Clinical Trial

Evaluation of Efficacy and Safety of Bonnispaz Drops in Abdominal Colic of Infants and Children

BHARAT J. PARAMAR, PRASAD S.R., MITRA S.K.

ABSTRACT

The present study was planned to evaluate the clinical efficacy and safety of Bonnispaz drops in abdominal colic in infants and children. Abdominal colic is a commonly encountered syndrome of infancy and childhood and many therapeutic interventions have been studied.

The study was an open clinical trial, conducted as per the ethical guidelines of Declaration of Helsinki. All infants and children suffering from abdominal colic were included in the study, and those having severe vomiting and diarrhea were excluded from the study. A thorough history, symptomatic evaluation and clinical examination were done for all patients before treatment and after treatment along with recording the occurrence of any adverse event/s.

A total of 105 patients were enrolled for the clinical trial and all the patients completed the study. 103 patients had excessive crying problem and abdominal bloating; and all the 105 patients had reduced food intake and; 67 patients were suffering from unclered bowels. After 5 days of treatment with Bonnispaz, a 100% significant symptomatic relief from excessive crying, abdominal bloating and abdominal tenderness was observed. All the infants who were suffering from reduced food intake and unclered bowels were relieved. These results were significant at the level of p<0.0001 as tested by Students ‘t’ test. A significant reduction (p=0.0001) in the mean time of relief from abdominal colic and mean percentage reduction in relief from flatulence was observed in children at the end of the 5-day treatment with Bonnispaz.

There were no clinically significant adverse events, either reported or observed, during the entire study period. Therefore, it may be concluded that Bonnispaz drops are clinically safe and effective in the management of abdominal colic in infants and children.

INTRODUCTION

Infantile colic, which affects up to one third of infants in their first 3 months of life, was defined in the mid-1950s as “the rule of three”: healthy, well-fed infants with paroxysmal irritability and crying lasting a total of 3 hours a day and occurring more than 3 days a week.1 Colic is a “noisy phenomenon”2 that manifests as excessive and inconsolable crying, usually in the evening. Episodes of crying sometimes occur in clusters during which babies can have increased body tonus and be excessively alert. While the etiology of colic is unknown, it is clear that this self-limiting condition resolves in up to 90% of infants by the age of 4 months.3

Those most affected by colic are the parents. Sleepless nights and the inability to console a newly arrived baby cause a great deal of stress, especially among first-time parents. Mothers of infants with colic were found to be more concerned about their infants’ temperament and even to feel dejection compared with mothers of infants without colic.

Despite over 40 years of research, the etiology of infantile colic remains unclear. Four main causes emerge from the literature. Firstly, infantile colic may be a problem with the gut in which excessive crying is the main symptom.4 According to this view, excessive crying is the result of painful gut contractions caused by allergy to cow’s milk, lactose intolerance, or excess gas. Secondly, it may be a behavioral problem resulting from a less than optimal parent-infant interaction, with a difficult temperament of the infant as a possible explanation for inadequate parental reactions.5 Thirdly, excessive crying in a child with infantile colic could be regarded as merely the extreme end of normal crying.6 Fourthly, infantile colic is just a collection of etiologically different entities that are not easy to discern clinically.7

But, there is no clinically effective and safe medication that can be recommended in management of infantile abdominal colic.

Bonnispaz drops is a polyherbal formulation containing oils of *Carum carvi*, *Carum copticum* and *Zingiber officinale*, all of which are recommended for the management of infantile abdominal colic. This study was planned to evaluate the clinical efficacy and safety of Bonnispaz drops in abdominal colic in infants and children.
PATIENTS AND METHODS

Inclusion criteria

All infants and children aged between 1 day and 3 years, suffering from abdominal colic with associated spasmodic abdominal pain and griping, bloating of abdomen and excessive crying were included in the study.

Exclusion criteria

Infants or children having severe vomiting and diarrhea, and those suffering with severe systemic disease were excluded from the study.

Study procedure

The study was an open, non-randomized and non-comparative, phase III clinical trial, conducted at B.J. Medical College, Civil Hospital, Ahmedabad, India, from August 2002 to April 2003 as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product related information and informed consent forms (in English, Hindi and Gujarati) were submitted to the Institutional Ethics Committee and were approved by the same.

The parents/guardians of the patient were informed about the study drug, its effects, patient’s duration of stay in the trial and overall plan of the study. The patient was included in the clinical study only after a written informed consent was obtained from his/her parent/guardian, and a witness, independent of the clinical trial, signed the informed consent form.

The history was noted by interviewing the parent/guardian. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. Parents/guardians of the patient were advised to administer the drug at a dose of 4 drops initially, followed by 2 drops thrice-daily for a period of 5 days.

All patients were followed up at the end of treatment on day 5 and symptomatic evaluation and clinical examination was done, alongwith recording the occurrence of any adverse event/s (either reported or observed).

Primary and secondary endpoints

The predefined primary endpoints were rapid symptomatic relief from abdominal colic, flatulence and excessive crying. The predefined secondary endpoints were short- and long-term safety, and overall compliance to the drug treatment.

Adverse events

All adverse events, either reported or observed, were recorded in the CRF with information about severity, onset, duration and action taken regarding the study drug. Relation of adverse events to the study medication was predefined as unrelated (a reaction that does not follow a reasonable temporal sequence from the time of administration of the drug), possible (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient), and probable (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study, if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take less than 80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

Statistical analysis

Statistical analysis was done according to intention-to-treat principles. The changes in various parameters from pre-treatment values and post-treatment values were analyzed by “Fisher’s Exact Test” and “Paired Student ‘t’ Test”. The minimum level of significance was fixed at 95% confidence limit and a 2-sided p value of <0.05 was considered significant.

RESULTS

A total of 105 patients were enrolled for the clinical trial and all the patients completed the study. 103 patients had excessive crying problem and abdominal bloating; and all the 105 patients had reduced food intake; and 67 patients were suffering from uncleared bowels (Table 1).

Table 1: Effect of Bonnispaz drops on crying, bloating, food intake, abdominal tenderness and uncleared bowels

<table>
<thead>
<tr>
<th>Indications</th>
<th>Pre-treatment (No. of patients)</th>
<th>Post-treatment (No. of patients)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
<td>Reduced</td>
<td>Moderate</td>
</tr>
<tr>
<td>Excessive crying</td>
<td>103</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>103</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Food intake</td>
<td>0</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>103</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Uncleared bowels</td>
<td>67</td>
<td>38</td>
<td>0</td>
</tr>
</tbody>
</table>

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After 5 days of treatment with Bonnispaz drops, a 100% significant symptomatic relief from excessive crying, abdominal bloating and abdominal tenderness were observed. All the infants suffering from uncleared bowels and reduced food intake were relieved within 5 days of treatment (Figures 1 to 5).

**Table 2: Effect of Bonnispaz drops on mean time of relief from abdominal colic and percentage of relief from flatulence**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time of relief from abdominal colic (min.)</td>
<td>67.70 ± 31.02</td>
<td>23.29 ± 11.28</td>
<td>p&lt;0.0001, t=18.18, df=104, R²=0.7760</td>
</tr>
<tr>
<td>Relief from flatulence (%)</td>
<td>48.14 ± 1.306</td>
<td>84.86 ± 1.315</td>
<td>p&lt;0.0001, t=25.22, df=104, R²=0.8595</td>
</tr>
</tbody>
</table>

**Figure 1: Effect of Bonnispaz drops on excessive crying**

**Figure 2: Effect of Bonnispaz drops on abdominal bloating**

**Figure 3: Effect of Bonnispaz drops on food intake**

**Figure 4: Effect of Bonnispaz drops on abdominal tenderness**

**Fig. 5: Effect of Bonnispaz drops on uncleared bowels**

**Fig. 6: Mean time of relief from abdominal colic with Bonnispaz drops treatment**
There was a significant reduction in the mean time of relief from abdominal colic from 67.70 ± 31.02 to 23.29 ± 11.28 (p<0.0001) at the end of treatment with Bonnispaz drops (Table 2 and Figure 6).

There was a significant increase in percentage of relief from flatulence from 48.14 ± 1.306 to 84.86 ± 1.315 in children at the end of 5-day treatment with Bonnispaz drops (p<0.0001) (Table 2 and Figure 7). These results were significant at the level of p<0.0001 as tested by Student's t test.

There were no clinically significant adverse events, either reported or observed, during the entire study period.

**DISCUSSION**

The cause of infantile colic remains unclear. Underlying organic causes of excessive crying must be considered during the evaluation. Organic causes account for less than 5 percent of infants presenting with excessive crying. Gastrointestinal, psychosocial, and neurodevelopmental disorders have been suggested as the cause of colic.

Gastrointestinal disorders have been implicated in colic because of the infant’s leg position and grimacing during a crying spell. Excessive crying or increased gas production from colon function can result in intraluminal gas formation and aerophagia. This mechanism does not appear to be the cause of colic, however, because radiographic images taken during a crying episode have shown a normal gastric outline. There is conflicting evidence showing that colic is caused by allergy to human and cow’s milk protein. It also has been speculated that abdominal cramping and colic may be a result of hyperperistalsis. The latter theory is supported by evidence that the use of anticholinergic agents decreases colic symptoms. Gut hormones such as motilin also may play a causative role in colic. Motilin is thought to cause hyperperistalsis, leading to abdominal pain and colic.

Behavior management, supportive counseling and parental reassurance are the mainstays of treatment. The family members, especially the mother, should be explained about benefits of breast feeding, correct advice about feeding such as burping post feeds, feeding in a propped-up position, laying the baby on right side and discouraging use of bottles.

The only drug which has been shown to be effective is dicyclomine; however, serious side effects have been reported. Other drugs such as simethicone, homatropine methylbromide and phenobarbitone have been shown to be ineffective. The recent drug, which has been found effective in a randomized, double blind, placebo-controlled trial is Cimetropium bromide.

This clinical study observed a significant symptomatic relief from abdominal colic and flatulence in all the patients included in the study. Total relief was observed in all patients suffering from abdominal bloating and tenderness. There were no clinically significant adverse events, either reported or observed, during the entire study period.

In one experimental study with Bonnispaz drops, potent antispasmodic activity was observed. Bonnispaz drops inhibited the contractions produced by various spasmogens like acetylcholine, barium chloride, histamine and oxytocin. Since these spasmogens have different modes of action, the antagonism elicited by Bonnispaz drops indicates that it might be acting at a common step in the contraction mechanism elicited by these agonists. The antagonism displayed was concentration-dependent. Bonnispaz drops altered the effects of acetylcholine, histamine, oxytocin and barium chloride and this indicated a non-specific antagonist action. This study revealed that Bonnispaz drops decreased gastric emptying and intestinal transit in a dose-dependent manner, which indicates the inhibition of gastro-intestinal motility in vivo. All these findings suggest that Bonnispaz drops has a non-specific antispasmodic activity.

Earlier research work on the extracts of individual ingredients of *Carum carvi, Carum cicutum* and *Zingiber officinale* were credited for their antispasmodic, analgesic, antiinflammatory, and antioxidant activities.

*Carum carvi* (seeds and essential oil) is used in food and medicine as carminative, and prescribed in flatulent colic and stomach derangement. The main components of *Carum carvi* oil (Caraway oil) are carvone, limonene, germacrene D, and trans-dihydrocarvone. Carvone is carminative in action. *Carum carvi* exhibits neurotropic antispasmodic activity. It is also attributed with antibacterial, cytoprotective, and antioxidant activities. Antibacterial activity of *Carum carvi*, determined with the agar diffusion method, has been observed against gram-positive and gram-negative bacterial species. The cytoprotective effect of *Carum carvi* could be partly due to flavonoid content and free radical scavenging properties. Another study revealed strong antioxidant activity of *Carum carvi* that was superior to known antioxidant, ascorbic acid.
Carum coticum is much valued for its antispasmodic, stimulant, tonic, and carminative properties. It is administered in flatulence, atomic dyspepsia and diarrhea, and often recommended for cholera. It is also prescribed in amebiasis and is a potent antimicrobial agent. Carum coticum is known for its antispasmodic and hepatoprotective activities. The essential oil extracted from the seeds of Carum coticum have been studied for antibacterial activity against eight pathogenic bacteria causing infections in the human body. It has been found that the oil is very effective against all tested bacteria. Carum coticum has antispasmodic action, especially in non-ulcer dyspepsia. Carum coticum also possesses analgesic effect.

The active ingredients of Zingiber officinale are gingerols and diarylheptanoids. Zingiber officinale is proven to be effective in inhibiting the gastric and intestinal motility and also has been found to inhibit the colonic motility in vitro. Zingiber officinale was proven effective in inhibiting the intestinal, gastric, and colonic motility and the spasmytic activity of Zingiber officinale might be attributed to gingerol that was found to inhibit prostaglandin (PG) biosynthesis and serotonergic activity. Zingiber officinale has inhibitory effects on COX-1 and -2 enzymes and the mechanism of action is hypothesized to be due to the attenuation of COX-1 and -2 (regulated by the eukaryotic transcription factor NF-kappaB) and thromboxane-synthase enzymatic activity. Ahmed et al., observed that the antioxidant effect of Zingiber officinale extract was comparable to ascorbic acid as demonstrated by lowered lipid peroxidation, while maintaining the activities of other antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase).

Therefore, the observed clinical benefits of Bonnispaz drops might be due to the synergistic actions of its ingredients.

**CONCLUSION**

Abdominal colic in infants and children is a commonly encountered syndrome. Being a multifactorial syndrome complex, many therapeutic interventions have been studied. But, there is no clinically effective and safe medication that can be recommended in management of abdominal colic. This study was planned to evaluate the clinical efficacy and safety of Bonnispaz drops in abdominal colic of infants and children.

This clinical study observed a significant symptomatic relief from abdominal colic and flatulence in all the patients. Total relief was observed in all patients suffering from bloating and abdominal tenderness. There were no clinically significant adverse events, either reported or observed, during the entire study period. Therefore, it may be concluded that Bonnispaz drops is clinically safe and effective in the management of abdominal colic in infants and children.

**REFERENCES**


