

# A Randomized Double-blind Placebo-controlled Trial of a Standardized Extract of *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* (ColiMil<sup>®</sup>) in the Treatment of Breastfed Colicky Infants

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**Objective:** The aim of this randomized, double-blind, placebo-controlled trial was to investigate the effectiveness and side effects of a phytotherapeutic agent with *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* in the treatment of infantile colic.

**Methods:** 93 breastfed colicky infants were enrolled, the diagnosis was made according to Wessel's criteria. After a 3 day observation period, the infants were randomly divided into two groups, one treated with phytotherapeutic agent (PA) and the other with placebo twice a day for 1 week. Crying time and side effects were recorded. **Results:** 88 infants completed the trial: 41 in the PA group and 47 in the control. The daily average crying time for the PA was 201.2 min/day (SD 18.3) at the baseline and 76.9 min/day (SD 23.5) at the end of the study; for the placebo it was 198.7 min/day (SD 16.9) and 169.9 min/day (SD 23.1) ( $p < 0.005$ ). Crying time reduction was observed in 85.4% subjects for the PA and in 48.9% subjects for the placebo ( $p < 0.005$ ). No side effects were reported.

**Conclusion:** The present study shows that colic in breastfed infant improves within 1 week of treatment with an extract based on *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis*. Copyright © 2005 John Wiley & Sons, Ltd.

**Keywords:** breastfeeding; infantile colic; phytotherapeutic agent; treatment.

## INTRODUCTION

Infantile colic, a behavioural syndrome characterized by paroxysmal, excessive and inconsolable crying without identifiable cause, is one of the most common problems within the first 3 months of life in the Western world, affecting as many as 15%–30% of newborn children (Hewson *et al.*, 1987).

As reported by Wessel's diagnostic criteria, crying lasts more than 3 hours a day and more than 3 days a week for more than 3 weeks (Wessel *et al.*, 1954).

In 90% of cases symptoms appear before the sixth week of life with a peak around the eighth week (Hide and Guyer, 1982). In 50% of cases symptoms disappear before the third month of life and do not usually last longer than the first year.

During a crying fit the infant is rigid, having legs drawn up, tenseness of abdomen, clenched fists, tightened or opened eyes, wrinkled forehead, flushed or pale face. Other symptoms may be present, such as meteorism and flatulence (Canivet *et al.*, 1996; Sampson, 1989).

Crying usually starts at the same time each day; it is more intense in the afternoon, in the evening and at night and lasts 2 or 3 hours (Illingsworth, 1954).

Although infantile colic is commonly reported and causes appreciable distress in parents and paediatricians, and despite 40 years of research, its aetiology still remains unclear. Many aetiopathogenetic hypotheses have been suggested to explain the cause of this trouble and can be summed up as organicistic and behavioural; probably infantile colic may be consequent to synergistic interaction between both the factors.

The organicistic hypothesis includes abnormal gastrointestinal function and allergic disorders and has led to such intervention as substituting cow's milk with soy milk or protein hydrolysate (hypoallergenic) or using herbal tea or drugs (Lucassen *et al.*, 1998). In the behavioural hypothesis, inadequate and inappropriate maternal–infant interaction, mother's anxiety and distress during pregnancy or infant's difficult temperament play an important role (Lucas and St James-Roberts, 1998).

Food hypersensitivity as a possible cause of infantile colic is well documented. It is well recognized that food allergies, as well as severe infantile colic, also occur in exclusively breastfed infants (Iacono *et al.*, 1991), however, only restricted research has shown that mother's

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dietary modification can improve symptoms in 50%–60% of colicky breastfed infants (Hill and Hosking, 2000). Estep has reported recently that a temporary substitution of breast milk with an amino acid based formula improves crying time in breastfed infants with colic. However, this kind of substitution can be proposed only as a last resort (Estep and Kulczicky, 2000).

As far as conventional therapies are concerned, the utility of antispasmodic therapy is reported by many studies in the literature (Savino *et al.*, 2002; Weissbluth *et al.*, 1984) and the anticholinergic and antiadrenergic activity of some herbal tea or drugs, such as fennel, lemon-balm and camomile is also well known (Forster *et al.*, 1980; Weizman *et al.*, 1993).

Providing an amount of supplementary fluids, such as herbal tea, has been reported to have negative effects on later breastfeeding success, therefore a phytotherapeutic agent (PA) that could be used without a massive quantity of liquid, became an interesting target in breastfed colicky infants' therapy (Savino *et al.*, 2001).

While a lot of dietetic opportunities are well documented to be harmless for bottlefed infants, it is still unclear if adding any other kind of food may have consequences for the breastfed ones (Saadeh and Akre, 1996; Kind *et al.*, 2000).

The aim of this study was to evaluate the effect of a PA based on enpowdered extracts of *Matricariae recutita* L., *Foeniculum vulgare* M. var. *dulce* and *Melissa officinalis* L. on breastfed colicky infants.

## METHODS

This prospective, randomized, double-blind, placebo-controlled study was conducted on severe colicky breastfed infants recruited consecutively from March 2001 to March 2003 among patients seen at the Department of Pediatrics of the Regina Margherita Children's Hospital, University of Turin.

Inclusion criteria were:

1. breastfed healthy infants with regular growth
2. age between 21 and 60 days
3. born at term (gestational age: 38–42 weeks) with a birth weight between 2500 and 4000 g.
4. no clinical evidence of gastroenterologic diseases
5. Apgar at 5' > 7

Infants were excluded if they were receiving any medication that could affect abdominal symptoms, such as antibiotic and probiotic drugs.

A diagnosis of colic was settled on Wessel's criteria. To be defined as severe colicky, infants should have a history of persistent, full-force crying with no apparent reason several times a day, for an overall duration  $\geq$  4 h/day, for more than 4 days a week with no response to the common consolation procedures.

Before starting the study, each infant underwent a clinical evaluation: anamnesis, medical examination were conducted by paediatricians from our Department. Parents were given a structured questionnaire about their infants' behaviour, temperament, sleeping and eating habits in the week before the entry in the study. Every question was followed by a four-alternative

answer. They were also asked if they had ever suffered from the same disorders evaluated in their children.

Patients were assigned randomly into two groups: one treated with the PA and the other administered with a placebo (P) looking like the phytotherapeutic agent with regard to colour, smell, taste and package, but containing only vitamins. Neither doctors nor parents knew whether the infants received treatment or not. Before starting treatment, parents were invited to record data concerning daily crying time for 3 days (day -2; day -1; day 0).

Both PA and P were administered twice a day at 5 p.m. and 8 p.m. some minutes before feeding at a dosage of 2 mL/kg/day. Infants had to take PA or P consecutively for 7 days. Each dose of PA consisted of one bottle with tank cap containing: *Foeniculum vulgare* M. var. *dulce* P.E. tit. in O.E. 0.05%–0.1% (164.29 mg), *Matricariae recutita* L. P.E. tit. in apigenin 0.3% (177.69 mg), *Melissa officinalis* L. O.E. tit. in rosemary acid 2% (96.89 mg), vitamin B1 (0.85 mg), calcium pantothenate (3.24 mg), vitamin B6 (1.20 mg), maltodextrin, Syloid 244 FP (ColiMil, Milte-Milan, Italy). At the administered dosage, PA provides: *Matricariae recutita* L. 71.10 mg/kg/day, *Foeniculum vulgare* M. var. *dulce* 65.71 mg/kg/day and *Melissa officinalis* L. 38.75 mg/kg/day.

Each dose of P consisted of one identical bottle with tank cap containing: water obtained by inverted osmosis, fructose, pineapple flavour, citric acid and sorbate potassium.

Parents wrote a daily structured diary, recording the start of crying time, when the medication was administered, the end of crying time and any side effects they observed for the 7 days of therapy and until day 21 from the enrollment (vomiting, sleepiness, restlessness, inappetence, cutaneous reactions, constipation, diarrhoea).

At day 1 and 7, infants were seen in our department and parents gave the diary to the researchers.

At day 21 after baseline the mothers were asked to complete a questionnaire about crying time during all the observational period.

To ensure that all the parents noted crying time in a uniform way and to ensure that the infants were given the medication correctly, one of the researchers was always available by phone to help parents.

The therapy was considered efficacious if the crying time was reduced by at least 50% per day; responders were infants who had such a reduction of crying time. The cutoff at 15 min derived from the minimal crying time of each crisis before treatment.

The study protocol was approved by our Institution's Ethical Committee; parents gave written consent to the inclusion of their children to the study.

**Statistical analysis.** All statistical calculations were performed using commercially available software (Statsoft Windows, version Release 5, 1995, copyright Statsoft, USA).

Statistical significance was set at  $p < 0.05$  and  $\beta$  risk value of 80%. Analysis of variance for repeated measurements (ANOVA) was performed to compare the variation of crying time between the two groups of infants. The Chi-square test and Fisher test were used to evaluate side effects and characteristics of the study population.

**Table 1. Clinical characteristics of the study population**

	PA	P	Statistical analysis
Subjects (number of infants)	41	47	
Age at study entry (weeks)	4.2 (SD 1.4)	4.4 (SD 1.6)	<i>t</i> -test: <i>p</i> = 0.537
Birthweight (g)	3420 (SD 390)	3510 (SD 330)	<i>t</i> -test: <i>p</i> = 0.244
Gender (M/F)	18/23	23/24	Fisher test: <i>p</i> = 0.673
Geographical (Caucasian/Others)	38/3	45/2	Fisher test: <i>p</i> = 0.661
Exposure to smoking (yes/no)	5/36	8/39	Fisher test: <i>p</i> = 0.563

**Table 2. Crying time (mean minutes per day) in each group of infants**

Colicky infants ( <i>n</i> = 88)	PA ( <i>n</i> = 41)	Standard Error	P ( <i>n</i> = 47)	Standard Error	<i>t</i> -test	CI 95%
Day -2	199.1 (SD 17.9)	2.80	198.1 (SD 17.2)	2.51	<i>p</i> = 0.790	-6.45; 8.45
Day -1	204.5 (SD 18.7)	2.92	199.8 (SD 17.4)	2.54	<i>p</i> = 0.226	-2.95; 12.35
Day 0	201.2 (SD 18.3)	2.86	198.7 (SD 16.9)	2.47	<i>p</i> = 0.507	-4.96; 9.96
Day 1	182.1 (SD 20.4)	3.19	176.7 (SD 17.9)	2.61	<i>p</i> = 0.189	-2.72; 13.52
Day 2	145.5 (SD 21.4)	3.34	153.7 (SD 21.8)	3.18	<i>p</i> = 0.079	-17.3; 0.98
Day 3	112.4 (SD 23.3)	3.64	154.3 (SD 22.6)	3.30	<i>p</i> < 0.005	-51.64; -32.16
Day 4	99.6 (SD 25.8)	4.03	157.5 (SD 24.3)	3.54	<i>p</i> < 0.005	-68.52; -47.28
Day 5	86.3 (SD 20.7)	3.23	161.4 (SD 22.3)	3.25	<i>p</i> < 0.005	-84.26; -65.94
Day 6	76.8 (SD 24.6)	3.84	168.6 (SD 21.9)	2.19	<i>p</i> < 0.005	-101.65; -81.95
Day 7	76.9 (SD 23.5)	3.67	169.9 (SD 23.1)	3.37	<i>p</i> < 0.005	-102.89; -83.11
Day 21	82.1 (SD 19.8)	3.09	165.3 (SD 20.7)	3.02	<i>p</i> < 0.005	-91.82; -74.58

## RESULTS AND DISCUSSION

The study initially enrolled 93 colicky infants seen at our Department.

Of these 93 infants, five dropped out (two from the treatment group and three from the control group): two did not come to the second visit, three were excluded because of fever. Nobody withdrew because of any problems related to the trial and so the study population may be considered homogenous.

The two groups did not differ in maternal instruction, parity, sex ratio, exposure to smoking.

The study population characteristics are described in Table 1.

The average crying time per day was similar in the two groups in the 3 days before starting treatment (Table 2).

Eighty-eight infants completed the trial: 41 for the PA-group and 47 controls. The daily average crying time at the baseline (day 0) was 201.2 min/day (SD 18.3) in the PA group and 198.7 min/day (SD 16.9) in the P group (CI 95% = -4.96; 9.96, *p* = 0.507). At the end of the study (day 7) the daily average crying time was 76.9 min/day (SD 23.5) in the PA group and

**Table 3. Effectiveness of phytotherapeutic agent versus placebo**

	Responders	Non-responders	<i>n</i>	$\chi^2$ test
PA	35 (85.4%)	6 (14.6%)	41	<i>p</i> < 0.005
P	23 (48.9%)	24 (51.1%)	47	
	58	30	88	

169.9 min/day (SD 23.1) in the P group (CI 95% = -102.89, -83.11, *p* < 0.001). At day 21 (15 days after the end of the therapy) the daily average crying time was 82.1 min/day (SD 19.8) in the PA group and 165.3 min/day (SD 20.7) in the P group (CI 95% = -91.82; -74.58, *p* < 0.005).

A reduction of crying time was observed in 35 (85.4%) subjects of the PA group and in 23 (48.9%) subjects in the P group (*p* < 0.005) (Table 3). No side effects were reported throughout the study period in either group (Table 4).

Many studies have recently shown a role of transient developmental dysmaturity in terms of increased gut sensitivity in the aetiopathogenesis of infant colic together with organic disorders (i.e. cow milk allergy,

**Table 4. Side effects of phytotherapeutic agent versus placebo**

Symptoms	PA (n = 41)	P (n = 47)	p value	Standard error	CI 95%
Vomit	8	2	0.057	0.067	0.019; 0.281
Sleepiness	2	1	0.853	0.039	-0.046; -0.106
Restlessness	0	1	0.857	0.022	-0.063; 0.023
Inappetence	1	3	0.687	0.043	-0.123; 0.043
Cutaneous reactions	1	0	0.890	0.021	-0.020; 0.060
Constipation	4	5	0.722	0.064	-0.126; 0.126

lactose intolerance) or psychological problems (infant-parent interaction) (Iacono *et al.*, 1991; Hill and Hosking, 2000; Forsyth *et al.*, 1985).

An excessive crying time due to abdominal pain has important implications for the parental approach to infants. Frequently it is a reason for consultations with the paediatrician who sometimes administers drugs with antispasmodic and antimetecoric activity even though not strictly necessary and despite several side effects (Iacono *et al.*, 1991; Hill and Hosking, 2000; Grunseit, 1977; Metcalf *et al.*, 1994; Hardoin *et al.*, 1991).

Common herbs such as *Matricariae recutita* L., *Foeniculum vulgare* M. var. *dulce* and *Melissa officinalis* L. have an antispasmodic and antimetecoric activity, as previously shown in animals and humans (Forster *et al.*, 1980).

*Matricariae recutita* L. has an important antispasmodic activity on the smooth muscle of the intestine, due to its flavonoid components, particularly apigenin and bisabolol (Middleton and Kandaswami, 1992; DellaLoggia *et al.*, 1986; Fintelmann, 1991; Avallone *et al.*, 2000). Another important property of this plant is its sedative action (Longo, 1996; Avallone *et al.*, 1996).

*Foeniculum vulgare* M. var. *dulce* has antifatulent and antispasmodic properties and inhibits intestinal fermentation (Wespal and Horning, 1996; Reiter and Brandt, 1985; Lis Balchin and Hart, 1997). So this herb is currently used as a symptomatic remedy for digestive alterations (abdominal meteorism, flatulence and irritable syndrome of the colon) (Forster *et al.*, 1980).

*Melissa officinalis* L. has antispasmodic activity on the smooth muscle of the intestine, due both to the essential oil and flavonoid components, above all those containing apigenin (Soulimani *et al.*, 1991; 1993).

The antiinflammatory properties of *Melissa officinalis* L. are well known, as its sedative and anxiolytic action (dose-dependent sedative central action and peripheral analgesic activity). In the experimental model the spasmodic effect is higher on ileum muscle, due to the depression of phasic contraction of the myoenteric ileal plexus and of the ileum longitudinal muscles. The effect is similar to that of catecholamines and of phosphodiesterase inhibitors. It seems to be due to the E-anetolo, the most important favourable principle of fennel that is able to inhibit the penetration of calcium into the cells by a calcium-antagonist mechanism (Avallone *et al.*, 1996).

Partially the effect is due also to apigenin, a flavonoid present both in fennel and in balm-mint. The phosphodiesterase inhibition is the mechanism of apigenin action, and this could explain the spasmolytic effect of the phytotherapeutic agent employed in our study.

In this context it should be taken into account that studies on the treatment of colicky infants with an emulsion containing only fennel seed oil or herbal tea preparation with camomile, vervain, licorice, fennel and lemon-balm have been already conducted (Alexandrovich *et al.*, 2003; Weizman *et al.*, 1993).

In contrast to herbal tea, the PA tested in this study contained a higher and standardized concentration of three herbs with the advantage of a defined dosage without an increased fluid intake.

The results of the present double-blind study indicate that the administration of the PA twice a day significantly reduced crying time (compared with placebo) by 4 days of treatment.

It is interesting to note that during the first 3 days of therapy, the improvement of the P group showed similar values to the PA group, possibly due to the placebo effect or to the incomplete effects of phytotherapeutic agents which are effective only after some days.

The effects of vegetable drugs were not as quick as those of pharmacological drugs. The real cause for this fact is still unknown; it could be hypothesized that a low expression of phytotherapeutic binding site is involved in the slowness of the response to therapy. Another explanation would be that the receptor affinity of vegetal drugs is lower than that of pharmacological drugs and a longer time is necessary for the expression of the effects. Finally it takes more time for vegetable drugs to reach a steady state and their bioavailability is influenced by the gut microflora.

Therefore it could be hypothesized that the herbs' action was shown only after some days; in fact it may be that their efficacy as a gut antispasmodic agent is related to their action as a calcium antagonist of the gut musculature; therefore, as opposed to antispasmodic drugs (Savino *et al.*, 2002) a period of time may be necessary to allow the binding with the specific receptor which regulates the calcium channels (Tanira *et al.*, 1996; Talalay, 2001) as reported for *in vitro* animal models.

Besides fennel might modulate the gut microflora producing ammonium and there is evidence that changes in gut microflora could be involved in infantile colic (Lehetonen, 1994; Savino *et al.*, 2004).

However, in contrast to the P group the improvement of infants treated with PA increased during the time of the study (1 week) with a reduction in crying time on day 7 of 134% with respect to day 0.

Therefore the herb substances could reach a therapeutic level only after 3 days at the tested dosage and last up to 15 days after the end of the therapy.

As far as side effects are concerned, the use of this PA seems safe in infants when used at the tested dosage. Moreover no increase was observed of side

effects such as sleepiness that occur with antispastic drugs (Grunseit, 1977; Hardoin *et al.*, 1991).

The treatment of infantile colic with dietary modification has been proposed by many authors that support an allergy to milk protein or to other kinds of food eaten by the mother during feeding as possible causes for colic (Jakobsson and Lindberg, 1983; Lothe and Lindberg, 1989; Clyne and Kulczycki, 1991).

However, while dietetic modification may be proposed in formula-fed infants, in breast-fed infants (which are the majority) this intervention cannot be performed with the same possibility of success and should only be a last resort for severely colicky infants who have not responded to more conventional therapies (Savino *et al.*, 2001).

Considering our positive findings and the absence of side effects of PA used at the tested dosage, we think

that a trial of 1 week with a PA based on camomile, fennel and lemon-balm for the treatment of infantile colic might be attempted before using drugs or dietetic intervention.

In conclusion, our data indicate that the use of the phytotherapeutic agent based on *Matricariae recutita* L., *Foeniculum vulgare* M. var. *dulce* and *Melissa officinalis* L. could be effective and harmless for the treatment of infantile colic in breast and bottle-fed infants and could be a possible primary outcome measure.

Each component of the phytotherapeutic agent should be evaluated in order to improve the effectiveness of the treatment. It could also be useful to test different dosages of the phytotherapeutic agent to enhance our acknowledgement on its supposed dose-dependent effect.

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