International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 22-02-2020; Accepted: 08-03-2020; Published: 25-03-2020
www.medicalsciencejournal.com
Volume 6; Issue 3; 2020; Page No. 153-158

Post marketing surveillance on safety and efficacy of Cymbi oral drops in various gastrointestinal indications: A survey-based study

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Abstract

Background: With the increase of acid suppressant medicine uses and many raised questions regarding the safety and efficacy of these agents, the present questionnaire-based survey was designed to access the safety and efficacy of Cymbi oral drop manufactured by Juggat Pharma, Bangalore against various gastrointestinal (GI) indications.

Method: A structured format survey consisting of an inventory chart for items that contain voluntary consent of doctors to participate in the survey, demographic details of doctors and safety, and efficacy parameter questionnaire which had 13 questions were distributed to doctors across PAN India. The completed survey forms were collected, and the answers to the questionnaire were analyzed and interpreted.

Results: There was a total of 288 completed questionnaire forms received across PAN India. Out of 288 doctors who took this questionnaire-survey based study, 255 doctors did not notice any side-effects in infants and children following the administration of Cymbi. 87.5% of doctors did not notice any interaction of Cymbi oral drop with food. In our survey, the majority of doctors *i.e.* 67.4% who took the questionnaire survey rated the efficacy of Cymbi in infants and children was much better than before medication with Cymbi. 279 out of 288 doctors reckoned that the product Cymbi was safe enough for the oral administration in infants and children, and 84.4% who took a survey prefer to prescribe Cymbi oral drop for infants and children over all the other options they have available against GI disorders.

Conclusion: The present survey demonstrated that Cymbi oral drop at the recommended dose was safe and efficacious in the treatment of GI disorders *viz.* infant colic pain, griping pain, flatulence, and bloating without any side-effects.

Keywords: cymbi, gi disorders, simethicone, dill, fennel, infant colic pain, gripping pain

Introduction

Throughout infancy, gastrointestinal disorders (GIDs) are major causes that force parents to visit healthcare settings [1, 4]. As such, FGID (functional gastrointestinal disorders) is a set of conditions that contain a mix of age-dependent, chronic or recurrent symptoms deprived of any apparent biochemical or structural abnormalities affecting the functioning of the gastro intestine (GI). An international group of nutritionists, educators, and physicians assessed on their perceived FGIDs incidence reported that up to 30% of children under the age of twelve months had an FGID [5].

Functional signs are physiological indications that appear in the absence of inflammation, anatomic abnormality, or damage to tissue. Psychosomatic and neuroscience literature accounts for historical explanations and hypotheses of complex interactions between psychological, biological, and social influences that predispose, precipitate, and/or sustain brain-gut axis disorders. Common issues that often determine visits to pediatric facilities are signs of feeding and eating and problems in toddlers and infants, such as nausea, regurgitation, vomiting, pain in abdomen and bellyaches, heartburn, abdominal distension, belching, bloating, constipation or chronic diarrhea, fecal soiling, food refusal or retching. Many lack biological ground to direct the process of recovery.

The 2013 Consensus [7] and Vandenplas *et al*. [8] review article evaluated the treatment efficacy of simethicone (anti-foaming agent), simethicone-lactase, cimetropium bromide (anticholinergic antimuscarinic antispasmodic molecule), dicycloverine (anticholinergic agent), trimebutine (weak opioid and antimuscarinic effects), and proton pump inhibitors (PPIs), and identified that none of the above procedures exhibited a considerable effect and some of them, such as cimetropium and dicyclomine [9], can potentially cause serious adverse reactions. Metcalf *et al* and Danielsson *et al*, however, stated that the duration of crying in infants preceding simethicone administration had decreased comparably [10, 11]. Different researchers stated that drugs with antispasmodic activity are used widely, based on the hypothesis that intestinal smooth muscles' contractions cause colic [12, 14] but dangerous side effects were described [15]. In another study conducted by Savino *et al* revealed that to reduce the crying duration, cimetropium bromide was more efficient compared to placebo but may cause motion sickness, lethargy, and drowsiness [16].

With this scenario, the present questionnaire-based survey was conducted to access the safety and efficacy of Cymbi oral drop manufactured by M/s. Juggat Pharma, Bangalore in various gastrointestinal indications *viz.* infant colic, griping pain, flatulence, and bloating among infants and children.

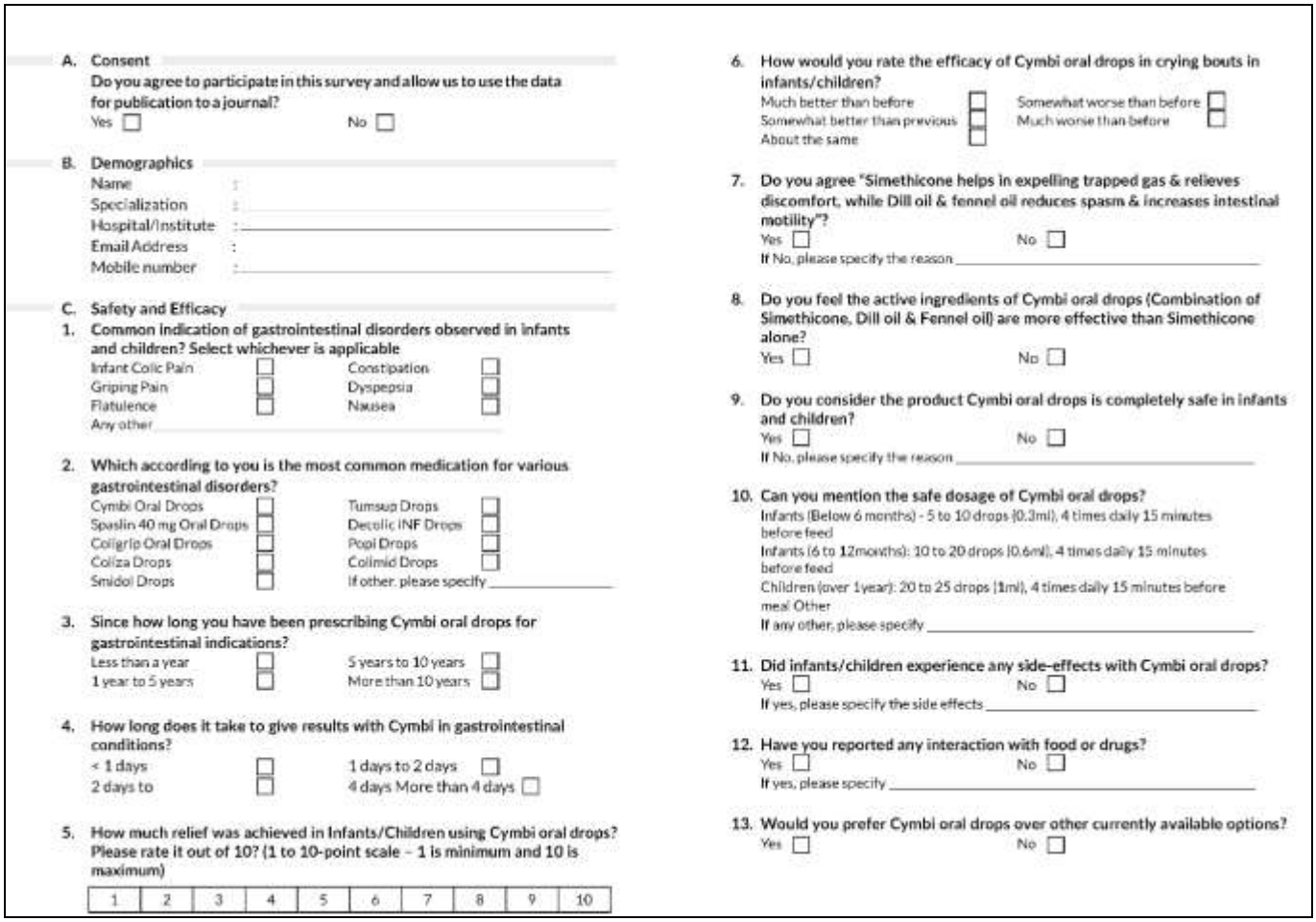
2. Materials and Methods

2.1 Test product

Cymbi is an oral drop manufactured by M/s. Juggat Pharma, Bangalore. Each ml (Approx. 25 drops) contains Simethicone (40 mg), added as simethicone emulsion USP Dill oil BP (0.005 mL), Fennel oil (0.0007 mL), and syrup base q.s.

2.2 Procedure

A structured format survey consisting of an inventory chart for items that contain voluntary consent of doctors to participate in the survey, demographic details of doctors and safety, and efficacy parameter's questionnaire which had 13 questions (Figure 1) were distributed to doctors across PAN India. The questions were on various gastrointestinal indications status before and after the administration of Cymbi oral drops and doctor's experiences on the patient's response. The completed survey forms were collected across PAN India. The answers to the questionnaire were analyzed and interpreted.



A. Consent
Do you agree to participate in this survey and allow us to use the data for publication to a journal?
Yes ☐ No ☐

B. Demographics
Name :
Specialization :
Hospital/Institute :
Email Address :
Mobile number :

C. Safety and Efficacy
1. Common indication of gastrointestinal disorders observed in infants and children? Select whichever is applicable
Infant Colic Pain ☐ Constipation ☐
Griping Pain ☐ Dyspepsia ☐
Flatulence ☐ Nausea ☐
Any other

2. Which according to you is the most common medication for various gastrointestinal disorders?
Cymbi Oral Drops ☐ Tumsup Drops ☐
Spaslin 40 mg Oral Drops ☐ Decolic INF Drops ☐
Coligrip Oral Drops ☐ Popi Drops ☐
Coliza Drops ☐ Colimid Drops ☐
Smidol Drops ☐ If other, please specify

3. Since how long you have been prescribing Cymbi oral drops for gastrointestinal indications?
Less than a year ☐ 5 years to 10 years ☐
1 year to 5 years ☐ More than 10 years ☐

4. How long does it take to give results with Cymbi in gastrointestinal conditions?
< 1 days ☐ 1 days to 2 days ☐
2 days to ☐ 4 days More than 4 days ☐

5. How much relief was achieved in Infants/Children using Cymbi oral drops? Please rate it out of 10? (1 to 10-point scale – 1 is minimum and 10 is maximum)

1	2	3	4	5	6	7	8	9	10

6. How would you rate the efficacy of Cymbi oral drops in crying bouts in infants/children?
Much better than before ☐ Somewhat worse than before ☐
Somewhat better than previous ☐ Much worse than before ☐
About the same ☐

7. Do you agree "Simethicone helps in expelling trapped gas & relieves discomfort, while Dill oil & fennel oil reduces spasm & increases intestinal motility"?
Yes ☐ No ☐
If No, please specify the reason

8. Do you feel the active ingredients of Cymbi oral drops (Combination of Simethicone, Dill oil & Fennel oil) are more effective than Simethicone alone?
Yes ☐ No ☐

9. Do you consider the product Cymbi oral drops is completely safe in infants and children?
Yes ☐ No ☐
If No, please specify the reason

10. Can you mention the safe dosage of Cymbi oral drops?
Infants (Below 6 months) - 5 to 10 drops (0.3ml), 4 times daily 15 minutes before feed
Infants (6 to 12months): 10 to 20 drops (0.6ml), 4 times daily 15 minutes before feed
Children (over 1year): 20 to 25 drops (1ml), 4 times daily 15 minutes before meal Other
If any other, please specify

11. Did infants/children experience any side-effects with Cymbi oral drops?
Yes ☐ No ☐
If yes, please specify the side effects

12. Have you reported any interaction with food or drugs?
Yes ☐ No ☐
If yes, please specify

13. Would you prefer Cymbi oral drops over other currently available options?
Yes ☐ No ☐

Fig 1: Simple to answer questionnaire to access the safety and efficacy of Cymbi

3. Results

The results of questionnaire survey on indications of gastrointestinal disorders reported in infants and children were infant colic pain (91%), gripping pain (74.3%), flatulence (72.2%), dyspepsia (31.9%), constipation (25.3%), and nausea (16%). The most common medication prescribed by medical practitioners was Cymbi oral drops (72.2%) followed by Coliza drops (39.6%), Colimid drops (9.7%), Tumsup drops (9%), Coligrip oral drops (8.3%), Decolic INF drops (7.3%), Spaslin 40 mg oral drops (5.6%), and Smidol drops-(3.8%). Among 288 doctors who undertaken questionnaire survey 143 (49.7%) doctors were prescribing cymbi drops less than a year; 118(41%) doctors were prescribing from 1 to 5 yrs., 17(5.9%) were prescribed in the past 5 years, and 9 (3.1%) doctors were prescribing since more than 10 years (Table 1 & 2; Figure 2).

Table 1: Distribution of Common Indications of Gastrointestinal Disorders in Infants and Children

Particulars	N (%)
Infant colic pain	262 (91%)
Gripping pain	214(74.3%)
Flatulence	208(72.2%)
Constipation	73(25.3%)
Dyspepsia	92(31.9%)
Nausea	46(16%)
Water-borne diseases and lack of	1(0.3%)
Unexplained cry	1(0.3%)

Table 2: Most Common Medication Prescribed by Medical Practitioners for Gastrointestinal Disorders

Particulars	N (%)
Cymbi Oral drops	208 (72.2%)
Spaslin 40 mg oral drops	16(5.6%)
Coligrip oral drops	24(8.3%)
Coliza drops	114(39.6%)
Smidol drops	11(3.8%)
Tumsup drops	26 (9%)
Decolic INF drops	21(7.3%)
Popi drops	3(1%)
Colimid drops	28 (9.7%)

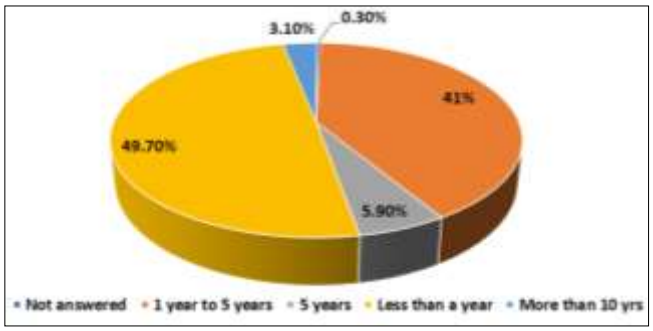


Fig 2: Distribution pattern of Cymbi prescription duration by doctors

Out of 288 doctors, 135 doctors (46.9%) revealed that infants/children medicated with Cymbi drops could able to recover from gastrointestinal conditions less than 1 day and 115 (39.9%) doctors observed results in between 1 to 2 days, 30 (10.4%) doctors observed that Cymbi could ameliorate the gastrointestinal disorders in 2 to 4 days.

The majority of doctors *i.e.* 194/288 (67.4%) who took the questionnaire survey rated the efficacy of Cymbi oral drops in infants and children was much better than before medication with Cymbi. However, 59/288 (20.5%) felt somewhat better, and 29/288 (10.1%) doctors felt the same as before medication (Figure 3).

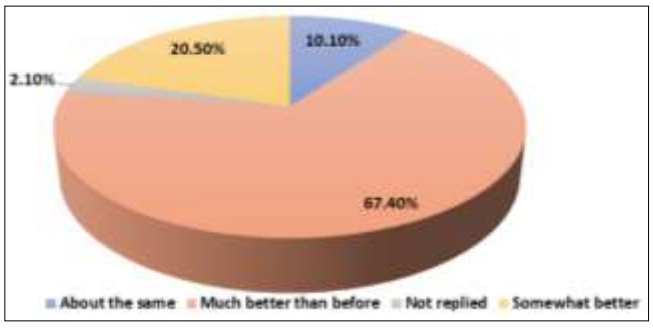


Fig 3: Distribution pattern of the efficacy of Cymbi

The results of present questionnaire-based survey study revealed that 281 out of 288 doctors agreed that main ingredient of Cymbi simethicone helps in expelling trapped gas and, and thereby eases from discomfort, while spasm is reduced with the use of dill oil and fennel oil, and thus intestinal motility increases (Figure 4). Furthermore, the questionnaire survey delineated that active ingredients of Cymbi oral drop *viz.* combination of simethicone, dill oil, and fennel oil are more effective than simethicone alone (Figure 5). Hence, 279 out of 288 doctors who have participated in the present questionnaire-based survey study reckoned that the product Cymbi was safe enough for the oral administration in infants and children against gastrointestinal indications *viz.* infant colic, griping pain, flatulence and bloating (Figure 6).

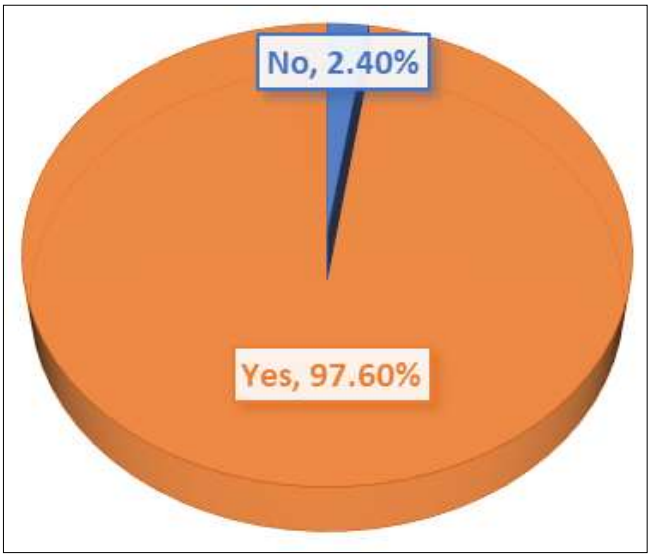


Fig 4: Results of the efficacy of Cymbi oral drop in infants and children

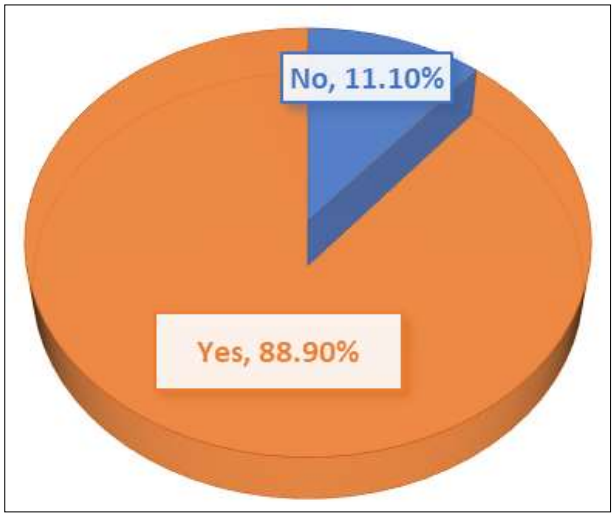


Fig 5: Results of ingredients effects of Cymbi oral drop in infants and children

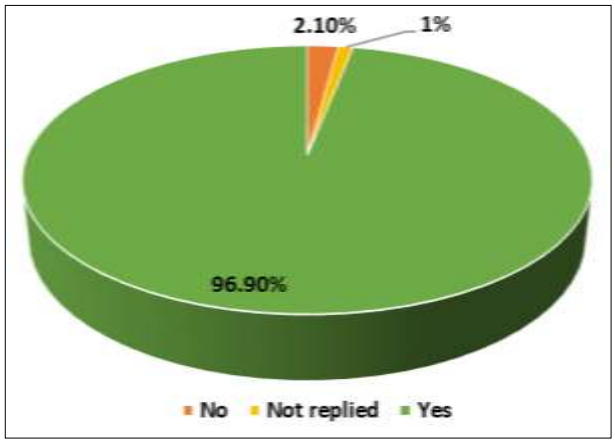


Fig 6: Results of Safety of Cymbi Oral Drop-in Infants and Children

154 out of 288 doctors (53.4%) recommended five to ten drops i.e. 0.3ml, four times daily fifteen minutes before a feed for infants below 6 months as the safe dosage of Cymbi oral drop. Whereas 30/288 (10.4%) doctors recommended ten to twenty drops i.e. 0.6ml, four times daily fifteen minutes before a feed for infants from 6 to 12 months as a safe dose, and only 5/288 (1.7%) doctors recommended twenty to twenty-five drops i.e. 1ml, four times daily fifteen minutes before a meal for children above 1 year as a safe dose (Table 3).

Table 3: The recommended dosage of Cymbi oral drop for infants and children

Dosage	Frequency	Percent
a	154	53.5
a + b + c	89	30.9
a + c	1	00.3
b	30	10.4
b + c	3	01.0
c	5	01.7
Not replied	6	02.1

[a]-Infants (below 6 months) - 5 to 10 drops (0.3ml), 4 times daily 15 minutes before a feed
[b]-Infants (6 to 12months): 10 to 20 drops (0.6ml), 4 times daily 15 minutes before a feed
[c]-Children (over 1year): 20 to 25 drops (1ml), 4 times daily 15 minutes before a meal

Out of 288 doctors who took this questionnaire-survey based study, 255 doctors did not notice any side-effects in infants and children following administration of Cymbi oral drop (Figure 7). Additionally, 252/285 (87.5%) doctors did not notice any interaction of Cymbi oral drop with food (Figure 8).

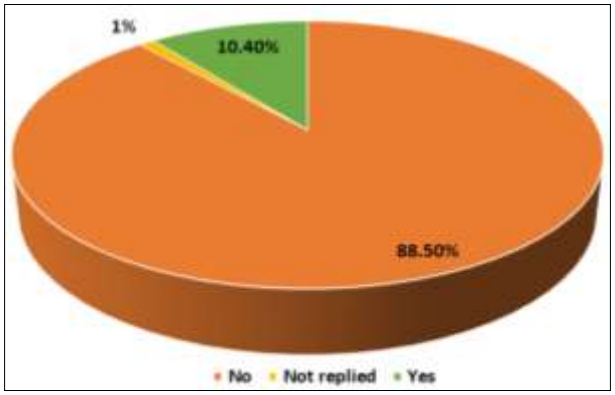


Fig 7: Results of side-effects of Cymbi oral drop in infants and children

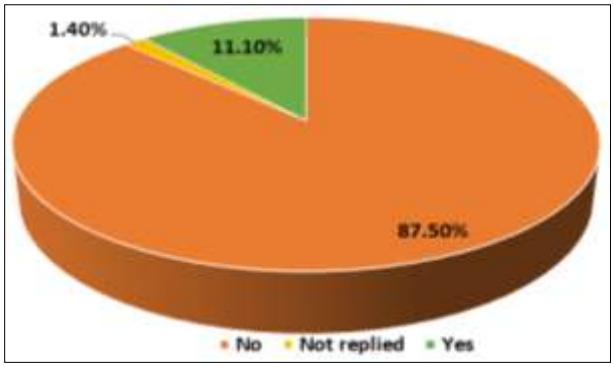


Fig 8: Results of the interaction of Cymbi oral drop with food in infants and children

The present questionnaire-based survey study revealed that 243 out of 288 doctors (*i.e.* 84.4%) who took the survey prefer to prescribe Cymbi oral drop for infants and children over all the other treatment options they have available against GI disorders *viz.* infant colic pain, griping pain, flatulence and bloating. However, 13.9% did not prefer to prescribe Cymbi oral drop (Table 4)

Table 4: Results of Cymbi oral drop as treatment preferences of doctors GIDs in infants and children

Particulars	Frequency	Percent
No	40	13.9
Not replied	5	1.7
Yes	243	84.4
Total	288	100.0

4. Discussion

GIDs are recurrent or chronic GI signs with no biochemical or structural malfunctions. GIDs are multifactorial disorders with various mechanisms of pathophysiology which include visceral hyperalgesia, altered motility, brain-gut disorder, genetic, psychological, and environmental influences. Even though the evidence-based research lacks, GI symptoms are often intermittent in most cases and with spontaneous resolution, in infancy, several changes in dietary and pharmacological treatment are often initiated. Infants with Gastrointestinal issues like cyclic vomiting syndrome, regurgitation, infantile colic, and problems with defecation frequently suffer a series of needless medical examinations and treatments. PPI prescriptions have increased dramatically in pediatric subjects over the past two decades. With the rise of acid-suppressant medicine use, many questions regarding the safety and efficacy of these agents have been raised. Therefore, our goal of the current questionnaire-based survey was to access the safety and efficacy of Cymbi oral drops manufactured by Juggat Pharma, Bangalore in various gastrointestinal indications *viz.* infant colic pain, griping pain, flatulence, and bloating among infants and children.

In dealing with infantile colic, most pediatricians don't feel very confident and are due to the fact of absence of a proof-based approach in managing persistent crying of an infant [17]. In managing infantile colic, parental reassurance is the foundation [18]. Given that infant colic decreases from 3 months of age and from 4to 6 months of age it disappears, it is clear that any planned medical intervention should be free of any adverse effects risk [19]. In our survey, majority of doctors *i.e.* 67.4% who took questionnaire survey rated efficacy of Cymbi oral drop in infants and children was much better than before medication with Cymbi as 281 out of 288 doctors agreed that main ingredient of Cymbi simethicone helps in expelling trapped gas, and thereby relieves discomfort. Hence, 279 out of 288 doctors who have participated in the present questionnaire-based survey study reckoned that the product Cymbi was safe enough for the oral administration in infants and children against gastrointestinal indications *viz.* infant colic pain, griping pain, flatulence and bloating. Infants with colic appear to be in pain. To decrease bloating, pain, or discomfort instigated by excessive gas, simethicone is used which is an anti-foaming agent. There were some positive reports from parents for the simethicone use for infantile colic as a pain-relieving agent [20]. For more than forty years ago, Debray *et al.* proposed that simethicone seems to act as a topical

buffer against irritants like gastric HCl, biliary salts, or acetylsalicylic acid to shield the mucosa [21]. Simethicone usually works in concert with surface-active endogenous substances lining the gut mucosa. The consequences of simethicone are those associated with the compound's intraluminal behavior in the digestive tract since it is not absorbed and is practical non-toxic [22, 23].

Since ancient times, Anethum *graveolens L.* (dill) is a common herb used widely as a spice and has been used in ayurvedic medicines and it could also yield essential oil. It is an annual herb of family Apiaceae and is aromatic. The dill seeds' ayurvedic uses are carminative, diuretic, and stomachic. An ingredient, anethum is used as in gripe water that alleviates baby colic pain and young child's flatulence [24]. The seed is carminative, aromatic, galactagogue, mildly diuretic, stomachic, and stimulant [25, 26]. Intestinal spasms and griping are relieved through vital oil in the seed, serving to settle colic [27, 28]. The volatile carminative oil increases appetite, soothes gas, and helps digestion.

Furthermore, Dennis Anheyer *et al.* reported evidence for different preparations of fennel *e.g.* oil, tea, an herbal compound in treating children suffering from infantile colic with no serious adverse side effects [29]. Besides, various researchers revealed sugar, cimetropium bromide, and herbal agents cannot be suggested for infants with colic [30]. Fennel-containing preparations are indicated to be effective in breastfeeding children, with an average mean difference of -72,1 minutes of crying/day [31].

As evident from the present questionnaire survey and literature study delineated that active ingredients of Cymbi oral drop *viz.* combination of simethicone, essential oils derived from dill, and fennel are more efficient in treating GI disorders in infants and children. Considering the safety, efficacy and with no side-effects of Cymbi oral drop 84.4% who took the survey to prefer to prescribe Cymbi oral drop for infants and children among all the other options they have available against GI disorders *viz.* infant colic pain, griping pain, flatulence and bloating.

5. Conclusion

In conclusion, a short and simple-to-answer questionnaire was developed as a tool to measure the safety and efficacy of Cymbi oral drop. The present questionnaire-survey study demonstrated that Cymbi oral drop was safe and efficacious in infants for the treatment of GI disorders *viz.* infant colic pain, griping pain, flatulence, and bloating without any adverse side-effects.

6. Abbreviations Used

GI: Gastrointestinal; PAN: Presence Across Nation; GIDs: Gastrointestinal Disorders; FGID: Functional Gastrointestinal Disorders; PPIs: Proton Pump Inhibitors; Q.S.: Quantity Sufficient; HCl: Hydrochloric Acid

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