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Efficacy of *Matricaria chamomilla* L. in Infantile Colic: A Double Blind, Placebo Controlled Randomized Trial

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Authors' contributions

This work was carried out in collaboration among all authors. Author FMS was the main investigator and she designed, conducted the experiments, acquired the data and wrote the manuscript. Author MT designed, supervised the study and critically evaluated the paper. Author HA designed and helped collect patients. Author RR made chamomile oil and placebo evaluated the study. Author MS analyzed and interpreted the data. Author MK was involved with study creation and revisions the manuscript. All authors read and approved the final version of the manuscript.

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ABSTRACT

Objective: Infantile colic is one of the most common problems in neonatal and early infancy, the prevalence of which has been reported as 10-20%. The present clinical trial was conducted to investigate whether topical use of chamomile oil reduces crying and fussing in breastfed colicky infants.

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Methods: A total of 102 breastfed colicky infants were divided into two groups to receive topical chamomile or placebo oil 6 times a day for 7 days. Both groups also received 5 mg of Simethicone syrup 4 times a day. Parents reported on crying and fussing duration, exertion times and side effects using a questionnaire.
Results: 90 babies could complete the trial including 47 patients in chamomile group and 43 patients in the placebo group. Babies in both groups were the same in terms of gestational age, birth weight, birth order, gender, delivery type, crying and fussing on the day before the treatment. At the end of the study, crying and fussing was found to be lower in chamomile group than the placebo group ($p < 0.001$). Also, 39 and 27 patients responded to the treatment in chamomile and placebo groups respectively. The effect of chamomile oil on crying ($p<0.01$) and fussing ($p< 0.001$) was significant. No serious adverse event was reported.
Conclusion: Results revealed that chamomile oil reduced symptoms in breastfed colicky infants compared to the infants in the placebo group. This suggests that topical use of chamomile oil may be effective in the treatment of colic.

Keywords: Infantile colic; Matricaria chamomilla; chamomile; traditional medicine; Persian medicine; a baby crying.

1. INTRODUCTION

Infantile colic is one of the most common problems in neonatal and early infancy, the prevalence of which has been reported as 10-20% [1,2]. Colic is characterized by high crying and sudden attack of restlessness, usually occurring in the evening and night, according to the Wessel's Triple Law, involving crying and fussing more than 3 hours a day, for more than 3 days a week, and more than 3 weeks [3,4]. The colic aetiology is unknown and usually resolves between 3 and 4 months spontaneously [5,6].

Although the colic has a good prognosis, it often causes serious stress for the parents. It damages mother-child relationship, increases the possibility of child abuse or shaken baby syndrome and prevalence of postpartum depression in mother [2,7], as well as causes fatigue and sense of inadequacy in the parents, and decreases patience level [2]. Colic causes early discontinuation of breastfeeding [2,7], as well as frequent changes in the formula, in formula-fed infants [2]. In this age group, colic is one of the major causes of medical referral and referring the patients to the medical specialist [1]. In the UK, 65 million dollars are annually paid for treatment and management of the colic [2].

The cause of colic is still unknown [5,6,8,9], although there are some theories about it. Among which, one theory investigates psychological causes and discusses the possible role of mother's stress and her poor relationship with the child and the other concentrates on gastrointestinal causes and describes factors such as increased intra-abdominal gas, visceral pain, and intestinal hyperperistalsis [10].

Numerous studies conducted in the field of colic indicate the importance of finding a safe way to treat this problem effectively. It seems that in the absence of safe and effective medication, using complementary therapies in treating infantile colic can play an important role in the management of this problem [8].

Matricaria chamomilla L. (Chamomile) is among the most ancient and famous herbs used for various medicinal purposes [11]. Chamomile is one of the herbs used in various digestive diseases [11,12]. Chamomile has been recognized as a safe herb in the U.S. Food and Drug Administration's (FDA'S) generally recognized as safe (GRAS) list [12]. Chamomile oil (chamomile extraction in sesame oil) is a formulation in Persian medicine that contains aqueous extract of chamomile in sesame oil [13]. Chamomile has been appreciated as a digestive relaxant and has been used to treat various gastrointestinal disorder such as flatulence, indigestion, diarrhoea, anorexia, motion sickness, nausea and vomiting. Additionally, it has been used in infantile colic, croup and fevers in children [13]. Chamomile oil is among the treatments for pediatric colic presented in authentic traditional medicine books, topical use of which has been suggested [14]. It has shown that chamomile has anti-inflammatory and antispasmodic virtues and can recovery gastrointestinal motility disorders. Chamomile is an effective herbal for removing gas and relaxation of the muscles of the intestinal wall due to its cholinergic effects [11]. Safe effects of

topical use of chamomile oil have been discussed and investigated in several studies [12,13,15,16].

Thus, this double-blind randomized clinical trial aims to evaluate the effect of topical use of chamomile oil on crying and fussing in infantile colic.

2. MATERIALS AND METHODS

2.1 Study Design

This study is a double-blind randomized clinical trial conducted on two groups of placebo and control groups in a parallel design.

2.2 Preparation of Chamomile Oil

Chamomile dried flowers were purchased from a local herbal store of Tehran, and a voucher specimen (*Matricaria chamomilla* L., No. PMP-336) was deposited in the herbarium of the Faculty of Pharmacy. Chamomile oil was prepared according to that proposed in traditional Persian medicine manuscripts [13]. For this purpose, 200 g dried flowers of *Matricaria chamomilla* var. chamomilla was soaked in 1 litre of distilled water for 24 h. Thereafter, it was boiled by medium heat until one quadrant of the content was remaining. Then it was filtered and the same volume of mineral oil was added to the filtrate and placed over medium heat until the water was fully evaporated and only the oil remained. The final product was packaged in airtight, light-resistant containers.

For standardization of chamomile oil, the chemical composition of its essential oil was determined by GC-MS. For this purposes, 100 ml of oil was mixed with 100 ml of distilled water and the essential oil was extracted by hydrodistillation using Clevenger apparatus for 5 hours. The obtained essential oils were dried using anhydrous sodium sulfate and stored at low temperature (+4°C) in amber vials for analysis. The essential oil was analyzed using an Agilent 6890 gas chromatography (GC) with BPX5 column (30m × 0.25 mm, ft 0.25 µm); carrier gas, He; split ratio, 1:25 and using Mass detector. The column temperature was programmed at 50°C for 5 min and heated at the rate of 3°C min-1 until 240°C, then raised to 300°C at a rate of 15°C min-1 and then kept constant for 3 min. The MS was operated at 70 eV ionization energy. Retention indices were calculated using retention times of n-alkanes. The essential oil components were identified based on the NIST and Wiley mass spectral library [17].

2.3 Inclusion and Exclusion Criteria

Infants (selected from Children's Medical Center Hospital and Ahmadie clinic, as a TUMS-affiliated academic centre) with healthy terms and birth weight of 2500-4000 g and adequate growth rate of 2-12 weeks, who were exclusively breastfed, met Wessel's criteria (crying and fussing for at least 3 hours a day, for at least 3 days a week) and whose diseases had been approved by a paediatrician were included in the study, after completing an informed consent form by their parents.

2.4 Intervention

In this placebo-controlled trial, colicky infants were randomly assigned to receive drug or placebo. In both groups, oil was administered 6 times a day, on two areas of the body each time (back and abdomen) for 7 days, so that chamomile oil was used for the intervention group and placebo was used for the control group.

5 to 7 drops of oil were poured on the baby's back and was spread on both sides of the spine, and then 5 to 7 drops of oil was poured on the baby's abdomen and was spread from under the ribs to underneath the abdomen so that it was thoroughly covered with the oil. Before the intervention, the mother was instructed to first apply 2 drops of oil (containing medication or placebo) on the baby's arm and wait for 3 hours, and if there were no inflammatory symptoms such as redness or rashes, the baby was allowed to receive the treatment.

Both groups received similar baseline treatment of 60 mg/day in the form of 5 drops of Simethicone syrup 5 times a day after breastfeeding for 7 days.

2.5 Outcome Measures and Follow-up

Our primary outcome was evaluating the changes in crying and fussing rates during the intervention period from day 0 to the end of the intervention for both placebo and intervention groups.

Our secondary outcome was the number of individuals treated in each group at the end of the study and a separated evaluation of crying and fussing changes during the intervention and

incidence of flatulence in the parents of both groups.

Parents completed a demographic questionnaire including the information on sex, age, weight, and type of childbirth on the day of visiting the babies by the paediatrician for the first time. Also, parents were asked to record the baby's crying and fussing on the first day after enrollment, and this day was known as day 0 or baseline.

Parents received oral and written information about the study and were asked to record daily crying and fussing duration in a structured notebook, from day 0 to day 7. A researcher was always available through phone call and was in touch with parents every day, to help them accurately record crying and fussing duration. Patients were visited on the 8th day by the same paediatrician.

2.6 Randomization, Blinding and Concealment of Allocation

2.6.1 Randomization

Colicky infants were divided into two groups to receive chamomile oil or placebo, by a statistician, based on a computer-generated random table in a 1: 1 ratio, with a permitted block size of 6.

2.6.2 Blinding

Chamomile oil and placebo oil poured into similar containers without label were similar in terms of smell and colour, and were coded. As this trial was a double-blind trial thus, all parents, researchers, and statistician were blind until the end of the study.

2.6.3 Concealment

To hide the randomization process, the research pharmacist placed randomization assignments in opaque and closed envelopes and numbered them respectively, based on a random product table.

2.7 Statistical Analysis

The sample size was determined concerning the alpha level of 0.05, power of 0.8 and the probability of 15% loss of 102 patients, consisting of 51 patients in the intervention group and 51 patients in the placebo group. The Intention -to - Treat (ITT) analysis was used in this study to preserve the random allocation process.

After collecting the data, patients' baseline variables were compared in intervention and control groups in the first stage to ensure the utility of the random allocation process. Independent Samples T-test, Chi-Square, and Fisher's exact tests were used to compare mentioned variables.

ANCOVA statistical test was used to analyze primary and secondary outcomes. Stata software (Stata Corporation, College Station, TX, USA) version 13.0 was used for data analysis.

3. RESULTS

3.1 Chemical Composition of Essential Oil

The hydrodistillation of chamomile oil yielded a blue-coloured oil (yield: 0.10% W/V). Fifteen constituents were identified in the essential oil representing 80.95% of the total. The most abundant components were α-bisabolone oxide A (33.10%) and α-bisabolol oxide A (17.18%), respectively (Table 1).

3.2 Enrollment

331 infants with colic were evaluated from June 2017 to December 2018.

102 patients were included in the study. 51 patients randomly received chamomile oil, and 51 patients received placebo. 9 patients were found to have skin allergy (red spot) to the oil. One patient was not followed-up. One patient did not use the drug correctly and one patient used another drug concurrently and finally, 90 patients completed the study. 47 patients received chamomile oil and 43 received placebo.

Further details are presented in tables.

Baseline characteristics including gestational age, birth order, birth weight, delivery type, gender, growth parameters, abdominal floating in the mother were similar in the two groups. In addition, there was no baseline difference in mean crying (MD: -2.64, 95%CI: -11.52, 6.22, P= 0.555) and fussing duration (MD: 4.94, 95%CI: -12.63, 22.52, P= 0.578) between the *Matricaria chamomilla* and placebo groups (Table 2).

3.3 Efficacy

Mean scores of crying and fussing duration from baseline to day 7 for both groups at each measurement point are presented in Figs. 2-4.

Table 1. Chemical composition of essential oil from chamomile oil

No	RT	%	Components	KI
1	36.68	5.98	(Z)-β-Farnesene	1456
2	42.12	1.12	Spathulenol	1591
3	44.99	2.67	α-Bisabolol oxide B	1667
4	45.44	2.90	Tumerone	1679
5	46.13	33.10	α-Bisabolone oxide A	1697
6	48.08	5.82	Chamazulene	1752
7	48.60	17.18	α-Bisabolol oxide A	1767
8	53.42	2.48	cis-ene-yne-Dicycloether	1907
9	65.34	0.73	Tricosane	2251
10	68.08	1.12	Tetracosane	2300
11	71.38	1.63	Hexacosane	2500
12	72.34	1.48	Heptacosane	2651
13	73.21	1.36	Octacosane	2697
14	74.14	1.30	Nonacosane	2799
15	74.91	2.08	Triacontane	2798
		80.95	Total Identified	

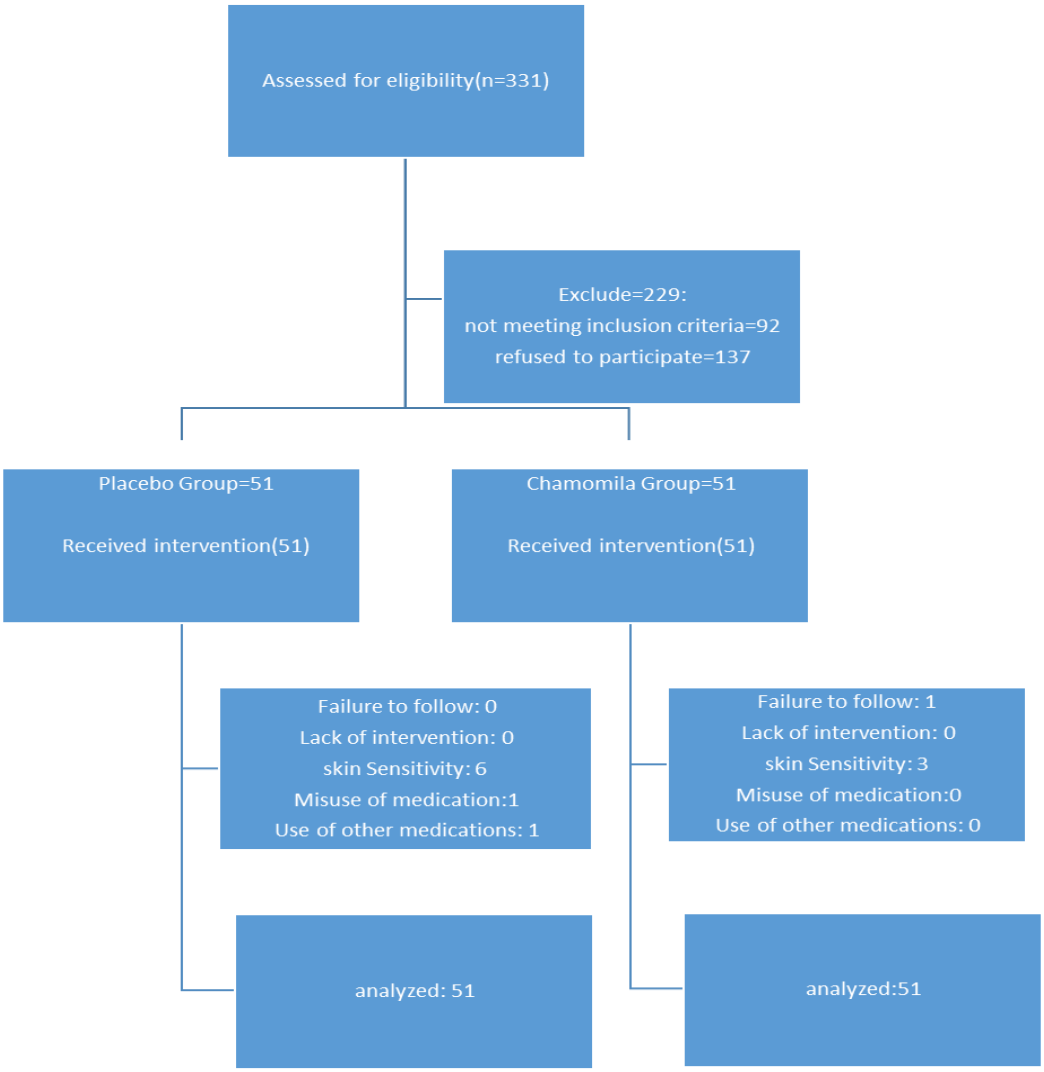

Fig. 1. CONSORT flow diagram of the research process

Table 2. Characteristics of the study population

	***Matricaria chamomilla* (n=51)**	**Placebo (n=51)**	**P-value**
Age at the entry to the study (days)[a]	42.84± (17.66)	42.47± (20.65)	0.922
Weight at the entry to the study (grams)[a]	3166.47± (383.74)	3193.72± (330.88)	0.702
Birth order[b]			
First	36(70.58)	36(70.58)	
Second or above	15(29.41)	15(29.41)	>0.999
Gender[b]			
Male	24(47.1)	22(43.1)	0.691
Female	27(52.9)	29(56.9)	
Delivery type[b]			
NVD	14(27.5)	17(33.3)	0.518
CS	37(72.5)	34(66.7)	

NVD: Natural vaginal delivery, CS: cesarean
a: Values given as mean ± SD (standard deviation)
b: Values given as number (percentage)

Table 3. Result in *Matricaria chamomilla* treatment and placebo group of infants diagnosed with colic

	***Matricaria chamomilla* (n=51)**	**Placebo (n=51)**	**P-value**
Number of infants who experienced relief of colic symptoms[1]	39 (76.5%)	27 (52.9)	0.013
Crying before treatment (Min/day)	27.17± (18.73)	29.82± (25.88)	0.555
Cumulative crying at the end of treatment (Min/week)	129.88± (66.42)	174.36 ± (113.45)	0.018
Fussing before treatment (Min/day)	204.90± (42.86)	199.96± (46.55)	0.578
Cumulative fussing at the end of treatment (Min/week)	907.21 ± (322.76)	1134.36± (303.85)	<0.001
Crying and fussing before treatment (Min/day)	232.07± (45.85)	229.78± (40.56)	0.790
Cumulative fussing and crying at the end of treatment (Min/week)	1037.10± (333.89)	1308.72± (334.63)	<0.001

1: Relief of colic symptoms defined as the decrease of cumulative crying and fussing to less than 21 hours per week

Table 4. Incidence of flatulence in the parents of both groups

Abdominal flatulence	**Yes**	**No**
Father	29(28.4)	73(71.5)
Mother	48(47.05)	54(52.9)

a: Values are given as a number (Percentage)

Mean of crying and fussing duration was significantly lower in *Matricaria chamomilla* group than placebo group at all points after randomization (F (1, 99) = 24.99, P< 0.001). No group-by-time interaction was found for crying and fussing duration (F (1, 99) = 0.081, P= 0.776). Crying of infants decreased by -37.79 (95%CI: -66.32, -9.26, P= 0.010) minutes per

week in *Matricaria chamomilla* group more than that of placebo group after adjusting for baseline variables of crying, age, gender and weight. Also, the mean of fussing was significantly lower in *Matricaria chamomilla* group than placebo group -241.20 (95%CI: -346.67, -135.73, P< 0.001). By the end of the treatment period (day 7), proportion of responders to the treatment was significantly higher in *Matricaria chamomilla* group compared to placebo group based on Wessel's criteria [Risk Ratio (RR): 1.44, 95%CI: 1.07, 1.93, Absolute Risk Reduction (ARR): 0.23, 95%CI: 0.04, 0.42, Number Needed to Treat (NNT): 4.34, 95%CI: 2.37, 20.83].

3.4 Safety and Tolerance

Chamomile oil was well tolerated and no side effects were reported by the patients.

4. DISCUSSION

This study was conducted to evaluate the effect of chamomile oil topical consumption on infantile colic. Results of this study indicated that topical consumption of chamomile oil reduces symptoms in breastfed colicky infants compared to those in the placebo group.

Results of our study were in agreement with the study conducted by Salehipour, et al., who showed that topical use of chamomile oil is effective in the treatment of colic [15].

However, despite the high prevalence of colic, its pathogenesis is still unknown, and it is known as a multi-factorial disease [8]. There are several hypotheses about the mechanism of action of chamomile oil in reducing symptoms of infantile colic.

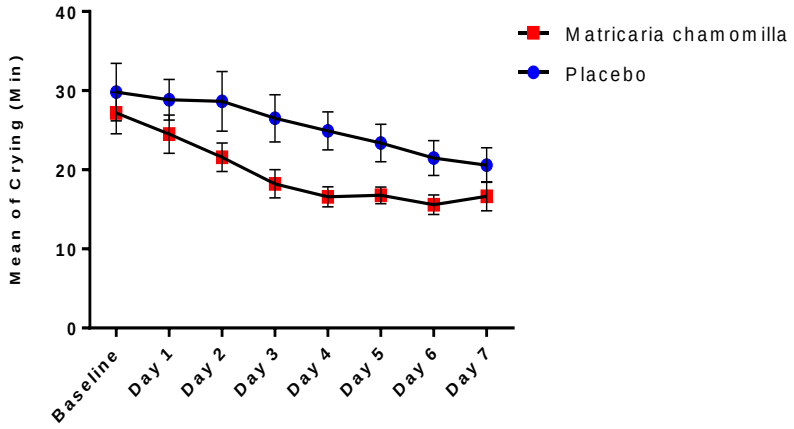

Fig. 2. Mean scores of crying from baseline to day 7

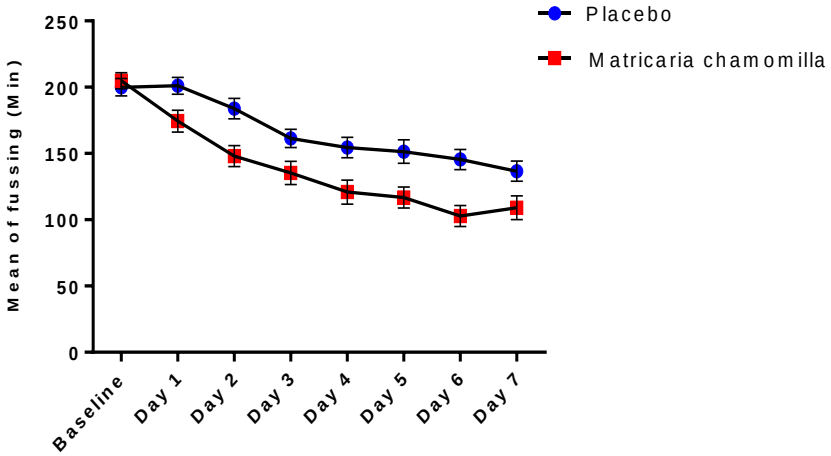

Fig. 3. Mean scores of fussing duration from baseline to day 7

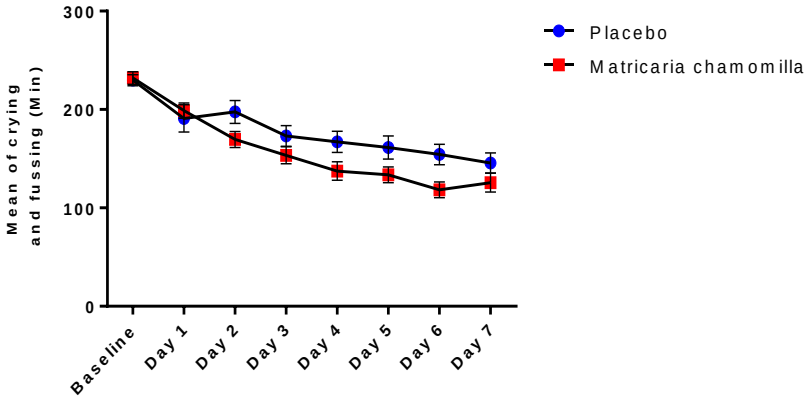

Fig. 4. Mean scores of crying and fussing duration from baseline to day 7 for both groups at each measurement point

The use of chamomile oil in treatment of infantile colic is based on previous studies suggesting that one of the causes of colic may be intestinal hypermotility probably caused by transient disturbance in nervous system during the first few weeks of life, resulting in incidence of hyperperistalsis and increased rectal pressure, in this regard, antispasmodics are effective in treatment of colic [18-20].

Chamomile has a K channel opening property. Potassium plays an important role in muscle tonus. The activity of voltage-dependent potassium channels inactivates calcium channels resulting in relaxation of smooth muscles [21,22].

Many studies suggested antispasmodic effects of chamomile in smooth muscles attributing to its flavonoid, apigenin, and bisabolol components [13,23]. Apigenin applies its spasmolytic effect by inhibiting phosphodiesterase and calcium infiltration [20].

Accordingly, it may be argued that the mechanism of action regarding the effect of chamomile oil in the treatment of colic is related to its antispasmodic property.

In a study, conducted on mice, chamomile-treated mice showed an obvious decrease in intestinal motility [24].

Perhaps, chamomile influences on colic due to its anti-flatulent effect, since there may be a lot of gas produced in the intestine of colicky babies [11,25,26] and chamomile can exert its anti-flatulent effect in response to this complication [11,27].

Chamomile has palliative and anxiolytic property [11,20,23,24]. Chamomile can relieve visceral pain [15].

Another explanation may be that some studies suggest this hypothesis that, colic has an atopic and food allergic cause, and that some prebiotics which has been effective in treating of atopic dermatitis, may also be effective in treating of colic through changing the intestinal flora [10]. As chamomile is effective in the treatment of atopic dermatitis [11,24] and has gastrointestinal effects especially in the intestines [21,24] and also due to its anti-inflammatory effects [11], thus it is assumed to be effective in the treatment of colic through changing normal intestinal flora.

The use of chamomile in infantile colic is quite safe. Efficacy of edible chamomile compounds has been investigated in many studies [20,23, 28]. Also, some studies have investigated topical use of chamomile oil in various diseases such as osteoarthritis, postoperative bowel activity after Cesarean Section, and infantile colic [12,13,15].

This study is the first clinical trial on chamomile oil investigated parental's bloating history and effect of chamomile oil on crying and fussing separately. Therefore, no study was available to compare this part of the results.

Savino, et al. indicated that the effect of herbal composition appeared late and on the 4th day [20]. But, an interesting thing in our study was that rubbing chamomile oil 6 times a day on the abdomen and both sides of the spine reduced amount of crying from the first day in colicky infants of the intervention group compared to those in the placebo group.

The exact cause for the incidence of colic is not known. However, the essential oils can easily cross the cell membranes and influence on ion channels to intracellular enzymes [22]. It can be stated that, in case of using essential oil, they can bond with special receptors of calcium channels and exert their antispasmodic effect, or it may be hypothesized that, the use of topical form of essential oils would require less time for herbal remedies to reach a constant level to influence on intestinal microflora. It is noteworthy that, as mentioned in Iranian Traditional Medicine, topical use of essential oils in gastrointestinal diseases is highly recommended as a treatment method [13,29].

4.1 Problems and Limitations

In this study, Simethicone was used for both groups. Because it is a well-known and available drug for colic and is not different from the placebo [10], but this may have influenced the outcomes.

Evaluating the effect of the drug on colic was done based on mother's self- reports of crying rate and we trusted their reports, this lack of a clinical subjective evaluation criterion for colic was a limitation in our study. However, it was attempted to correct the error in medication consumption, while preventing recall error, by collecting daily reports and phone calls.

Selecting breastfed babies was another limitation of our study, which may not allow generalization of the results to all colicky patients.

The short duration of research and lack of patients' follow-up were other limitations of this study.

Today, reassuring the mothers and reducing parental distress are among the factors contributing in improvement of colic [8,30] Availability of a medical team may have reassured the parents and reduced their stress and may have had an effect on results of the study. In this study, it was attempted to make the situation quite similar for both groups by assigning one evaluator.

5. CONCLUSION

This study was conducted to investigate the effect of topical use of chamomile oil as a new therapeutic approach based on complementary medicine in infantile colic. In this treatment method, a non-edible form of the drug was used and therefore, the amount of consumed milk was not limited. It seems that it could be considered as a simple and safe solution to infantile colic along with other treatments. On the other hand, it is suggested to evaluate the efficacy of chamomile oil applying massage and different doses of oil in future researches.

CONSENT

As per international standard or university standard written Parents consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study protocol complied with the Declaration of Helsinki (1989 revision) and approved by the Local Medical Ethics Committee of Tehran University of Medical Sciences (TUMS) with Reference number: IR.TUMS.VCR.REC.1395. 1531. The trial protocol was registered in Iranian Registry of Clinical Trials database under registration ID: IRCT 2016111530903N1. All of the enrolled participants returned their signed informed consent forms.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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