Effects of Simethicone and Multilac Baby in Infantile Colic
Study Protocol

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Cover page

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1. General Information

Infantile colic or extensive crying is a major burden for newborns, their parents and healthcare providers [1]. In most of the cases infantile colic will disappear after the first three to five months of life [2]. Nevertheless, due to its stressful nature for parents, infant colic is among the leading causes to consult a health care professional during early infancy [3]. The parental burden associated with infantile colic finally results in enormous pressure on pediatricians to prescribe at least some kind of remedy. Diagnosis of infantile colic can be based on the Wessel's criteria, defined by crying and restlessness for more than three hours a day for more than three days per week for more than three weeks [4]. Depending on diagnostic details, occurrence rates between 3 to 40% of all infants have been found [5,6].

2. Background Information

The etiology of infant colic remains unclear [7], with a variety of potential causes (gastrointestinal, hormonal, neurodevelopmental, and psychosocial) discussed. This has resulted in a broad range of therapeutic approaches aiming to address the problem [3,8].

Simethicone [9], a mixture of dimethicone and SiO_2, is a rather old product that, it is claimed, acts as a topical barrier for protecting the gut mucosa against irritants. It is not absorbed and is virtually non-toxic. While its use in diagnostic procedures is well-established, the therapeutic effects in a number of gastroenterological indications are contradictory [10]. In infantile colic, a number of smaller simethicone trials [11-13] have been published, but evidence did not reach the threshold of significance. Despite the absence of evidence for beneficial effects, simethicone is widely used for the treatment of infantile colic in some countries.

There is growing evidence that the gut microbiotas of colicky infants significantly differ from those of non-colicky babies [14-16]. In the gut microbiota of colicky babies a lower level of commensal bacteria like lactobacilli and bifidobacteria and higher numbers of proteobacteria have been found. Among these proteobacteria were Escherichia and Klebsiella bacteria [17], which are well known for their gas-producing properties, as well as the potential production of inflammatory lipopolysaccharides (LPS). In addition, it has been described that the gut microbiota of colicky infants exhibits a slower bacterial colonization, a reduced microbiota diversity and a lower microbiota stability [18]. These findings have triggered a number of studies investigating the effect of supplementation of the gut microbiota of colicky babies with products containing probiotic bacteria without a prebiotic component (probiotics), or with (synbiotics).

Although infantile colic is in most cases a self-limiting condition, pediatricians are writing a prescription for most of the affected infants. Unpublished results from

surveys, performed by our research team among German and Polish pediatricians, revealed that in these two countries simethicone and pro-/synbiotics were the most frequently prescribed products for infantile colic. In our study we want to evaluate the effects of simethicone and of a food supplement multi-strain synbiotic (Multilac® Baby), which is frequently used by German and Polish pediatricians. The multi-strain synbiotic preparation contains six lactobacilli (L. acidophilus, L. casei, L. paracasei, L. plantarum, L. rhamnosus GG, L. salivarius), three bifidobacteria (B. lactis, B. bifidum, B. longum) and the prebiotic fructooligosaccharides (FOS). In a study, recently published by us [19], it was found that this multi-strain synbiotic antagonizes the in-vitro growth of the pathogenic bacteria Escherichia coli EPEC, Shigella sonnei, Salmonella typhimurium, Klebsiella pneumoniae and Clostridioides difficile.

During the preparation phase of this study, we learned that pediatricians willing to participate were not ready to treat colicky babies with a placebo, as this would not be acceptable for the majority of parents of the colicky babies. In addition, placebo preparations are neither available for us for simethicone nor for the multi-strain synbiotic. Consequently, our study has to be performed as an open trial, comparing the two products. Effects of simethicone in infantile colic have been shown not to differ significantly from treatment with a placebo [11-13], therefore the simethicone treatment group in our study has to be considered as the control group against which the effect of the multi-strain synbiotic has to be evaluated.

3. Objectives/Purpose

The objective of the study is to compare the effects of simethicone and a multi-strain synbiotic (Multilac Baby) on the crying behavior of colicky babies.

4. Study Design

Open label comparing treatment with simethicone (Arm 1) versus treatment with Multilac Baby (Arm 2). Treatment duration of four weeks. Assessment of crying behavior with parental daily diary during the last three weeks before enrollment and during last three weeks before the end of treatment.

5. Selection and Exclusion of Subjects

Inclusion criteria

The study is aiming to recruit babies aged 3 to 6 weeks of aged diagnosed for infantile colic based on Wessels criteria. Wessel's criteria for infantile colic diagnosis (Rule of Three) [4]: extensive evening crying for at least three hours per day, during at least three days per week, during the last three weeks.

Exclusion criteria

- Organic causes for crying
- Previous treatment with antibiotics
- Previous treatment with probiotic
- Previous treatment with synbiotic

6. Treatment of Subjects

Simethicone (Arm 1)

Treatment for four weeks with simethicone (Espumisan®, 100 mg/ml, Berlin-Chemie / Menarini Polska Sp z o.o., Warsaw, Poland). Simethicone administered 3-6 times per day with each treatment comprising 6 drops of the 100 mg/ml emulsion. It is planned to include 30 patients to this arm.

Multilac Baby (Arm 2)

Treated for four weeks with one stick pack of a multi-strain synbiotic (Multilac® Baby, Vivatrex GmbH, Aachen, Germany) per day. Each stick pack of Multilac® Baby contains a total of 10^9 colony forming units (CFU) with equal CFU amounts of the following probiotic bacteria: L. acidophilus LA-14, L. casei R0215; L. paracasei Lpc-3; L. plantarum Lp-115; L. rhamnosus GG, L. salivarius Ls-33, B. lactis Bl-04, B. bifidum R0071, B. longum R0175 and 1.43 g of the prebiotic fructooligosaccharides. It is planned to include 50 patients to this arm.

7. Assessment of Efficacy

Crying behavior will be assessed by using a parental diary (24-hour Parental Daily Report).

8. Assessment of Safety

Safety will be assessed by using a parental diary (24-hour Parental Daily Report).

9. Adverse Events

Adverse Events will be reported by the standard procedure established to report adverse events of pharmaceutical products by physicians.

10. Discontinuation of the Study

The study will be discontinued in case of:

- occurrence of adverse events,
- failure to recruit patients.

11. Statistics

The statistical analyses will be conducted with GraphPad Prism software version 8.2 (GraphPad Software, Dan Diego, California, USA) or MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd., Ostend, Belgium). The Student t-test will be used to compare mean values of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney U test will be used. The X2 test or Fisher exact test will be used, as appropriate, to compare percentages. The MedCalc Statistical Software version 19.2.1 will be used to calculate the relative risk (RR) and number needed to treat (NNT) [20], all with a 95% confidence interval (CI). The difference between the treatment groups will be considered significant when the p-value will be less than 0.05, when the 95% CI for RR will not include 1.0, or when the 95% CI for mean difference will not include 1.0, or when the 95% CI for mean difference will not include 0. One-way ANOVA followed by Dunnett's multiple comparisons test as well as Cochran-Armitage Chi-squared test for trend will be performed using GraphPad Prism software. All statistical tests will be two-tailed and will be performed at the 5% level of significance. All analyses will be conducted on an intention-to-treat basis, including all patients in the groups to which they will be allocated.

12. Quality Control and Assurance

According to local GCP SOPs.

13. Ethics

Study will have to be approved by the Ethics Committee of The President Stanisław Wojciechowski State University of Applied Sciences in Kalisz.

Informed consent of parents of colicky babies will be collected from parents in writing before enrolling of the babies into the study.

14. Data handling and Recordkeeping

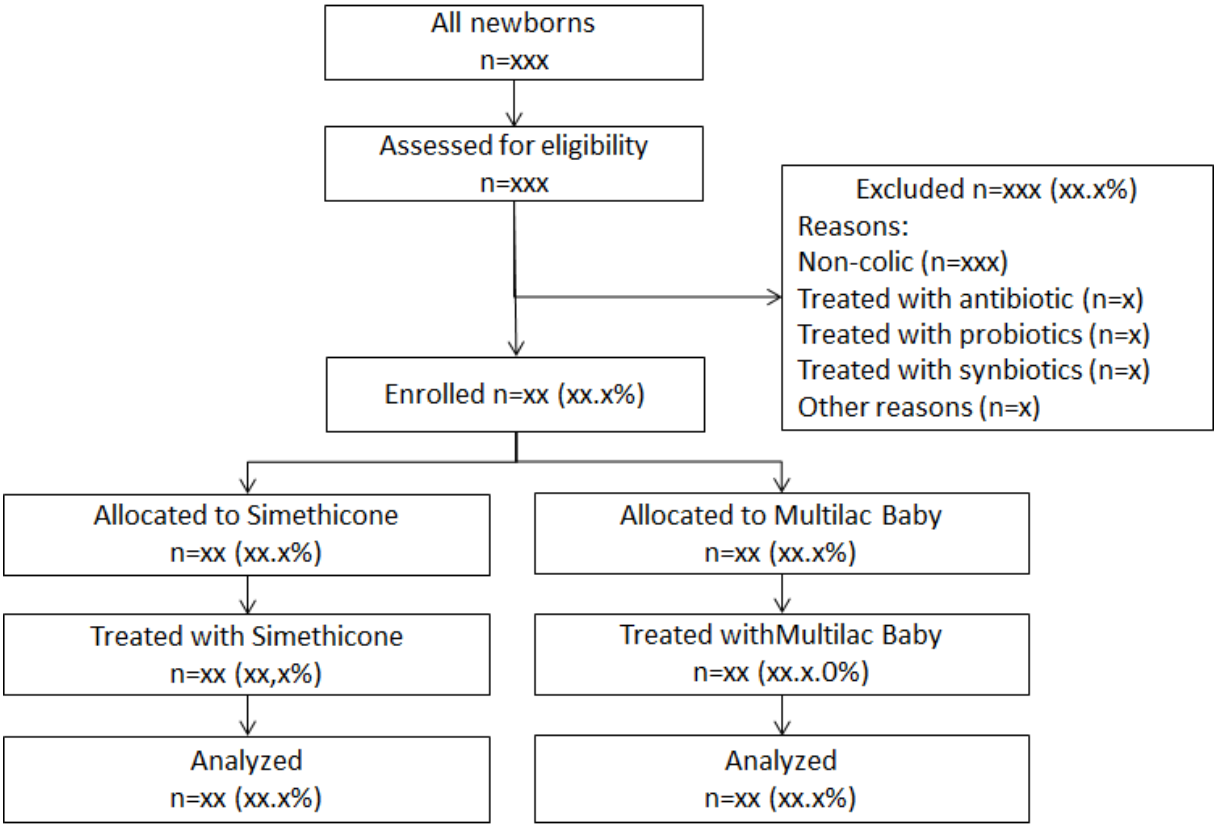
Data will be handled by study investigators monitored and supervised by the principle investigator of the study (Prof. Dr. Hanna Kraus). Records will be kept at the office of the principle investigator applying all local regulations of data protection provisions.

15. Publication Policy

It is planned to publish the study results in a peer-reviewed scientific/medical journal.

16. Project Timetable/Flowchart

Start of study immediately after approval by the ethics committee.



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18. Supplements/Appendices

Patient Assessment Sheet Day 0 PL

24 Hours Parental Diary Form PL