## **Effectiveness of the fixed dose combination of Digestive enzymes, Carminatives and *Bacillus Coagulans* GBI 30, 6086 in infantile colic.**

**ABSTRACT**

**Background:** Infantile colic, characterized by repeated episodes of intense crying, is a distressing condition for parents, and its unknown causes complicate treatment. This study investigates the efficacy and safety of a fixed-dose combination of probiotics, digestive enzymes, and carminatives (Tummysoft Drops) in infantile colic.

**Methods:** 108 infants (aged < 6 months) fulfilling the Rome-IV diagnostic criteria for infantile colic were randomly allocated to receive 10 drops of Tummysoft Drops (Intervention group) or placebo drops (placebo group) daily for 4 weeks. The primary outcomes of the study were reduction of the duration of crying, crying frequency, defecation frequency and the number of infants whose crying duration was reduced to > 50% from the baseline.

**Results:** 100 Infants completed the study. At the end of 4 weeks, the mean crying duration changed from 261.30 ± 41.684 to 52 ± 12.857 min/day in the intervention group and from 262 ± 39.046 to 77 ± 27.408 min/day in the placebo group. The episodes of crying were reduced from 6.34 ± 2.387 to 0.20 ± 0.495 episodes/day in the intervention group and from 7.32 ± 2.453 to 1.30 ± 1.298 episodes/day in the placebo group. The number of infants with >50% decrease in crying time from baseline on day 14 was 49 infants in the intervention group and 30 infants in the placebo group (p = 0.05). By the end of 4th week, it was noted that parental satisfaction was better in the intervention group.

**Conclusion:** Administration of a comprehensive formula (Tummysoft Drops) containing *Bacillus Coagulans* GBI 30, 6086, digestive enzymes and carminatives was found to be safe and effective in the treatment of infantile colic.

**Keywords:** *Bacillus Coagulans* GBI 30, 6086, Digestive enzymes, Carminatives, Infantile colic

**INTRODUCTION**

Crying is a typical habit for infants during infancy. It is the infant's way of signalling and requesting assistance for physiological demands like hunger, temperature, diaper changes, and pain or discomfort [1]. While crying is accepted as "normal behaviour," between 5% and 40% of new-borns cry uncontrollably and excessively, along with periods of fussiness and gas passing [2, 3, 4]. Infantile colic is characterized by episodes of persistent, inconsolable crying and irritability lasting 3 hours or more, with no identifiable cause, in an otherwise healthy infant. [5, 6, 7]. Infant crying usually follows a predictable pattern, increasing around 2 weeks, peaking at 5-6 weeks, and decreasing by 12 weeks. There's a circadian rhythm to infant crying, with more frequent fussiness during the evening period [8]. Paroxysms of crying and gassy episodes can occur and disappear without clear reason or trigger, hence treating and preventing infantile colic can be challenging [9].

The exact cause of infantile colic remains unknown but potential contributing factors include alterations in fecal microflora, intolerance to cow's milk protein or lactose, gastrointestinal immaturity or inflammation and poor feeding technique [10]. Research indicates that gut microbiome composition varies significantly between colicky and non-colicky infants [11,12]. Supporting that role, children with colic are more likely to be colonized by *Clostridium difficile, Escherichia spp*., and *Klebsiella spp.,* and may have low levels of *lactobacilli* in the early stages of infancy, which impacts intestinal fatty acid balances [12]. Numerous studies have endorsed the fact that infantile colic is strongly linked with gut inflammation and dysbiosis [13, 14].

Probiotics are live microorganisms which offer beneficial effects when administered in adequate quantities [15]. Probiotic supplementation helps to alter the gut bacterial patterns by promoting the colonization of beneficial bacteria [16, 17]. Probiotics have the ability to reduce intestinal inflammation by inhibiting the overgrowth of inflammation-inducing microbes and gas-forming coliforms [18, 19]. *Bacillus coagulans* GBI-30, 6086 is an extremely stable probiotic due to the cell’s ability to form a protective spore. This protective spore gives *Bacillus coagulans* GBI-30, 6086 the ability to survive harsh manufacturing processes, during product shelf life and finally, the journey through the digestive system. *Bacillus coagulans* GBI-30, 6086 has been shown to exert a wide range of functions on the digestive system facilitating the synthesis of digestive enzymes and aiding the breakdown of a wide range of carbohydrate substrates. [20] *Bacillus coagulans* GBI-30, 6086 has been granted Generally Recognised As Safe (GRAS) status by the US Food and Drug Administration (FDA) and is being used in infant formulas. [21] *Bacillus Coagulans* GBI-30, 6086 along with digestive enzymes was found to be effective in the treatment of functional abdominal pain (FAP) in pediatric population [22].

Digestive enzymes ensure the digestion of complex food substances like carbohydrates and proteins. They reduce the accumulation of undigested food particles in the infantile gut and hence decreases the flatulence [23]. Digestive enzymes also ensure proper utilization of food including milk (catalysed by lactase enzyme) in infants and improves overall growth and development. Alpha Amylase hydrolyzes the glycosidic bonds in starch molecules, converting complex sugars to simple sugars. The simple sugars are absorbed easily in the intestine thus reducing the accumulation of complex carbohydrates and improving overall digestive health. Papain (Proteolytic enzyme) is an enzyme found in the white fluid (latex) that occurs in raw papaya fruit. It breaks the peptide linkage present in proteins, thus converting proteins into simpler amino acids. [24]

Lactase enzyme plays a vital role in breaking down of lactose in milk. In infants with lactase deficiency, undigested lactose can lead to lactose intolerance, resulting in flatulence and colic. Administering lactase enzyme can support lactose digestion and provide relief from colic symptoms

Carminatives helps to relieve flatulence. It leads to decreased stretching of gastrointestinal tract and reduce abdominal pain. It helps in significant decrease in colic and crying. Carminatives has an additional action of soothing the gut and helps in digestion of certain food substances.

Dill (*Anethum graveolens L.*) has been used since ancient times for relieving colic pain in babies and flatulence in young children. It relieves intestinal spasms and griping and helps to settle colic. It has a significant mucosal protective, antisecretory and anti-ulcer activities against stomach acid.In addition, dill oil is also used as stomachic, which Improves digestion and increases appetite [25]. Fennel oil is obtained from the seeds of *Foeniculum vulgare*. These are proven to be an effective remedy for many digestive disorders and ensures a healthy digestive system in growing babies. Fennel seeds have effective digestive properties that can help in easing cramps. They are packed with antioxidants that help in building the child's immunity and promote overall health. [7]

**MATERIALS AND METHODS**

This randomized, double-blind, placebo-controlled trial was carried out between September 2023 to February 2024 at the Department of Paediatrics in Chettinad Hospital and Research Institute, Kelambakkam. Before study initiation, approval was obtained from The Chettinad Institutional Human Ethics Committee and the same was registered in Clinical Trial Registry India (CTRI Number: CTRI/2023/08/056153).

After obtaining written informed consent from a parent or guardian, eligible new-borns were included to the study. The study protocol, possible risks and benefits of the study were informed to the parents. Subsequently, written informed consent were obtained. Following were the inclusion criteria (a) Crying or fussy/gassy episodes three or more hours per day during three or more days in 7 days, according to Rome-4 criteria, (b) age < 6month, (c) both breastfeed and non-breastfeed infants; (d) term delivery (≥37 weeks’ gestation at birth), and (e) birth weight ≥2500 g.

Exclusion criteria: (a) Infants with known gastrointestinal disorders, (b) previous abdominal surgery, (c) severe dehydration, (d) presence of systemic infections, (e) known immunocompromising morbidities, (f) cystic fibrosis, (g) severe acute malnutrition, (h) chronic or severe respiratory, (i) cardiovascular, (j) central nervous system, (k) endocrine, and other gastrointestinal disorders were excluded from the study.

The primary endpoints of the study were reduction in the duration of crying and crying frequency, defecation frequency, and the number of infants whose crying duration was reduced to 50% of the baseline. Secondary endpoints were parental satisfaction and adverse events. Furthermore, the visual analog scale (VAS) was used to measure the severity of colic at the beginning and the end of the study.

Eligible infants were randomly allocated to receive 10 drops of Tummysoft Drops (Intervention group) or Placebo drops (Placebo group) daily for 4 weeks. Each ml of Tummysoft drops contains 500 million CFU of *Bacillus Coagulans* GBI 30, 6086, Alpha-Amylase 20 mg, Papain 10 mg, Lactase 6 mg (600 FCC), Dill Oil 2 mg, and Fennel Oil 0.0007 ml. The placebo drops contained all the excipients except active ingredients, looked the same, and had the same taste, and texture as the study medication.

On enrolment (day 0), parents/guardians were interviewed to obtain the following information: (a) gestational age; (b) type of delivery; (c) personal medical history; (d) smoking status of parents; (e) history of gastrointestinal disease; (f) infant birth weight; and (g) description of colic symptoms. The referring paediatrician performed a medical examination and infant growth parameters on day 0 which were recorded on day 0 and on subsequent follow-up visits (days 7, 14, 21 and 28).

Parents were instructed to record the frequency of colic episodes and the daily crying and fussing time (in minutes), feeding schedule, stool frequency, and characteristics, and any adverse effects experienced (e.g., constipation, vomiting, erythema), along with the frequency and duration of each adverse event. When necessary, parents and caregivers were informed to get in touch with the study team investigators and the paediatrician who referred them.

**Statistical analysis**

Statistical analysis was done using IBM SPSS software 27 Version. Sample t-test was used to compare between the intervention and placebo group. For comparing the crying duration, frequency, and defecation, repeated measures ANOVA was used. For comparing the visual analog scale paired sample t-test was done. The p-value <0.05 was considered as a significant at 95% confidence interval.

108 participants diagnosed with infantile colic were eligible to enrol in the study. On randomization, 52 were allotted to the intervention group and 56 to the placebo group. Five infants were excluded from the study due to the unwillingness of parents, and three due to not complying with follow-up. Finally, 100 patients completed the study, including 50 infants in the intervention group and 50 infants in the placebo group (Figure 1).

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**Figure:1** Schematic diagram of participant enrolment and study progress

The demographic data of the studied infants are summarized in Table 1.

* The mean age of infants was 2.52 ± 1.4 and 2.48 ± 1.5 months in the intervention and placebo groups.
* The mean weight of infants was 2.72 ± 0.167 and 2.73 ± 0.166 kgs in the intervention and placebo groups, respectively.
* In the intervention group, 28 infants (56%) were male and 22 infants (44%) were female.
* In the placebo group, 29 infants (58%) were male and 21 infants (42%) were female.

|  |  |  |
| --- | --- | --- |
| **Variables** | **Intervention Group, n (%)** | **Placebo Group, n (%)** |
| **Gender**MaleFemale | 28 (56)22 (44) | 29 (58)21 (42) |
| **Type of Feeding**Breast milkMixed | 39 (78)11 (22) | 37 (74)13 (26) |
| **Type of Delivery**Normal Vaginal deliveryC-Section | 32 (64)18 (36) | 29 (58)21 (42) |

**Table 1:** Demographic characteristics of patients in intervention and placebo groups.

**RESULTS**

1. **Reduction in crying duration:** The mean crying duration changed from 261.30 ± 41.684 to 52 ± 12.857 min/day in the intervention group and from 262 ± 39.046 to 77 ± 27.408 min/day in the placebo group (Table 2).

|  |  |  |
| --- | --- | --- |
| **Variable** | **Mean** | **p^ value** |
| **Crying Duration (min/day)** | **Intervention Group** | **Placebo Group** |
| Day 0Day 7Day 14Day 21Day 28 | 261.20 ± 41.684155.60 ± 29.92662.80 ± 23.03953.60 ± 15.45452.00 ± 12.857 | 262.10 ± 39.046192.80 ± 42.476118.70 ± 32.08490.80 ± 23.67677.20 ± 27.408 | 0.921<0.001 (HS)<0.001 (HS)<0.001 (HS)<0.001 (HS) |
| **P^^ value** | <0.001 | <0.001 |

**Table 2:** Duration of crying in intervention and placebo groups.

P^^ - Repeated measure ANOVA p^- Independent sample t test



**Figure 2:** Duration of crying in intervention and placebo groups.

1. **Reduction in the frequency of crying:** The episodes of crying were reduced from 6.34 ± 2.387 to 0.20 ± 0.495 episodes/day in the intervention group and from 7.32 ± 2.453 to 1.30 ± 1.298 episodes/day in the placebo group (Table 3).

|  |  |  |
| --- | --- | --- |
| **Variable** | **Mean** | **P^ value** |
| **Crying Frequency (episodes/day)** | **Intervention Group** | **Placebo Group** |
| Day 0Day 7Day 14Day 21Day 28 | 6.34 ± 2.3874.60 ± 2.2953.12 ± 1.9861.66 ± 1.3340.20 ± 0.495 | 7.32 ± 2.4535.78 ± 1.8774.28 ± 1.9382.62 ± 1.6401.30 ± 1.298 | 0.0460.0060.0040.002<0.001(HS) |
| **P^^ value** | <0.001 | <0.001 |

**Table 3:** Frequency of crying in intervention and placebo groups.

P^^- Repeated measure ANOVA p^- Independent sample t test



**Figure 3:** Frequency of crying in intervention and placebo groups.

1. **Reduction in crying duration of ≥50% from baseline:** A higher proportion of infants in the Intervention group responded to treatment (defined as a reduction in crying duration of ≥50% from baseline) compared with the placebo group. By day 7, statistical significance was achieved in the intervention group with p = 0.005. (Table 4)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Intervention****Group** | **Placebo****Group** | **p Value** |
| Number of infants with >50% decrease in crying time on day 7 | 7 (14%) | 0 (0%) | 0.005 |
| Number of infants with >50% decrease in crying time on day 14 | 49 (98%) | 30 (60%) | 0.05 |
| Number of infants with >50% decrease in crying time on day 21 | 50 (100%) | 46 (92%) | - |
| Number of infants with >50% decrease in crying time on day 28 | 50 (100%) | 48 (96%) | - |

**Table 4:** Number of infants with >50 % crying from the baseline during the study in both groups.

p – chi square test

1. **Reduction in defecation frequency:** The defecation frequency was decreased from 4.14 ± 1.512 to 2.24 ± 0.771 in the intervention group and from 4.18 ± 1.453 to 2.22 ± 0.790 in the placebo group (Table 5). No significant difference in defecation frequency were observed between the two groups.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Mean** | **P^ value** |
| **Frequency of Defecation (episodes/day)** | **Intervention Group** | **Placebo** **Group** |
| Day 0Day 7Day 14Day 21Day 28 | 4.14 ± 15123.28 ± 1.3252.84 ± 1.0172.54 ± 0.7342.24 ± 0.771 | 4.18 ± 1.4533.40 ± 1.2623.04 ± 0.8802.92 ± 0.9862.22 ± 0.790 | 0.8930.6440.2960.0310.898 |
| **P^^ value** | <0.001 | <0.001 |

**Table 5:** Frequency of defecation in intervention and placebo groups.

P^^- Repeated measure ANOVA p^- Independent sample t test

1. **Reduction in Pain:** We used Visual analog scale (VAS) and “faces” rating pain scale for assessment of infant’s pain. On day 28, the mean rating was significantly reduced to 0.08 ± 0.274 and 1.34 ± 1.437 in the intervention and placebo groups respectively (p = <0.001 which was highly significant) (Table 6).

|  |  |  |
| --- | --- | --- |
| **Variable** | **Mean** | **P^ value** |
| **Visual Analog Scale** | **Intervention Group** | **Placebo Group** |
| Day 0Day 28 | 4.68 ± 0.5800.08 ± 0.274 | 4.68 ± 0.6211.34 ± 1.437 | 0.868< 0. 001 (HS) |
| **P^^ value** | <0.001 | <0.001 |  |

**Table 6:** Visual analog scale ratings for intervention and placebo groups.

P^^ - Paired sample t test P^ - Independent sample t test

1. **Parenteral Satisfaction:** By the end of 4th week, parental satisfaction in terms of infant's mood, activity, alertness, comfort, and oral intake were better in intervention group. On using Likert scale, 43 parents were ‘strongly satisfied’ with the treatment in intervention group and 26 parents in placebo group. 7 and 14 were ‘satisfied’ with the treatment in intervention and placebo group respectively. In ‘neither satisfied’ nor ‘dissatisfied’ opinion, none were in treatment group and 10 parents were in placebo group.



**Figure 4:** Parental satisfaction using Likert Scale

1. **Adverse events:**

No adverse events were noticed in both intervention and study group

**DISCUSSION**

We have conducted a randomized double blind placebo controlled trial in infants suffering from infantile colic. The intervention group received Tummysoft drops comprising of digestive specific probiotic (*Bacillus coagulans* GBI-30, 6086), carminatives (dill oil & fennel oil) and digestive enzymes (alpha amylase, papain and lactase). Administration of Tummysoft drops to infants proved superior to placebo in reducing the daily crying duration and frequency of crying. The number of infants who had >50% decrease in crying time from baseline on day 14 was more in the intervention group compared to the placebo group. Moreover, parental satisfaction in terms of the infant's mood, activity, alertness, comfort, and oral intake was better in the intervention group.

Few studies have used probiotics, carminatives and digestive enzymes independently in infantile colic and found them to be safe and effective. Yan Ping Liu et al. conducted a meta-analysis of nine clinical studies and found that probiotics were effective than placebo in treating infantile colic. [26] Dewan et. al administered a drop preparation containing dill oil & fennel oil to infants and was found to be effective and safe to use in infants. [27] Fennel oil can be used as a safe and efficient treatment for infantile colic, according to a study by Irina et. al [28] Similar conclusion on Fennel oil was made by Attarha et al. [29] In a study conducted by Narang et al in infants suffering from infantile colic, it was noted that oral administration of lactase in infantile colic reduced the duration of crying and was well tolerated by infants. [30] Similar conclusion on the usage of lactase in infantile colic was made by Ahmed et al. [31] In our study, we have shown for the first time that infantile colic can be safely and successfully treated with a comprehensive formula containing probiotics, carminatives and digestive enzymes, this opens up a new treatment approach in the management of infantile colic.

This study has some limitations. The different levels of education of parents, particularly mothers, were not evaluated. Using a video recording device will be preferable for better analysis of study because our data gathering was totally dependent on the mother's interview. Moreover, intestinal flora was not evaluated after our intervention in this study.

**CONCLUSION**

Our study provides evidence, that supplementation of probiotics, digestive enzymes and carminatives in early infancy is effective in managing infantile colic symptoms. It was noted that the intervention of Tummysoft Drops in infants was well tolerated and was not associated with any adverse events.

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**AUTHORS’ CONTRIBUTIONS**

This work was carried out in collaboration among all authors. All authors have read and approved the final manuscript

**CONSENT & ETHICAL APPROVAL**

Ethical approval was acquired from the Institutional Ethics Committee, and written informed consent was ensured from all contributors.

**COMPETING INTERESTS**

No competing interests exist.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT) are used in this manuscript.

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