitude of antral contraction × frequency of contraction)/100

Statistical Methods

Sample Size Calculation

Previous trials conducted in children with AP-FGIDs, have reported an estimated treatment response of 70% and 40% placebo response (7). Using a standard statistical method, we calculated that 39 patients per group are adequate to detect a difference of 20% in response rate between domperidone and placebo with a power of 80% and 0.05 of significance. Anticipating the possible dropouts and noncompliance, we included 50 patients to each arm.

Data Analysis

All data were anonymous and coded and both subjects and investigators were blind to the randomization code. All statistical evaluations were completed using PSPP version 0.8.3-g5f 9212 statistic software (32). Data were analyzed using intention to treat analysis. Means and standard deviations were calculated for continuous variables and frequencies and percentages for categorical variables. For continuous data, an independent sample ''*t*'' test was used to assess differences between the intervention and the placebo groups. For dichotomous data, the Chi-square test was used to assess differences between the 2 groups. A 2-tailed level of significance of 0.05 was used.

Ethical Approval Trial Registration

Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka. The trial was registered in the Sri Lanka Clinical Trial Registry (SLCTR), which is the primary registry linked to the WHO International Clinical Trials Registry Platform. The registration number of SLCTR was SLCTR/2012/008.

RESULTS

One hundred sixty-two patients were screened. Forty did not meet the inclusion criteria. Twelve declined to participate. Ten did not attend the initial assessments. Hundred children with AP-FGIDs were recruited with 50 each in intervention and placebo groups (FAP = 54, IBS = 33, FD = 13).

Forty-seven in the therapeutic arm and 42 in the placebo arm completed the trial (Fig. 1). Eight patients (16%) in the placebo group and 3 (6%) in the domperidone group did not attend the follow-up at 8 weeks and 21 did not attend the 6-month follow-up. All participants completed the study in original assigned groups. None were identified as noncompliant. Baseline demographic, motility, and pain characteristics were similar in both groups (Table 1).

Assessment of Primary Efficacy Endpoints

At 8 Weeks

In intention to treat analysis, number of children who reported cure was higher in the domperidone group but this was not statistically significant. The difference in patient-reported general improvement was statistically significant (Table 2).

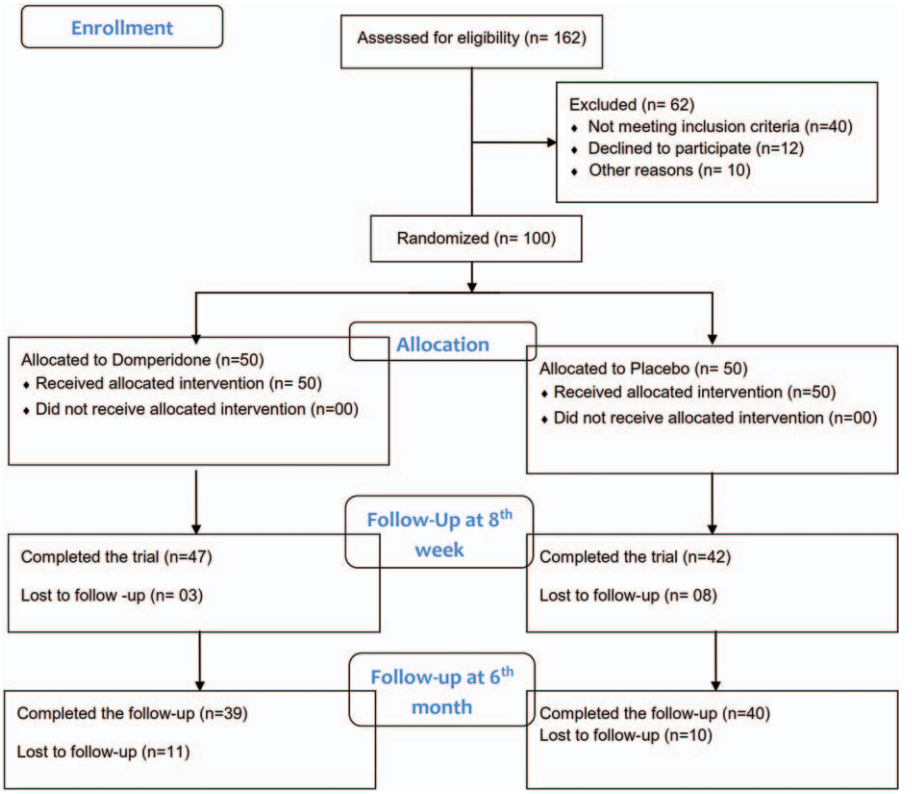

FIGURE 1. Consort diagram of the trial.

TABLE 1. Demographic and baseline pain characteristics and motility parameters among domperidone and placebo groups

Characteristics	Domperidone group (n = 50)	Placebo group (n = 50)
Sex (n %)		
Male	16 (32.0)	23 (46.0)
Female	34 (68.0)	27 (54.0)
Age in years (mean(SD))	8.4 (2.1)	7.5 (2.0)
Body mass index (BMI) (mean[SD])	15.1 (2.2)	15.3 (3.7)
BMI *z* score in boys (mean[SD])	−0.67 (1.5)	−1.1 (1.5)
BMI *z* score in girls (mean [SD])	−0.92 (1.5)	−0.46 (1.5)
Diagnosis (n [%])		
Functional abdominal pain	27 (54.0)	27 (54.0)
Functional dyspepsia	5 (10.0)	8 (16.0)
Irritable bowel syndrome	18 (36.0)	15 (30.0)
Pain characteristics (mean (SD))		
Pain severity, mm	60.3 (15.5)	56.9 (17.1)
Pain frequency, days/wk	4.4 (2.4)	4.5 (2.4)
Pain duration, min	69.9 (51.7)	67.6 (61.0)
Motility parameters (mean [SD])		
Gastric emptying rate (%)	46.6 (12.2)	44.7 (17.4)
Motility index	4.0 (1.2)	4.16 (1.2)

$P > 0.05$ for all comparisons between domperidone and placebo group.
SD = standard deviation.

At 6 Months

The domperidone group showed a significantly higher cure rate and patient-reported general improvement in intention to treat analysis (Table 2). When the data were analyzed using per protocol analysis (excluding treatment defaulters at 8 weeks and nonresponders at 6 months), both cure rate and improvement became nonsignificant (Supplementary Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B183*).

Assessment of Secondary Efficacy Endpoints

The domperidone group showed a statistically significant reduction of pain severity (assessed by the VAS) and improvement of antral motility index compared to the placebo group at the 8th week (Table 2). No such difference was, however, observed in improvement of GER.

Comparison of Primary and Secondary Outcomes According to Baseline Gastric Motility Status

In the domperidone group, at baseline analysis there were 26 with normal GER and 24 with delayed gastric emptying. When primary outcomes were compared between those with normal motility and abnormal motility, there was no difference in primary outcome (Table 3).

When secondary outcomes were compared, reduction in pain severity was not different between the 2 groups. Domperidone

TABLE 2. Primary and secondary outcomes after intervention in 8th weeks and 6 months

		Domperidone group (n = 50)	Placebo group (n = 50)	P
Primary outcomes	At 8 wk			
	Cure (n [%])	22 (44.0)	14 (28.0)	0.096*
	Improvement (n [%])	37 (74.0)	25 (50.0)	0.013*
	At 6 mo			
	Cure (n [%])	30 (60.0)	19 (38.0)	0.028*
	Improvement (n [%])	44 (88.0)	33 (66.0)	0.009*
Secondary outcomes	At 8 wk			
	% Reduction of pain severity (mean [SD])	54.1 (35.8)	29.7 (50.2)	0.008†
	% Increase in gastric emptying rate (mean [SD])	14.8 (7.6)	7.4 (11.2)	0.423†
	% Increase in antral motility index (mean [SD])	27.5 (5.3)	7.2 (4.4)	0.029†

*Chi-square test.
†Independent—sample *t* test.

resulted in significant increase in GER and antral motility index in children with normal gastric motility ($P < 0.05$), but not in those with abnormal motility (Table 3). The placebo had no effect on gastric motility parameters.

Comparison of Primary and Secondary Outcomes According to the Type of AP-FGID

When primary and secondary outcomes were assessed according to the type of AP-FGID, FAP showed significant improvement at 8 weeks and 6 months ($P < 0.01$) and significant reduction in pain severity at 8 weeks ($P < 0.05$). No such difference was observed in IBS and FD (Supplementary Table 2, Supplemental Digital Content 2, *http://links.lww.com/MPG/B184*).

Safety and Adverse Effects During the Trial

No treatment associated adverse events were noted during the trial period. One patient in the domperidone group developed a skin rash during the trial. This presentation was not considered to be an adverse effect of treatment.

DISCUSSION

This is the first prospective, randomized, double-blind, placebo-controlled clinical trial on therapeutic effects of domperidone, on children with AP-FGIDs. After 8 weeks of therapy, domperidone was found to have a significant patient reported general improvement in children with AP-FGIDs. At 6-month follow-up, a significantly higher percentage of children treated with domperidone were able to achieve cure. In addition, significant reduction in the severity of pain and increase in the gastric antral motility index were observed in the domperidone group.

When the therapeutic effect of domperidone was compared with respect to the baseline gastric motility status, the percentage of cure, percentage of patient-reported clinical improvement, and decrease in the pain severity were not different between subgroups of patients with normal gastric emptying and abnormal gastric emptying. In addition, domperidone increased the GER and antral motility index significantly only in patients with normal baseline gastric motility, whereas those with abnormal baseline gastric motility failed to show a significant improvement in motility parameters.

Therapeutic value of domperidone is not assessed in children with AP-FGIDs. Several studies conducted in adults have, however, demonstrated the therapeutic benefits of domperidone in the treatment of FD (19–25). Similar to these previous studies, in the current study on children with AP-FGIDs, we have shown a significantly higher patient-reported general improvement of overall symptoms after 8 weeks of therapy with domperidone. We also reported a significantly higher cure rate at 6-month follow-up indicating potential long-term benefits of domperidone in children with AP-FGIDs. None of the previous trials among adults had long-term follow-up. The subgroup analysis clearly shows the efficacy of domperidone in treating children with FAP. In contrast to the data from adult studies, we, however, did not find a significant therapeutic benefit of domperidone in FD both at 8 weeks and 6 months (19–25). Similarly, children with IBS did not show a

TABLE 3. Primary and secondary outcomes after 8 weeks of intervention according to the baseline motility status

		Domperidone			Placebo		
Outcomes		Normal motility (n = 26)	Low motility (n = 24)	P	Normal motility (n = 22)	Low motility (n = 28)	P
Primary	Cure (n [%])	13 (50.0)	9 (37.5)	0.374*	5 (22.7)	9 (32.1)	0.462*
	Improvement (n [%])	20 (76.9)	17 (70.8)	0.624*	10 (45.4)	11 (39.2)	0.369*
Secondary	% Reduction of pain severity (mean [SD])	57.3 (39.4)	54.3 (33.2)	0.782†	24.6 (47.7)	33.8 (52.5)	0.523†
	% Increase in gastric emptying rate (mean [SD])	55.6 (37.8)	39.4 (36.6)	0.001†	−10.8 (30.2)	34.9 (28.9)	0.074†
	% Increase in antral motility index (mean [SD])	38.5 (34.1)	15.8 (14.4)	0.045†	15.9 (14.5)	13.4 (13.8)	0.823†

*Chi-square test.
†Independent sample *t* test.

significant cure or improvement of their symptoms with domperidone therapy.

The gastroprokinetic effects of domperidone are mainly due to its ability to enhance lower esophageal sphincter pressure, gastric emptying, and antropyloric motility (13–16). Prokinetic agents have repeatedly been shown to be beneficial in the management of AP-FGIDs. A meta-analysis of effects of prokinetic agents on adults with FD has shown the therapeutic value of gastroprokinetics in treating FD (23). Another meta-analysis specifically focusing on domperidone and cisapride has also found beneficial effects of domperidone in treating patients with nonulcer dyspepsia (22). Therefore, we hypothesized that improvement of gastric emptying could possibly provide symptomatic relief in patients with AP-FGIDs and expected a higher clinical improvement in patients with abnormal baseline GER. In contrast to our hypothesis, the cure, patient-reported improvement, and decrease in severity of pain following treatment with domperidone, did not differ according to the baseline motility status. In addition, we observed a significant prokinetic effect of domperidone only in the group with normal baseline GER. In a previous study, Davis et al included 16 patients with nonulcer dyspepsia in a double blind randomized controlled trial for 6 weeks with measurement of solid gastric emptying at the baseline and 6 weeks. The patients who were in the domperidone arm showed a significant improvement of their symptoms. The symptom improvement, however, had no correlation with improvement in gastric emptying (33). In contrast, another study conducted by Duan et al in 60 adults with FD has shown a significant therapeutic effect in patients with abnormal gastric motility. In that study, after administration of domperidone for 7 days, there was a significant reduction in gastric emptying time in the subgroup of patients with delayed gastric emptying. The patients with delayed baseline gastric emptying had higher improvement of both bloating and early satiety after treatment with domperidone suggesting that the reduction of gastric emptying time has an association with improvement of symptoms (25). The technical aspects of measuring gastric emptying time in this study was, however, different from our study.

In the present study, the response to the placebo (overall patient-reported clinical improvement) was 50%. Similar high rates of placebo responses have been reported in previous studies. In a therapeutic trial assessing the value of mebeverine, the placebo response was 53.4% and it was 75% in a trial assessing the value of amitriptyline (7,34). A recent meta-analysis conducted by Hoekman et al (35) found a 41% placebo response among children included in clinical trials assessing treatment efficacy of therapeutic agents for AP-FGIDs. It is thereby noted that effects of placebo are contributing toward the therapeutic effect seen in randomized controlled trials on FGIDs (36). Spontaneous improvement and good patient-practitioner relationships could contribute to the placebo effect (37).

Adherence to protocols was excellent in the present study. Parents were pleased to receive treatment from a tertiary care center under specialist supervision. This could be a contributory factor for the good compliance. We had only 11 defaulters at 8 weeks and there were no significant adverse reactions during the trial. Cardiac conduction abnormalities including prolonged QT syndrome are reported as possible complications of therapy with domperidone. Liver dysfunction, underlying cardiac diseases, and coadministration of QT prolonging medicine are the main risk factors for developing these complications. Measures that were taken to reduce the risk of these complications during the trial were as follows. We performed complete physical examination, liver function tests, and electrocardiographies to rule out possible cardiac or liver abnormalities at recruitment. Subjects were requested to refrain from taking drugs that could lead to prolonged QT during the trial period to prevent potential drug interactions. We did not encounter any significant side effects related to domperidone therapy during the trial.

AP-FGID is a common problem in children and effective therapeutic modalities are not widely available. Interventions such as amitriptyline has shown no benefits over placebo (7). Mebeverine, famotidine, cyproheptadine, and rifaximin had only shown a modest effects and long term follow-up data were not available (34,38–40). Other interventions such as hypnotherapy and yoga therapy are time consuming and need specially trained professionals and therefore, difficult to implement in busy clinical settings (41,42). In such a context, finding a potentially effective, widely available and low-cost therapeutic agent has far-reaching benefits to children. During the study concealment of allocation was maintained in accordance with current guidelines. Low dropouts and excellent adherence to the protocol provided the final sample size with adequate power to detect the originally proposed differences in the study outcomes. We also used physiological parameters of gastric motility to explore the mechanism of clinical improvement and managed to follow-up the majority of patients up to 6 months.

A heterogeneous group of patients with AP-FGIDs was evaluated considering abdominal pain as the main disease entity. This could be considered the main limitation of the study. However, we were able to perform a subgroup analysis, with the available numbers. Pain, the main symptom which was evaluated, is a subjective phenomenon, although we used objective, standardized, and validated tools to assess pain. Potential bias was, however, minimized by random allocation of participants and following a standardized protocol by the investigators. Approximately 70% of the participants screened for participation in the trial met eligibility criteria. Out of the eligible participants, approximately 10% refused to participate in the trial. When we analyzed the 6-month data using per protocol analysis (considering all the dropouts as nonresponders at 6 months), cure and improvement of the domperidone group became nonsignificant. This could be considered as another limitation of the study.

The exact mechanism of achieving symptomatic relief following domperidone in our study is not clear and this effect is unlikely to be related to the prokinetic properties of the drug. It is possible that domperidone acts in a different pathway to modulate pain and improve symptoms in AP-FGIDs. Although dopamine is a neurotransmitter in the brain that deals with pain, it is unlikely that domperidone modulated pain in the central pain centers as it does not cross the blood-brain barrier (43,44). Further studies are needed to find the exact mechanism of reduction of pain severity and overall sustainable clinical improvement of AP-FGIDs in children when they are treated with domperidone.

In conclusion, while performing a double blind, randomized, placebo-controlled trial, we have shown that domperidone, may be a safe, and effective therapeutic modality to achieve a lasting remission of symptoms in children with AP-FGIDs, specially with FAP. Approximately two third of children treated with domperidone were able to sustain the clinical improvement and were able to achieve our stringent criteria for cure at 6-month follow-up. The efficacy of domperidone is not related to its gastroprokinetic effect and our findings indicate that there is a therapeutic benefit of using domperidone in children with AP-FGIDs irrespective of baseline gastric motility status.

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