

Efficacy and Safety of Drotaverine Hydrochloride in Children with Recurrent Abdominal Pain: A Randomized Placebo Controlled Trial

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Objective: To evaluate the efficacy and safety of Drotaverine hydrochloride in children with recurrent abdominal pain.

Design: Double blind, randomized placebo-controlled trial.

Setting: Pediatric Gastroenterology clinic of a teaching hospital.

Participants: 132 children (age 4-12 y) with recurrent abdominal pain (Apley Criteria) randomized to receivedrotaverine (n=66) or placebo (n=66) orally.

Intervention: Children between 4-6 years of age received 10 mL syrup orally (20 mg drotaverine hydrochloride or placebo) thrice daily for 4 weeks while children >6 years of age received one tablet orally (40 mg drotaverine hydrochloride or placebo) thrice daily for 4 weeks.

Outcome Measures: *Primary:* Number of episodes of pain during 4 weeks of use of drug/placebo and number of pain-free days. *Secondary:* Number of school days missed during the study period, parental satisfaction (on a Likert scale), and occurrence of solicited adverse effects.

Results: Reduction in number of episodes of abdominal pain [mean (SD) number of episodes 10.3 (14) vs 21.6 (32.4); $P=0.01$] and lesser school absence [mean (SD) number of school days missed 0.25 (0.85) vs 0.71 (1.59); $P=0.05$] was noticed in children receiving drotaverine in comparison to those who received placebo. The number of pain-free days, were comparable in two groups [17.4 (8.2) vs 15.6 (8.7); $P=0.23$]. Significant improvement in parental satisfaction score was noticed on Likert scale by estimation of mood, activity, alertness, comfort and fluid intake. Frequency of adverse events during follow-up period was comparable between children receiving drotaverine or placebo (46.9% vs 46.7%; $P=0.98$),

Conclusion: Drotaverine hydrochloride is an effective and safe pharmaceutical agent in the management of recurrent abdominal pain in children.

Keywords: Abdominal pain, Parental satisfaction, Treatment.

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Recurrent abdominal pain (RAP) is one of the most common chronic pain conditions of childhood. Between 4% to 25% of school-age children complain of RAP of sufficient severity to interfere with daily activities [1-4]. Most common cause of recurrent abdominal pain in children is functional abdominal pain (FAP) which may be caused by alterations of homeostatic reflexes in gut-brain axis that is involved in control of gastrointestinal functions. This can be associated with dysregulations in intestinal secretions, motility, blood flow and afferent sensitivity [5]. This may respond to cognitive behavioral therapy, but medications are frequently prescribed for relief of pain [6].

Drotaverine, a selective inhibitor of phosphodiesterase (PDE) isoenzyme IV, has been found to be useful in spastic and motility disorders of the smooth muscle in adults [7-9]. However, good quality data about its efficacy in children are lacking. Drotaverine is the most commonly used off-label medication in Europe for alimentary tract problems in preschool and school

children [10]. Although drotaverine is frequently used as spasmolytic in children, its efficacy in control of functional abdominal pain – the most common chronic pain condition – has not been evaluated in children. As RAP is a chronic condition requiring frequent doses of the drug, the safety over prolonged/repeated use also needs to be documented. The present randomized placebo-controlled trial was conducted to assess the efficacy and safety of drotaverine in children with recurrent abdominal pain.

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METHODS

This double-blind, randomized placebo-controlled trial was conducted at Pediatric Gastroenterology and Hepatology Clinic of a tertiary care hospital in Northern India catering mainly to urban poor population. The study was conducted over 12 months period ending September 2013. The study protocol was approved by Institutional

Ethics Committee (Human Research) of GTB Hospital, Delhi. Written informed consent was obtained from parents, and assent was taken from children aged ≥ 7 years.

Children aged between 4 to 12 years with recurrent abdominal pain, defined as at least three episodes of pain interfering with normal activities within a three month period [1], were screened for potential inclusion into the study. Patients were excluded from the study if they had organic etiology (*e.g.*, cholelithiasis, nephro/urolithiasis, acute pancreatitis, viral hepatitis, previous abdominal surgery) of abdominal pain (as apparent from history, clinical examination or investigations), cognitive-developmental delay, cerebral palsy, previous abdominal surgery, acute illness (fever, diarrhea or respiratory tract infection in last 3 days), known immunodeficiency, or chronic cardiac, hepatic or renal disease.

Initial evaluation included a detailed medical history and complete physical and systemic examination. Blood investigations in all patients included hemoglobin, total and differential counts, erythrocyte sedimentation rate, serum bilirubin, alanine aminotransferase, serum albumin, urea, sodium and potassium. Microscopy and culture of urine, stool examination, plain abdominal radiograph, and ultrasonography of abdomen were also performed in all eligible children.

Enrolled children were randomly assigned to either receive the drug or the placebo with the use of a randomization list using computer-generated block randomization with variable block size. Stratification was done equally for ages 4-6 years and for >6 years. Allocation concealment was done in sealed opaque envelopes using six codes to avoid guessing of code; bottles were labelled with one of these codes. Participants, their parents, investigators and outcome assessors were blind to the treatment assigned. The drugs and placebo were packaged identically, and were similar in appearance, taste and smell. The placebo contained identical components to those in the active treatment group, with the exception of drotaverine hydrochloride. Randomization was done by a person not directly involved in the study. The code was kept in a sealed envelope in a locked cupboard. This code was broken only after complete data entry and cleaning.

For children aged between 4 to 6 years, 10 mL of the drug suspension or placebo (providing 20 mg of drotaverine hydrochloride in those receiving drug) was administered orally thrice a day for duration of four weeks. For children aged more than six years, one tablet containing 40 mg drotaverine hydrochloride or placebo was given orally thrice a day for a period of four weeks. If

the child encountered an episode of pain, the next dose was preponed if it was due in next two hours. One additional dose was given if he/she had not received the maintenance dose in last one hour or if next dose was not due in next two hours.

On a daily basis from week 1 to week 4, patients recorded the frequency/severity of pain and school absence in a structured diary provided by investigators. To assess the severity of pain, a combination of the self-reported visual analog scale (VAS) [11] and the Faces Pain Scale (FPS) [12] were used. These scales were printed in the patient diary for assessment by parents during the episode of pain. The caregiver satisfaction was assessed on a Likert scale based on their perception of child's mood, activity, alertness, oral intake and comfort. The parent's response was rated on a 5-point scale ranging from bad (1) to completely normal (5); subscale scores were computed by calculating the mean rating for each response. Higher scores indicated higher level of parental satisfaction. Number of school days missed during treatment due to pain was obtained by parent report. The question asked was 'Has the child missed school due to abdominal pain during last week'?

Enrolled children were called weekly in the clinic to examine their symptom diary. Entries were copied from the patient diary to the case record form. Any missing entry into the diary was clarified during each visit. The drug/placebo bottles (containing tablets or syrup) were dispensed on a weekly basis, the supply being sufficient to last for 10 days to take care of any additional doses required. Compliance to treatment was assessed by measuring/counting the remaining drug. All empty containers were preserved till the end of the study. Children missing more than 20% of the medication were considered non-compliant. Adverse events (both solicited and unsolicited) were monitored throughout the study in a symptom diary.

Primary outcome measures included number of episodes of pain during 4 weeks of use of drug/placebo and number of pain-free days. Secondary outcome measures included number of school days missed during the study period, parental satisfaction (on a Likert scale) and occurrence of solicited adverse effects (vertigo, headache, nausea or vomiting).

A sample size of 110 (55 in each group) was calculated to be sufficient to detect 15% difference in number of pain episodes during the 4 week observation period in two groups assuming a coefficient of variation of 30%, with power of 80% and alpha of 0.05. Accounting for 15% attrition, we planned to enroll 132 (66 in each group) children.

Statistical analysis: Analysis was performed as *per protocol* analysis. Details of patients who were lost to follow-up were compared in the two groups. The mean number of episodes of pain and number of pain-free days were compared in two groups by Student-*t* test. Frequencies were compared using Chi-square test or Fischer Exact test, as applicable. *P* value <0.05 was considered as significant. Data were entered into Microsoft Excel spreadsheet and analyzed by SPSS Version 17.0 statistical software.

RESULTS

Two-hundred-four participants with recurrent abdominal pain were screened for inclusion in the study. **Fig. 1** shows the flow of participants through the study. There were no significant differences between the groups in baseline characteristics (**Table I**).

There was a significant reduction in episodes of abdominal pain in children receiving drotaverine in comparison to those receiving placebo (**Table II**). Frequency of children missing school days were significantly lesser in drotaverine group as compared to placebo group. A total of 8 additional doses (in 4

TABLE I Baseline DEMOGRAPHIC CHARACTERISTICS OF CHILDREN RECEIVING DROTAVERINE OR PLACEBO

	Drotaverine group (n=66)	Placebo group (n=66)
Age, y	7.1 (2.1)	7.4 (2.6)
Boys; No. (%)	33 (50)	39 (59)
Weight, kg	20.4 (6.2)	21.1 (6.1)
Height, cm	115.9 (15.0)	115.9 (15.7)
Duration of pain, mo	10 (10.0)	9.6 (10.2)
Severity (VAS) of a typical episode, score	5.5 (1.5)	5.9 (1.9)
<i>*Site of Pain; No (%)</i>		
Umbilical	53 (80.3)	55 (83.3)
Epigastric	10 (15.2)	10 (15.2)
Others	8 (12.1)	(6.1)4

**Some children had pain at more than one site; All values are in Mean (SD) unless specified.*

TABLE II OUTCOME VARIABLES IN EACH TREATMENT GROUP

Outcome	Drotaverine (n= 64)	Placebo (n=60)	<i>P</i> value
Pain episodes	10.3 (14)	21.6 (32.4)	0.015
Pain-free days	17.4 (8.2)	15.6 (8.7)	0.234
School days missed	0.25 (0.85)	0.71 (1.59)	0.054
Any school absence; No. (%)	6 (9.4)	14 (23.3)	0.034
Patients with additional dose requirement; No. (%)	4 (6.2)	10 (16.7)	0.090
Episode of pain during follow-up period; No. (%)	7 (10.9)	3 (5.0)	0.326
Adverse events; No. (%)	30 (46.9)	28 (46.7)	0.981
<i>*Adverse Events; No. (%)</i>			
Fever	10	6	
Cough	8	7	
Cold	5	4	
Vomiting	7	8	
Nausea	6	2	
Giddiness	4	2	
Diarrhea	4	3	
Macular rash	4	1	
Headache	3	5	
Urticaria	1	0	
Eating poorly than usual	1	3	
Epistaxis	0	1	
Black Stools	0	1	

**Some children had more than one adverse event; All values are in Mean (SD) unless specified.*

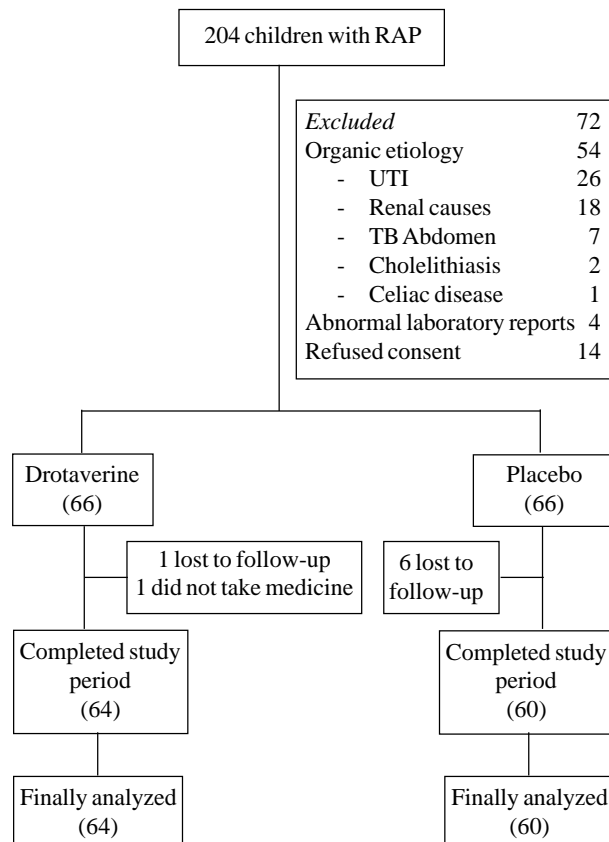


FIG. 1 Study flow chart.

children) were consumed by children receiving drotaverine as against 21 doses (in 10 children) in placebo group. The number of patients requiring additional drug doses, number of additional doses and mean number of additional drug doses in drotaverine group and placebo group were not significantly different. Frequency of adverse events was comparable between two groups. Most of the local and general adverse events were intercurrent illnesses such as upper respiratory infection or fever, not causally related to the study drug. All the adverse events resolved before completion of the study without sequela. There were no deaths or any serious adverse events. One patient in drotaverine group developed urticaria which required discontinuation of the drug.

The parental satisfaction scores are compared **Table III**. The overall mean scores for mood, activity, alertness, comfort and fluid intake were higher in the drotaverine than the control group during the 4 weeks of treatment.

DISCUSSION

In this randomized controlled trial on children with non-organic recurrent abdominal pain, we documented that drotaverine given orally for four weeks results in fewer episodes of abdominal pain and school absence, and improves parental satisfaction as compared to placebo group. No significant drug-related adverse effects were observed.

There were several limitations to this study. First, our definition of recurrent abdominal pain was based on Apley's criteria [1], which considers recurrent abdominal pain as a single entity, and not as per the new Rome III criteria which considers this too wide for useful application and sub-classifies functional abdominal pain by symptomatology and cause [13]. However, a Cochrane review concluded that it remains unclear the extent to which separating children into sub-groups (as per Pediatric Rome Criteria II of 1999) [14] defines groups who have different psychological or

pathophysiological mechanisms underlying their symptoms or whether they are likely to respond differently to interventions [6]. Second, the drug was administered by parents thrice daily while children were examined once weekly by clinicians in the study clinic. However, we ensured compliance by counting the tablets or measuring the volume of remaining drug at every visit. Evaluation of pain was done by parents who are likely to vary in the way they engage in certain type of responses. No biochemical monitoring of adverse events was done. The drug was given on regular basis rather than as-and-when required basis to assess safety and acceptability of repeated doses, which may not be always required in a clinical setting. The study was carried out in recurrent functional abdominal pain with other causes of abdominal pain not being addressed. Single-center trial and short follow-up period are the other limitations of the study. Strengths of our study were: randomized placebo-controlled trial design, detailed work-up to exclude other causes of abdominal pain, and evaluation of functional outcomes such as episodes of abdominal pain, school absenteeism and parental satisfaction.

A Cochrane review assessing effectiveness of medication in 5-18 years old school age children with RAP concluded that there is paucity of placebo-controlled trials for all of the drugs recommended for use in children with RAP [6]. However, individual studies have documented efficacy of other treatments in children with functional abdominal pain [15-18]. Evidence is inconclusive for some other treatment modalities such as H₂-receptor antagonists [19], fiber supplement intake or lactose free diet in children with RAP [20,21]. There is a paucity of comparative efficacy data for drotaverine in children. However, in adults, drotaverine has proven to be effective antispasmodic in renal colic [22,23] and irritable bowel syndrome [24], with no serious side effects. In the current study, drotaverine was associated with fewer episodes of abdominal pain during its regular use. The precise mechanism by which drotaverine can relieve abdominal pain is due to its antispasmodic properties, which is devoid of anticholinergic activity. It acts mainly by inhibiting type IV PDE, leading to an increase in intracellular cyclic AMP and cyclic GMP leading to smooth muscle relaxation.

We conclude that drotaverine hydrochloride is an effective and safe pharmaceutical agent in the management of recurrent abdominal pain of childhood. Further studies of its efficacy in organic abdominal pain conditions of childhood are desirable. Future studies should address the issue of its efficacy when given on as-and-when required basis, along with biochemical monitoring of any adverse effects.

TABLE III PARENTAL SATISFACTION SCORE (AFTER 4 WEEKS OF TREATMENT) IN EACH TREATMENT GROUP

Outcome	Drotaverine Mean (SD)	Placebo Mean (SD)
Mood	3.7 (0.7)	3.3 (0.9)
Activity	3.7 (0.7)	3.4 (0.9)
Alertness	3.8 (0.8)	3.5 (0.9)
Comfort	3.7 (0.8)	3.4 (0.9)
Fluid Intake	4.0 (0.7)	3.7 (0.8)

P < 0.05 for all comparisons

WHAT IS ALREADY KNOWN?

- Drotaverine is useful for providing relief from pain in spastic and motility disorders of smooth muscles in adults.

WHAT THIS STUDY ADDS?

- Drotaverine provides symptomatic relief in children with recurrent abdominal pain.

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