Bonnispaz Drops

Evaluation of its efficacy and safety in abdominal colic of infants and children

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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. However, there is no clinically effective and safe medication for the management of abdominal colic.

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. The predefined primary endpoint was rapid symptomatic relief, and the predefined secondary endpoints were short- and long-term safety and overall compliance to the drug treatment.

A total of 23 patients were enrolled for the clinical trial and all the patients completed the study. All 23 patients had excessive crying problem, 20 patients had abdominal bloating, 13 patients had reduced food intake, 10 patients had abdominal tenderness, and 20 patients had uncleared bowels. 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 who were suffering from reduced food intake and uncleared bowels were relieved of the symptoms. These results were significant at the level of p<0.001 as tested by Students ‘t’ test. A significant reduction (p<0.001) in the mean time of relief from abdominal colic and mean percentage reduction in relief from flatulence was observed in the children at the end of 5 days of treatment with Bonnispaz drops.

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 concerns about 10-30% of all newborns and is defined as a condition characterized by paroxysmal episodes of unexplained full force crying for at least three days a week and continuing for one week or more in a thriving, well-nourished infant. The disorder more likely occurs in the evening, without identifiable causes and resolves spontaneously by the fourth month of life.1

Despite its salience in terms of both prevalence and distress occasioned in parents, the nature and causes of infantile colic remain poorly understood. Causes in the gut (abnormal sensitivity to dietary
components, excessive gas, intestinal hypermotility, hormonal factors) and alternative explanations (variant of normal crying behavior, effect of atypical parenting, manifestation of problems in parent-infant interaction) are critically reviewed. Gut pathology may, at best, explain a minority of cases.2

The several factors involved in the etiopathogenesis (food intolerance or allergy to cow’s milk protein, intolerance to lactose, intestinal hyperperistalsis, neuro-hormonal immaturity, maternal anxiety, and familial stress) make the management of infants with colics difficult. But there is no clinically effective and safe medication that can be recommended in the management of infantile abdominal colic.

**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 gripping, 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.

**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>Excessive crying</td>
<td>Moderate 23 Reduced 0</td>
<td>Moderate 0 Reduced 23</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal bloating</td>
<td>Moderate 20 Reduced 3</td>
<td>Moderate 0 Reduced 23</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Food intake</td>
<td>Moderate 13 Reduced 10</td>
<td>Moderate 23 Reduced 0</td>
<td>p&lt;0.0006</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>Moderate 10 Reduced 13</td>
<td>Moderate 0 Reduced 23</td>
<td>p&lt;0.0006</td>
</tr>
<tr>
<td>Uncleared bowels</td>
<td>Moderate 20 Reduced 3</td>
<td>Moderate 0 Reduced 23</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

**Study procedure**
The study was an open, non-randomized and non-comparative, phase III clinical trial, conducted at Heritage Hospital, Lanka, Varanasi, India, 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 and Hindi) 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, along with 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 23 patients were enrolled for the clinical trial and all the patients completed the study. All 23 patients had excessive crying problem, 20 patients had abdominal bloating, 13 patients had reduced food intake, 10 patients had abdominal tenderness, and 20 patients had uncleared bowels (Table 1).

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 who were suffering from uncleared bowels and reduced food intake were relieved of the symptoms within 5 days (Figures 1 to 5). These results were significant at the level of p<0.001 as tested by Students ‘t’ test.

There was a significant reduction in the mean time of relief from abdominal colic from 0.4174 ± 0.05944 to 1.157 ± 0.1809 hours (p<0.003) 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 26.09 ± 5.325 to 53.39 ± 4.468 in infants at the end of 5-day treatment with Bonnispaz drops (p<0.0005) (Table 2 and Figure 7).

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

DISCUSSION
Although infantile colic is reported commonly and causes appreciable distress for both parents and pediatricians, its pathogenesis remains unclear despite 40 years of research. The available evidence suggests that this condition has multiple independent causes. Infantile colic has been attributed to infants’ difficult temperament, inadequate or inappropriate mother-infant interaction or mothers’

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**Table 2. Increase in percentage of relief from flatulence and intensity of relief with Bonnispaz drops treatment**

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>After treatment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of relief</td>
<td>0.4174 ± 0.05944</td>
<td>1.157 ± 0.1809</td>
<td>p&lt;0.003, t=4.315 df=22, R^2=0.4583</td>
</tr>
<tr>
<td>Relief from flatulence (%)</td>
<td>26.09 ± 5.325</td>
<td>53.39 ± 4.468</td>
<td>p&lt;0.0005, t=4.047 df=22, R^2=0.4267</td>
</tr>
</tbody>
</table>
Bonnispaz drops decreased gastric emptying and intestinal transit in a dose-dependent manner, which indicates the inhibition of gastrointestinal motility in vivo. All these findings suggest that Bonnispaz drops has a non-specific antispasmodic activity.\(^{18}\)

Earlier research works on the extracts of individual ingredients of *Carum carvi*, *Carum copticum* and *Zingiber officinale* were credited for their antispasmodic, analgesic, anti-inflammatory, 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.\(^{19}\) Carvone is carminative\(^{20}\) in action. *Carum carvi* exhibits neurotropic antispasmodic activity.

In an experimental study to evaluate its potential antiulcerogenic and cytoprotective activities\(^{21}\), *Carum carvi* extract produced a dose-dependent antiulcerogenic activity associated with a reduced acid output and an increased mucin secretion, an increase in prostaglandin E2 release and a decrease in leukotrienes.\(^{22}\)

*Carum copticum* is much valued for its antispasmodic, stimulant, tonic, calming, anti-emetic, anti-ulcerogenic and antispasmodic activities. In one of the experimental studies on 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

![Figure 3. Effect of Bonnispaz drops on food intake](image)

In a 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.

![Figure 4. Effect of Bonnispaz drops on abdominal tenderness](image)

anxiety,\(^{5}\) abnormal gastrointestinal function,\(^{6-8}\) transient relative lactase deficiency,\(^{9}\) and allergic problems such as exposure to cow’s milk protein in formula or breast milk.\(^{10-13}\) Recent studies indicate that exposure of the child to tobacco smoking by the mother during pregnancy and after delivery, and smoking by the father were associated with excessive crying.\(^{14}\) Moreover, it is suggested that smoking is linked to increased plasma and intestinal motilin levels;\(^{15}\) higher-than-average intestinal motilin and ghrelin levels seem to be related to elevated risk of infantile colic.\(^{16}\)

Oral sucrose has an analgesic effect in newborn infants and has been shown to have a significant ameliorating effect on infant colic. The anticholinergic drugs dicyclomine hydrochloride and dicycloverine have been effective in treating colic but are no longer used because of serious side effects. Simethicone is often used, but controlled trials have failed to show benefits.\(^{17}\)

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.
and carminative properties. It is administered in flatulence, atonic dyspepsia and diarrhea, and often recommended for cholera. It is also prescribed in amebiasis and is a potent antimicrobial agent. *Carum copticum* is known for its antispasmodic and hepatoprotective activities. The calcium channel blocking effect of *Carum copticum* was confirmed in a study when *Carum copticum* shifted the Ca\(^{2+}\) dose-response curves to right, similar to verapamil. These results indicate the presence of calcium antagonist(s) in *Carum copticum* seeds.

The essential oil extracted from the seeds of *Carum copticum* have been studied for antibacterial activity. *Carum copticum* has antidyspeptic action, especially in non-ulcer dyspepsia. *Carum copticum* 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 spasmolytic 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. The [6]-gingerol of *Zingiber officinale* acts by interfering with intracellular signaling cascades, those involving NF-kappaB and mitogen-activated protein kinases. Thomson et al. documented significant inhibitory effects of *Zingiber officinale* extract on PG-E2 production. 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 the 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**


