

## Constipated Patients Fed Goat Milk Protein Formula: A Case Series Study

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### Abstract

**Aim:** To observe the impact of an infant formula containing goat milk proteins and fat in infants exhibiting symptoms of constipation.

**Methods:** This study employed a case-series design with infants aged between 1 and 4 months. Infants with symptoms of constipation were recruited at two paediatric clinics in Barcelona, Spain. At the time of recruitment, all infants were fed a standard formula made with cow milk protein. Infants were provided with a formula based on goat milk protein and 55% of total fat from goat milk. After 3 weeks, stool consistency, stool frequency, crying and infant behaviour were measured. Fat, nitrogen, water and carbohydrates in the stools were also determined by NIRA (near-infrared reflectance analysis).

**Results:** A total of 23 infants were enrolled and 20 completed the study. Two infants withdrew due to causes considered unrelated to formula and one due to persistent irritability. Fat percentage of stools declined from 8.6 to 6.8 g/100g ( $P < 0.001$ ) and crying from 3 to 1 h/24 h ( $P < 0.001$ ) after three weeks compared to enrolment. Crying immediately after feeding was more common in infants at enrolment compared to the second visit, 75% vs 25% respectively. Parents reported change in infant behavior 3-5 days after the study formula was introduced. The mean consistency score of the stools was significantly ( $P < 0.05$ ) lower (harder) at enrolment than at the second visit. Stool frequency did not change.

**Conclusion:** The improvement of stool characteristics and reduction in crying in infants indicates that formula with proteins and fat from goat milk in infants does not adversely affect gastro-intestinal comfort.

**Keywords:** Formula; Infants; Goat Milk; Constipation; Stools

### Introduction

Parents pay close attention to the frequency and characteristics of their children's defecation, especially during the first months of life [1-3]. Any deviation from what is perceived to be normal may trigger paediatric consultation. In an observational study of formula fed infants, the prevalence of constipation in infants presenting to paediatric clinics was 7.8-22% [4,5]. Constipation is classified as a change in frequency, size, consistency of stools or difficulty in defecating [6]. Fewer bowel movements and/or hard stools may result in distension of the colon, pain, irritability and crying in the infant [7,8]. A greater median number of stools has been associated with crying in infants in the first 2 months of life compared to those who cried less often [2]. Excessive crying in infants with gastrointestinal disturbances can also have a negative impact on family dynamics due to disrupted sleep and family routines as well as increased parental anxiety, stress and frustration [9-11]. Therefore, it is important that formula is shown not to have any adverse impact on gastro-intestinal function in young infants.

Breast-fed infants have significantly more stools per day than formula-fed ones and only a few (1.1%) have hard stools compared with 9.2% of formula-fed infants [1,3,12]. There are instances where some formulas can lead to harder and less frequent stools in the infant than others. For example infants fed formulas containing more palmitate from palm olein had less calcium absorption, more insoluble calcium soaps in stools and harder stools than when formula without palm oil is used [13-15].

Goat milk was approved as a source of milk for infant formula in Europe following consideration of the scientific evidence of the essential composition of goat milk based infant and follow-on formulae and data from double blinded randomized control trials [16,17]. The assessed formula contained protein and also fat from goat milk to provide saturated fatty acids such as palmitic acid [17,18]. While double blinded control trials provided strong evidence of the nutritional adequacy of this formula for healthy infants, there is little data concerning the behavior of infants suffering from functional gastrointestinal disturbances when provided

this formula under clinical settings [16,17].

A case series study was therefore designed to record the response to infant formula containing goat milk fat in infants exhibiting symptoms of constipation. The outcomes measured were stool fat content and consistency, episodes of crying, formula acceptance and parental satisfaction with the product.

## Cases and Methods

### Recruitment of Patients

This open study was conducted at two paediatric clinics at Hospital General de Catalunya, Sant Cugat del Vallès and Clínica Quirón in Barcelona, Spain in 2016-2017. The trial employed a case-series design with infants aged between 1 and 4 months when presenting with symptoms of constipation. Symptoms included difficulty in elimination of hard stools and at least one of the following characteristics: excessive crying/irritability, painful defecation, difficult passage or the need for external help to defecate [19]. Infants were included if they had no history of neonatal disease, were from healthy mothers and had a normal birth weight. At the time of the consultation, all infants were fed a standard formula made with cow milk protein.

Approval of the study protocol was provided by Department of Pediatrics, Hospital General de Catalunya, Sant Cugat del Vallès (Barcelona). Written informed consent for participation in the study was also obtained from parents.

### Procedure

After enrolment, infants were fed with a formula based on goat milk protein and fat that is commercially available in Europe under the brand name of Capricare-1 (Dairy Goat Co-operative (NZ) Ltd, Hamilton, New Zealand). The composition of the formula is provided in table 1. This is the same formula evaluated by EFSA and used in several clinical studies [16,17]. According to the manufacturer, the formula is made with goat milk and is supplemented with lactose, vitamins and minerals and essential fatty acids to meet requirements. The formula contains 55% of total fat from goat milk fat and 45% from a mixture of unmodified high oleic sun-flower, canola, and sunflower oils in a ratio of 44:30:26. Concentrations of main fatty acids is shown in (Table1).The infants did not receive any other formula or supplement other than the study formula during the observation period.

| Nutrient                       | Unit Per 100mL prepared feed |       |
|--------------------------------|------------------------------|-------|
| Energy                         | kJ                           | 280   |
|                                | kcal                         | 66    |
| Protein                        | g                            | 1.3   |
| Carbohydrate (lactose)         | g                            | 7.4   |
| Fat                            | g                            | 3.4   |
| C8:0 Caprylic                  | g                            | 0.06  |
| C10:0 Capric                   | g                            | 0.17  |
| C12:0 Lauric                   | g                            | 0.08  |
| C14:0 Myristic                 | g                            | 0.18  |
| C16:0 Palmitic                 | g                            | 0.55  |
| C18:0 Stearic                  | g                            | 0.23  |
| C18:1 Oleic                    | g                            | 1.58  |
| C18:2 Linoleic acid            | g                            | 0.39  |
| C18:3 $\alpha$ -Linolenic acid | g                            | 0.058 |
| % C16:0 in sn-2 position       |                              | 31    |
| Calcium                        | mg                           | 65    |
| Iron                           | mg                           | 0.71  |

**Table 1:** Composition of study formula

### Evaluation

The evaluation was designed using assessments that can be normally applied in clinics. This included a questionnaire about the number of stools per day, episodes of crying, restlessness or complaints during 24 h and stool consistency. These information was recorded by the parents at inclusion and after 3 weeks of using the study formula. To evaluate stool consistency, the photographic Bristol stool form scale was used [20]. In this scale, 1-2 corresponds to hard stools; 3-4 is intermediate or mushy, 5 is soft and 7 completely liquid. The pediatrician made contact with the parents by telephone after 14 days to check on progress. The satisfaction of the parents with the study formula was assessed by means of a Likert-type scale with possible answers from very satisfied to very dissatisfied.

A stool sample was taken from each infant at inclusion and after 3 weeks of feeding with Capricare-1. Fat, nitrogen, water and carbohydrates in the stools were determined by NIRA (near-infrared reflectance analysis). The NIRA technique is based on measuring radiation in the near-infrared spectrum (FENIR 8820 infrared analyser, Perten, Hamburg, Germany) on the surface of the sample, i.e., the matrix/substrate ratio, and the infrared reflection on the faecal surface at a given wavelength. The components measured belong to certain functional groups (CH, NH, OH) with specific absorption bands in the near-infrared spectrum (700-2500 nm). The spectroscopic response (reflection) of a faecal sample is thus related to the concentration of the components (functional groups). The correlation of the reflection taken at 12 wavelengths is determined using a computerized algorithm. Prior to the current study, NIRA measurements of stool fat, nitrogen, water and carbohydrate content in eighty stool samples from infants and children were compared to the same measurements performed using traditional methods [21-24]. Our own results for stool composition, which are comparable to results from other authors, expressed as g/100 g of stools are: fat: <5, nitrogen: <1.8, carbohydrates: <2 and water: between 80 and 85. However, the fat content of formula fed infants is usually higher during the first 6 months of life (between 7 and 11 g/100g) [25,26].

## Statistical Analysis

The non-parametric Wilcoxon sign rank test was used to test the statistical significance of differences in stool frequency, consistency and biochemical composition as well as crying episodes between enrollment and the second visit. The level of significance was set at 0.05. Descriptive statistics such as mean and 95% confidence interval was calculated for all other observations.

## Results

A total of 23 infants were enrolled and 20 completed the study. One was withdrawn due to a Rotaviral infection unrelated to formula feeding. Another had low weight gain of unknown causes and a third started the study, but then switched to a hydrolysed formula due to continued symptoms of irritability. The baseline characteristics of the 20 infants that completed the study is provided in Table 2. No organic cause of constipation was found at the time of initial consultation. None of the infants had IgE mediated allergy to milk. None of the infants had been given any treatment for the constipation such as an infant formula with oligosaccharides or hydrolysates or laxatives prior to the study or during the study. By chance, twice as many female infants were enrolled as males. All infants were within the -10 to 10th percentile range for weight. None of the mothers smoked or took drugs or alcohol during pregnancy. None of the mothers presented with complications during pregnancy.

|                          |           |       |
|--------------------------|-----------|-------|
| Age at enrolment (days)  | 58        | (38)  |
| Gestational age (weeks)  | 40        | (0.5) |
| Weight at birth (kg)     | 3.3 (0.3) |       |
| Weight at enrolment (kg) | 4.7 (0.9) |       |
| Gender (% female)        | 70        |       |

Table 2: Baseline characteristic of participants Mean (SD)

The mean consistency score of the stools was significantly lower (harder) at enrolment than at the second visit (Table 3). Stool consistency scores for all infants at enrolment were within the 1-3 range, whereas at the second visit they were 3-5.

|                   | Visit 1 | Visit 2 | p value * |
|-------------------|---------|---------|-----------|
| Stool consistency | 2       | 3       | <0.05     |
| No. Stools / day  | 2       | 2       | >0.2      |
| Crying hours 24 h | 3       | 1       | < 0.001   |

\*Wilcoxon signed rank test statistics

Table 3: Parental assessments at inclusion and follow-up

Infants passed 1 to 2 stools per 24 h over the duration of study. The average number of stools in one day did not differ significantly between the start and end of the study (Table 3).

All infants were reported to show symptoms of restlessness or crying for 1-3 h/24h at enrolment, compared to 75% at the second visit. The total duration of crying was significantly reduced at the second compared to the first visit (Table 3). Crying immediately after feeding was more common in infants at the first visit compared to the second visit, 75% vs 25% respectively.

All parents reported an increase in satisfaction with the formula based on Likert-type scale (Table 4). The average duration from when the formula was introduced before any change in symptoms or behaviour was noticed by parents was 4 days (95%CI 3.7, 4.3).

The composition of the stool samples measured by NIRA is provided in table 5. Stool fat content decreased significantly ( $P<0.001$ ) from 8.6% (wt/wt of stools) at enrolment to 6.8% at the second visit. There was no significant change in the other parameters.

|                   | visit 1 | visit 2 |
|-------------------|---------|---------|
| very satisfied    | 0       | 14      |
| satisfied         | 6       | 6       |
| neutral           | 3       | 0       |
| dissatisfied      | 10      | 0       |
| very dissatisfied | 1       | 0       |

\* Number of parents in each category of Likert-type scale

**Table 4:** Parental satisfaction score\*

|              | Normal Values | Visit 1 | Visit 2 | p value * |
|--------------|---------------|---------|---------|-----------|
| Fat          | 7-11          | 8.6+1.9 | 6.8+2.1 | <0.001    |
| Water        | 80-85         | 78+6    | 80+5    | >0.2      |
| Nitrogen     | <1.8          | 1.4+0.3 | 1.4+0.3 | >0.2      |
| Carbohydrate | <2            | 1.1+1.1 | 1.2+1.4 | >0.2      |

Values are expressed as mean+SD % (wt/wt of stools)

\*Wilcoxon signed rank test statistics

**Table 5:** Composition of stools at inclusion and follow-up

## Discussion

This case series study investigated the response to a formula type that has only been present in Europe since 2014. The formula contains goat milk proteins instead of cow milk proteins and a mixture of milk fat and vegetable oils [17,18]. Of the 23 infants initially enrolled, two withdrew due to causes considered unrelated to formula. One infant had persistent irritability and did not complete the study, but parents of the other 20 infants reported seeing improvements in infant behaviour within 3-5 days after starting the study formula. These parents also reported that acceptance of the formula was excellent and there was a high level of parental satisfaction with the formula. There was a significant reduction in fat percentage of stools and crying and a small change in stool consistency at the three weeks visit after the formula was introduced. These are indicative of an improvement in fat absorption and reduction in symptoms of constipation over the duration of the study. Stool nitrogen levels were unchanged between visits, similar to a lack of differentiation in nitrogen content of stools of breast fed and formula fed infants [12].

The results of the current study might be attributed to the unique source of fats in the study formula. Traditionally, formulas have contained substantial quantities of milk fat, but progressively they have tended to be richer in vegetable oils to supply essential polyunsaturated fatty acids [27]. The main vegetable oils used in formulas are coconut oil, corn oil, soybean oil, palm olein, palm kernel oil, palm oil, high oleic safflower oil, peanut oil, and, in Europe, low-erucic acid canola oil [27]. Fats are better absorbed from human milk than from formulas containing vegetable oils [28]. This has been attributed in part to the high proportion of palmitic acid in the middle sn-2 position in human milk compared to vegetable oils where most of palmitate resides at the outer sn-1,3 positions [14,15,29-34]. During normal digestion, triacylglycerol hydrolysis by sn-1,3 specific pancreatic lipase liberates free fatty acid in the gut [35]. Pal-mitate in the free form is rapidly converted into insoluble hydrated acid soaps at the pH of the intestine. If sufficient free calcium is present in the intestinal lumen, calcium soaps can also be formed. These soaps have very high melting points that limit their absorption and result in their recovery in stools [12,29,32,36]. Reviews and meta-analysis have concluded that the use of palm olein to match the content of palmitic acid in infant formulas to that of the human milk produced a harder stool consistency compared to formulas without palm oil [13,15]. In contrast, formulas with less palmitic acid or with more palmitic acid in sn-2 position results in improvement of fat and calcium absorption, and stool consistency [13-15, 29-34].

The fat in the formula evaluated in the present study contains 55% of fat from goat milk and 45% from a mixture of unmodified high oleic sun-flower, canola, and sunflower oils in a ratio of 44:30:26 to provide the appropriate fatty acid profile, including the palmitic. It contains no palm oil. The fatty acid profile and the relative positioning of the fatty acids in the triglycerides have been reported previously [18]. The total amount of palmitic acid in sn-1, 3 positions in the formula is 0.36 g/100ml compared to 0.7-0.8 g/100ml in conventional formula containing vegetable oils only [37,38]. The amount of palmitic acid in sn-1, 3 in the goat milk based formula is similar to formula used in other studies to prevent the malabsorption of palmitic acid [13-15,30,31,36] and also reduced crying and symptoms of constipation [39,40]. It is likely that the use of a cow formula with a fat blend that has lower amounts of palmitic acid in sn-1,3 position would have a similar outcome to the formula used in this study.

## Strengths and Weaknesses of Study

A limitation of this study is that neither the mothers nor the clinicians were blinded to the intervention and there was no parallel control group. However, there was no evidence to suggest the formula had an adverse effect on gastro-intestinal symptoms in infants that already had constipation. The improvement in stool fat content is also relatively independent of observer bias. The improvement of stool characteristics between visits, in parallel to a reduction of the number of crying episodes would suggest a

potential benefit for wellbeing of infants with functional gastro-intestinal disorders. A follow-up randomized cross-over trial is needed to determine whether improvement can be directly attributed to the inclusion of the goat milk fat in the goat milk formula.

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## Conflict of Interest

Colin G Prosser is an employer of Dairy Goat Co-operative (NZ) Ltd. Neither Dámaso D Infante nor Ramon Tormo declares a conflict of interest.

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