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# Osteopathic treatment of infants with infantile colic/excessive crying: a prospective, multicentric, randomized controlled trial and nested observational trial

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## Abstract

**Background** Colic in infants is defined as excessive crying in an otherwise healthy and thriving baby. Colic is a common but poorly understood and often frustrating problem for caregivers.

**Objective** To study whether osteopathic treatments of infants with infantile colic / excessive crying (IC/EC) have an impact on the subjectively perceived psychological stress of caregivers compared to usual care.

**Methods** The study was designed as a prospective, multicenter, randomized controlled trial. Infants aged 1 week to 3 months and who met Rome IV criteria for IC/EC were included. By means of external randomization, infants were allocated to an intervention group or a control group. Infants in the intervention group received three osteopathic treatments at intervals of one weeks. The treatments were custom-tailored and based on osteopathic principles. Controls received their osteopathic treatment after a 3 week untreated period. The primary outcome parameter was the assessment of parental psychological stress (three questions), measured using a numeric rating scale (NRS; 0–10). Furthermore, the average daily crying time (measured using the Likert scale), the crying intensity (measured using the NRS) and the parents' self-confidence (measured using the Karitane Parenting Confidence Scale) were assessed.

**Results** A total of 103 infants (average age 39.4 ±19.2 days) were included, 52 in the intervention group and 51 in the control group. An inter-group comparison of changes revealed clinically relevant improvements in favor of the intervention group for the main outcome – parameter psychological stress – for all 3 questions (e.g., for question 2 respectively 3, NRS: between group difference of means 3.5; 95% CI: 2.6 to 4.4;  $p < 0.001$ ). For the secondary outcome parameters of crying intensity and crying time/day, the changes were of similar magnitude.

**Conclusion** Three osteopathic treatments given over a period of two weeks led to statistically significant and clinically relevant positive changes of parental psychological stress.

**Trial registration** German Clinical Trials Register: DRKS00025867, registration date 10.08.21.

**Keywords** Osteopathic medicine, OMT, Infants, Infantile colic, Excessive crying

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## Background

Colic in infants is defined as excessive crying in an otherwise healthy and thriving baby. In the literature, this health disorder is often referred to as infantile colic (IC) / excessive crying (EC). The crying typically starts in the first weeks of life and usually resolves within 6 months [1]. IC/EC is a common but poorly understood and often frustrating problem for parents and caregivers [2]. Although IC/EC is classified as benign and self-limiting, it is one of the most common causes of medical consultations in the first months of a child's life due to the excessive crying and the accompanying distressing impairment to parents [3].

## Definitions

Three types of infant crying are distinguished: physiological crying (due to physical and emotional needs), pathological crying (due to organic causes), and non-specific crying (without an apparently reasonable cause) [4]. To date, however, there is no exact definition for IC/EC, which makes it difficult to compare different studies and scientific papers on this topic. Traditionally, the definition of IC/EC was based on the "rule of three": unexplained episodes of paroxysmal crying for more than three hours per day for three days per week for at least three weeks [5]. The Rome III Committee describes IC/EC as a behavioral syndrome in infancy that involves prolonged crying episodes and behavior that is difficult to soothe, without an obvious cause, and without failure to thrive [6].

## Epidemiology

Reported incidence rates of IC/EC vary between 2% and 40%, not least because of differences in the criteria used to define the condition [7, 8]. Twenty-one percent of UK families report having sought advice for persistent infant crying [9]. A review by Vandenplas et al. [10] identified 30 studies that reported a prevalence of IC or crying problems ranging from 2% to 73% in infants younger than 12 months of age. In a meta-analysis by Wolke et al. [11], pooled estimates of IC/EC cry duration were 117 min at 1–2 weeks of age, 118 min at 3–4 weeks, 133 min at 5–6 weeks, followed by a significant decrease to 68 min at 10–12 weeks of age.

## Etiology

IC/EC is considered a clinical pathology for which several explanations have been suggested, but its etiology remains unclear [12]. Suggestions that environmental factors such as psychosocial problems, domestic violence, inadequate parent–child interaction, or parental anxiety play a major role are highly controversial

[13]. There are conflicting ideas about the relationship between gastrointestinal issues such as lactose intolerance, cow's milk allergy, and gastroesophageal reflux disease and IC /EC [14]. Fortunately, IC/EC is not long-lasting: it usually begins at approximately two weeks of age and its severity tapers by the fourth month [15].

## Diagnosis

There is no reliable evidence that crying in infant colic is caused by abdominal pain or by pain in any other part of the body. Nevertheless, parents often assume that the cause of EC is abdominal pain of gastrointestinal origin [6]. Accordingly, IC is also classified as a functional gastrointestinal disorder in the so-called Rome criteria. In 2016, the Rome IV criteria were introduced, with the most important change affecting the diagnostic criteria for IC/EC in newborns and young children [16]. Rome IV is establishing different diagnostic criteria for clinical and research purposes. For clinical purposes, the criteria are no longer based on the "rule of three" by Wessel et al. [5]; instead, they are now being based on symptoms that have been shown to cause greater psychological stress in parents.

## Treatment

To date, there is no established golden standard concerning the management and treatment of IC/EC. Therapies described in the literature can be divided into pharmacological treatments, dietary advice, probiotics, and complementary and alternative therapies. The Cochrane Review by Biagioli et al. [17] included 18 original papers and a total of 1014 infants. The authors concluded, "At this time, the evidence for the efficacy of analgesic agents for the treatment of infant colic is sparse and prone to bias."

A 2018 Cochrane Review of 15 randomized controlled trials (RCTs) and 1121 infants addressed dietary modifications and concluded that, "Currently, the evidence for the effectiveness of dietary modifications for the treatment of infant colic is sparse and at significant risk for bias" [18]. The use of probiotics is based on the hypothesis that abnormal intestinal microflora may cause intestinal dysfunction and gas production, which explain the symptoms. There is another Cochrane Review of 6 RCTs and 1886 infants investigating the probiotic therapeutic option [19], whose authors concluded, "There is no clear evidence that probiotics are more effective than placebo in preventing infant colic."

In the absence of safe and effective pharmacologic interventions, complementary therapies have taken on an increasingly important role in the treatment of infant colic [15]. For example, behavioral therapies [20], acupuncture [21], and manipulative therapies [22] have been

studied in clinical trials. However, the effectiveness of these forms of therapy is also not clearly proven.

### Osteopathic view

In their desperation, parents of “cry babies” often seek help in osteopathic practice, also because osteopathy is not infrequently recommended by midwives or pediatricians. So far, only a few RCTs that have investigated IC/EC exist (e.g., Hayden and Mullinger [23]). In a recently published observational study [24], 219 infants with IC/EC were treated osteopathically, resulting in an improvement of symptoms of approximately 70% within three 3 weeks. Based on these findings, the following research question was formulated for investigation in a RCT:

### Research question

Does a series of osteopathic treatments of infants with IC/EC (according to the Rome IV criteria) affects subjectively perceived suffering of caregivers compared to usual care?

The aim of the study was therefore to obtain pragmatic, yet reliable evidence on the perceived effectiveness of an osteopathic intervention of IC/EC babies as reflected by caregivers' level of distress, the core motive for consulting an osteopath.

### Methods

The present study was designed as a prospective, multi-center RCT with a comprehensive osteopathic physical examination at the beginning of any treatment session to determine the consecutive custom-tailored treatment of actual dysfunctions. Infants randomized into the control group received “usual care” only for three weeks, and an identical osteopathic treatment thereafter.

### Setting

Four osteopaths (MZ, JG, PL, and SL) carried out the study in their private practices in Germany. All of them are experienced “Heilpraktiker” (the only medical profession in Germany approved to treat patients without supervision/delegation of a physician, with particular emphasis on complementary and alternative medicine modalities), having successfully completed 5 years of osteopathic training (approximately 1350 h), and having successfully passed a final clinical exam (thus representing the highest possible standard of osteopathic training in Germany). All participating osteopaths have additionally completed special postgraduate training in the treatment of children that meets defined quality criteria. Other osteopathic practices in Germany were contacted and invited to treat infants as part of this study.

### Recruitment

Infants and their parents were recruited directly through osteopathic practices or indirectly through posters, referrals from midwives, or childbirth education groups who learned about the study through word of mouth, social media, and/or promotional posters. In addition, advertisements were placed in the local press promoting participation in the study.

### Inclusion and exclusion criteria

Included were infants of both sexes aged 1 week to 3 months, with a birth weight > 2500 g, and without pathological neuropediatric findings.

The Rome IV criteria for IC/EC) had to be met [25]:

- Infant is less than 5 months of age at the onset of symptoms.
- Caregivers report on recurrent and prolonged periods of infant crying, fussing, or irritability that occur without obvious cause and cannot be prevented or resolved by caregivers.
- No evidence of infant failure to thrive, or of fever, or illness.
- Caregiver reports by telephone or face-to-face screening interview with a researcher or clinician that the infant had cried or fussed for 3 or more hours per day for 3 or more days within a week.
- A total of 24 h of crying plus fussing in the selected group of infants, which was confirmed to be 3 h or more when measured using at least one prospectively kept 24 h behavior diary.

Infants were excluded if they had active comorbidities (e.g., drug treatment such as antibiotics, gastroesophageal reflux, gastrointestinal tract disorders, and other etiologic predisposing factors for irritability) that required medical treatment at the time of inclusion into the study. U2 or U3 examinations (depending on the infant's age) by a pediatrician had to be performed, and the results of the examinations had to be free of findings that would preclude participation in the study. Infants undergoing ongoing physiotherapy or manual treatment were also excluded.

### Randomization

Participants were randomly allocated to two groups: an intervention group that received proper osteopathic treatment and a control group, which in parallel did not receive osteopathic treatment but “usual care” only during the study period of three weeks, and was offered osteopathic treatment only thereafter. Assignment to the groups was performed externally by the German

Association of Osteopaths (VOD) based in Wiesbaden, Germany, where computer-generated randomization lists with variable block lengths (permuted block randomization; 4 or 6) were held for every osteopathic practice (block lengths were not revealed to any party involved in the trial). When parents agreed that their baby be included into the study, the osteopath would contact the VOD randomization office, and the participant's allocation to the respective groups would be revealed immediately after the date of birth and initials of the infant had been conveyed, and had been documented in the original randomization list. If a baby was randomized to the intervention arm, treatment was started right away.

### Outcome measures

The main outcome parameter was an external evaluation – a recording of the psychological stress of caregivers. The level of stress was assessed using a numerical rating scale (NRS; 0 = not present to 10 = maximum imaginable). NRS is a widely used, short, easy to administer, and validated measurement instrument [26].

Parents were asked the following 3 questions:

- Question 1: When dealing with your baby, do you feel you have everything under control or do you feel insecure, helpless, and worried?
- Question 2: How stressed do you feel at the moment due to baby crying?
- Question 3: To what extent are your daily activities restricted by the infantile crying/whining?

Secondary outcome parameters included documentation of daily crying time over 21 days. A Likert scale was created to record crying times/day in 30 min increments (0–30, 30–60, ....., 270–300, and more than 300 min), and the crying intensity, which is a subjectively perceived assessment by parents. For the analysis of longitudinal changes in crying times, the mean from day 1 and day 2 in week 1 was compared with the mean from day 6 and day 7 in week 3. To make the outcome quantifiable, NRS (0 = minimum and 10 = maximum intensity) was used.

For obvious reasons, the following secondary outcome parameters were documented in the intervention group only: To assess parents' self-confidence, the Karitane Parenting Confidence Scale (KPCS) was used [27]. Furthermore, the parents' satisfaction with the treatment outcome as well as data on undesirable side effects were assessed.

### Study groups

At the first consultation, inclusion and exclusion criteria were checked and eligible patients were randomized into one of two groups after receiving comprehensive

information about the study before signing a consent form. Then a timely first treatment session was scheduled for infants in the osteopathic group, who received a series of 3 osteopathic examinations and treatments lasting 20–30 min each and delivered at intervals of 1 week. Treatments were scheduled at week 0 (T0), 1 (T1), and 2 (T2). Before each visit (T0, T1, T2) and 1 week after the last visit (T3, which was the primary end point of the trial), the questions on psychological stress had to be answered. The forms for recording crying times were handed over at T0 and were used to document the crying behavior during the 3 weeks study period.

At each visit, a comprehensive examination was performed according to osteopathic principles (for a more detailed description of osteopathy see the discussion). In keeping with the principles of osteopathy, there was no pre-defined, standardized treatment protocol; each osteopath was free to decide which techniques to use, but the techniques applied had to be documented in detail. For documentation purposes, a standardized examination documentation form was used by all practitioners. This form was also important to monitor changes in dysfunctions during the course of treatment.

At the baseline visit (T0), accompanying caregivers of infants of the control group were asked to provide the same bits of information as caregivers of infants in the intervention group. An osteopath then told them that their baby would be placed on a waiting list for osteopathic treatment that was scheduled to happen 3 weeks later. During this 3 week period, the crying times had to be documented. At weeks 3, (T3) the control participants filled out all assessment instruments for the second time. Three consecutive free osteopathic treatments were then offered (which was no longer the subject of the RCT).

Parents in both groups were allowed to seek and apply additional therapeutic measures (considered as "usual care") during the study period (but this had to be documented).

Before the actual treatment phase began, training was provided to participating osteopaths on study procedures, including standardized consultation, infant health screening, recording of findings, parent/caregiver counseling, and adverse event recording procedures.

### Statistical analysis

Sample size was calculated using the response rates and variances of the main outcome measures from the trials by Hayden and Senger [23, 28]. According to common standards in clinical trials, type I error was set at 0.05 and type II error at 0.2 (i.e., a power of 80%). Crying hours/day were used to determine sample size. The trial was designed to detect an overall clinically important difference in changes of 30% points, with assumed

standard deviations (SD) of 15, equivalent to an effect size of 0.75. Sample size calculation estimated that 96 participants would be required. We decided to aim for 100 participants to account for potential additional variation as well as drop outs.

All statistical evaluations were performed using PASW Statistics (version 17; SPSS, IBM). Results of the descriptive analysis at baseline were reported as means and SD. Differences between groups at baseline were examined using unpaired two-sided t-tests. In the confirmatory analysis, longitudinal changes of different aspects of the main outcome in the course of treatment (i.e., between the baseline and end of treatment) were compared between both groups using unpaired, 2-sided t-tests. For the analysis of longitudinal changes in crying times, the mean from day 1 and day 2 in week 1 was compared with the mean from day 6 and day 7 in week 3.

For all comparisons,  $p < 0.05$  was considered statistically significant; and 95% CIs were calculated for all point estimates. The confirmatory analysis was performed as an intention-to-treat analysis, and the last observation was carried forward for dropouts.

### Results

Parents of 175 infants responded to some form of invitation, and 103 of these infants qualified for the study: 52 were randomized into the intervention group, and 51 into the control group (Fig. 1 shows the flow of subjects through the trial). A total of 24 osteopathic practices specialized in the osteopathic treatment of infants had been invited to participate, of which 5 took part. Of a total of 3 dropouts, 2 were in the intervention group. Both did not show up for the first treatment appointment. In one case parents had moved abroad, in the other case caregivers had withdrawn their consent. The only dropout in the control group did not show up for the first treatment appointment, because the infant had stopped crying after inclusion in the study. Clinical and demographic characteristics did not differ between groups at the baseline (Table 1).

### Main outcomes

For all 3 questions concerning the psychological distress of the caregivers, positive changes in the intervention group – 2.6 to 3.5 points (total range = 10 points) – were more pronounced than they were in the control group ( $p < 0.001$ ; Table 2), where the changes in the comparison

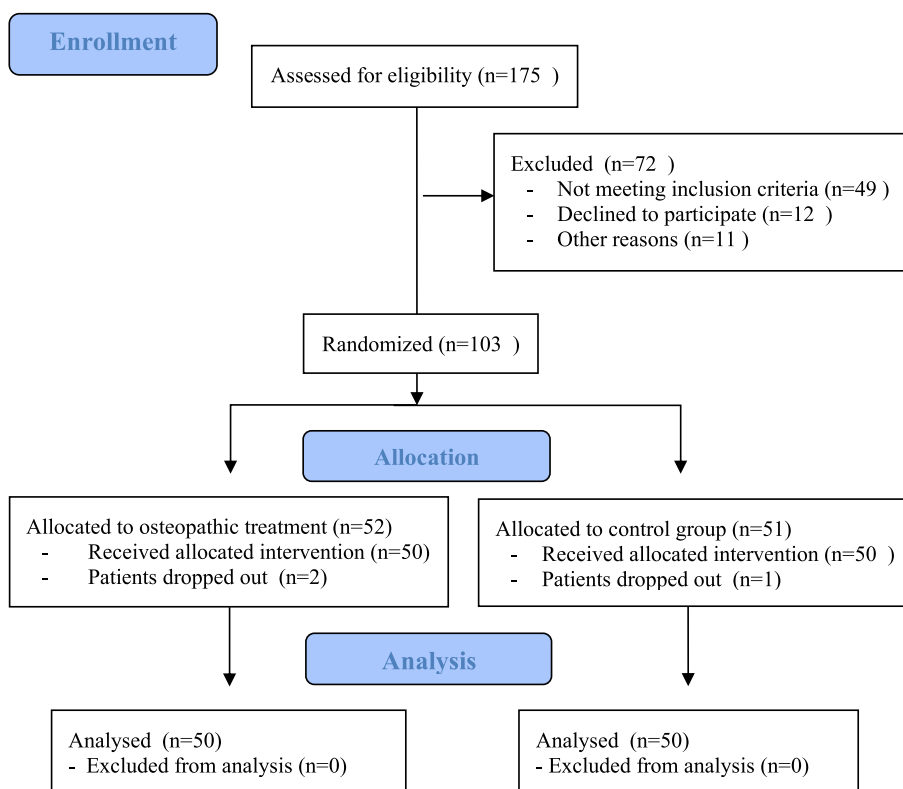


Fig. 1 Flowchart

**Table 1** Baseline characteristics of study patients

Characteristics	Osteopathic group (n = 50)	Control group (n = 50)	p - value
Age of baby, mean ± SD, days	37.3 ± 17.7	41.5 ± 20.8	0.3
Gender			
Female, n	28	21	0.2
Male, n	22	29	
Age of mother, mean ± SD, years	32.3 ± 3.3	32.0 ± 4.3	0.7
Siblings, n			
None	34	30	0.5
One	13	18	
Two	3	2	
Mode of delivery, n			
Vaginal	29	24	0.2
Caesarean	15	23	
Assisted vaginal delivery	6	3	
Duration of delivery, mean ± SD, hours	14 ± 8.5	13 ± 12.7	0.7
Birth weight, mean ± SD, g	3356 ± 408	3425 ± 468	0.4
Nutrition			
Breastfeeding (n)	47	45	0.5
Bottle (n)	3	5	
Psychological stress, mean ± SD, NRS (0-10)			
Question 1: Feeling of insecurity, helplessness	5.4 ± 2.2	5.7 ± 2.6	0.5
Question 2: Level of stress	7.1 ± 1.6	7.1 ± 2.2	0.9
Question 3: Limitation of daily activities	7.1 ± 1.9	7.4 ± 2.0	0.5
Intensity of crying, mean ± SD, NRS (0-10)	7.5 ± 1.5	7.5 ± 1.9	0.9

NRS Numeric Rating Scale, SD Standard deviation, CI Confidence interval

**Table 2** Intergroup differences; comparison of mean values of both groups between baseline (T0) and the end of the treatment series (T3)

Mean ± SD	Longitudinal changes T0 to T3		Difference of longitudinal changes, and 95 % CI	p - value
	Osteopathic group (n=50)	Control group (n=50)		
<b>Psychological stress</b>				
(Suffering caused by infants crying), NRS (0-10)				
<b>Question 1:</b> Feeling of insecurity, helplessness	-2.9 ± 3.3	-0.3 ± 2.4	2.6 (1.4 to 3.7)	<0.001
<b>Question 2:</b> Level of stress	-4.2 ± 2.7	-0.7 ± 1.7	3.5 (2.6 to 4.4)	< 0.001
<b>Question 3:</b> Limitation of daily activities	-4.2 ± 2.8	-0.7 ± 1.6	3.5 (2.6 to 4.4)	< 0.001
<b>Intensity of crying,</b> NRS (0-10)	-4.7 ± 2.8	-0.7 ± 1.6	4.0 (3.1 to 4.9)	< 0.001
<b>Crying time /day,</b> h	-1.3 ± 1.3	-0.4 ± 0.9	0.9 (0.4 to 1.3)	< 0.001

NRS Numeric Rating Scale, SD Standard deviation, CI Confidence interval

period were minute and probably clinically insignificant (Table 3).

For the secondary outcome parameters, crying intensity and crying time/day, changes (and differences of changes between groups) were analogous and of similar dimensions.

Looking at longitudinal changes between the beginning and the end of the study, there was an improvement of 2.9 points (53%) for question 1 and 4.2 points or approximately 60% (NRS;  $p < 0.001$ ) for questions 2 and 3 in the osteopathic group. The control group remained unchanged on question 1 and improved by only 0.7

**Table 3** Within-group longitudinal changes

Mean ± SD	Beginning of treatment (T0) (n=50)	End of treatment (T3) (n=50)	Intragroup difference of longitudinal changes, and 95% CI	p-value
<b>Psychological stress</b> (Suffering caused by infants crying), NRS (0-10)				
<b>Question 1:</b> Feeling of insecurity, helplessness				
Osteopathic group	5.4 ± 2.2	2.5 ± 2.0	-2.9 (-3.8 to -2.0)	<0.001
Control group	5.7 ± 2.6	5.4 ± 2.6	-0.3 (-1.0 to 0.3)	0.3
<b>Question 2:</b> Level of stress				
Osteopathic group	7.0 ± 1.6	2.8 ± 2.0	-4.2 (-5.0 to -3.5)	< 0.001
Control group	7.1 ± 2.2	6.4 ± 2.1	-0.7 (-1.2 to -0.3)	0.004
<b>Question 3:</b> Limitation of daily activities				
Osteopathic group	7.1 ± 1.9	2.9 ± 2.1	-4.2 (-5.0 to -3.4)	< 0.001
Control group	7.4 ± 2.0	6.7 ± 2.1	-0.7 (-1.1 to -0.2)	0.003
<b>Intensity of crying</b> , NRS (0-10)				
Osteopathic group	7.5 ± 1.5	2.8 ± 2.3	-4.7 (-5.5 to -3.9)	< 0.001
Control group	7.5 ± 1.9	6.8 ± 2.0	-0.7 (-1.1 to -0.3)	0.003
<b>Crying time /day</b> , h				
Osteopathic group	2.4 ± 1.0	1.1 ± 1.0	-1.3 (-1.6 to -0.9)	<0.001
Control group	3.3 ± 1.2	2.9 ± 1.1	-0.4 (-0.6 to -0.1)	0.004
<b>KPCS score (0-45)</b>				
Osteopathic group	29.8 ± 5.2	37.2 ± 4.9	7.3 (5.4 to 9.2)	< 0.001
Control group	documented in the intervention group only			

SD Standard deviation, NRS Numeric Rating Scale, CI Confidence interval, KPCS Karitane Parenting Confidence Scale; Clinical cut-off scores and clinical range specifiers for mothers completing the KPCS: *Severe* clinical range (31 or less), *Moderate* clinical range (31-35), *Mild* clinical range (36-39), Non-clinical range (40 or more)

points (approximately 10%) on questions 2 and 3, respectively (Table 3).

Cry intensity decreased from 7.5 to 2.8 points (>60%) in the osteopathy group and from 7.5 to 6.8 points (approximately 9%) in the control group. Crying times were halved in the osteopathy group, whereas a reduction of approximately 12% was observed in the control group (Table 3). Total crying times summed up to a mean of 36.4 h in the osteopathy group and 65.4 h in the control group during the 3-week study period (difference: 29 h, 95% CI 21.8 to 36.4;  $p < 0.001$ ). KPCS showed similar behavior over the course of the study. Figure 2 shows a change in parents' psychological distress (exemplified by question 2).

#### Additional outcomes

Figure 3 shows a clear, statistically significant heterogeneity in the decrease of psychological distress (exemplified by question 2) between osteopathic practices (ANOVA F-test = 6.3;  $p = 0.002$ ).

Adverse reactions with a temporal relation to the osteopathic sessions occurred in 21 (of the 100) infants after the first treatment and in 11 infants after the second treatment. Without exception, however, the "reactions" were typical fluctuations such as, for instance, restlessness, fatigue, restless sleep, or increased crying,

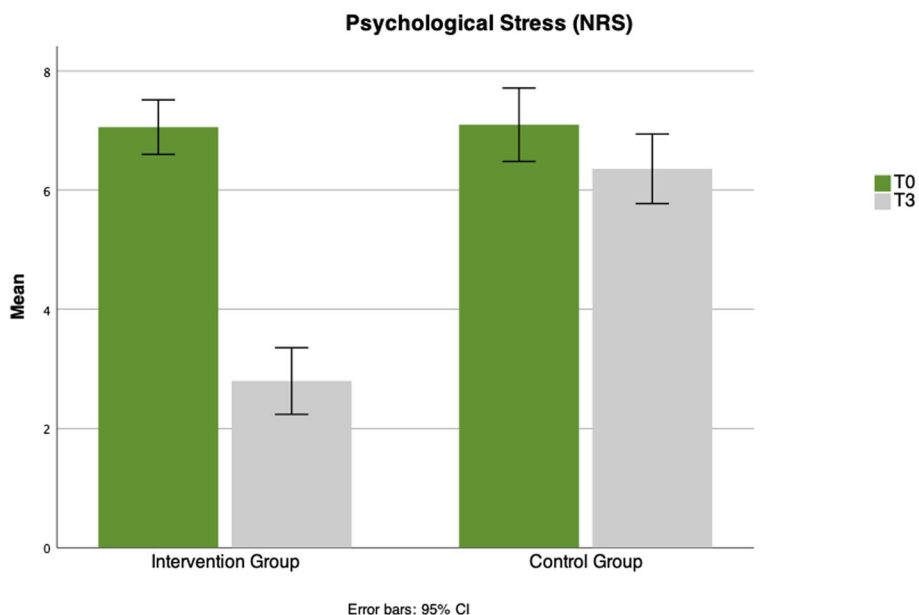
occurring repeatedly during the course of the day. Clinically relevant, severe, or non-transient side effects did not occur in any case throughout the study. Among the osteopathic dysfunctions found, intraosseous dysfunction at the occipital bone (85% in the intervention group) and C0/C1 dysfunction (67%) were most prevalent. In the cases with vegetative disbalance, a marked sympathetic reaction was often present (52%). Other frequently occurring dysfunctions were: dysfunctions of thoracic spine (65%), pelvis (60%), clavicle (58%), diaphragm (52%) lumbar spine (48%), and intraosseous dysfunctions of the temporal (40%) and sphenoid bone (44%).

The infants in the control group were treated osteopathically 3 times after the untreated period of 3 weeks. This set of data allowed for a nested observational study to test the reproducibility of the changes in the osteopathic group as a consequence of the intervention. The data confirmed almost identical improvements in responses to the questions about psychological stress as in the osteopathic group (Table 4).

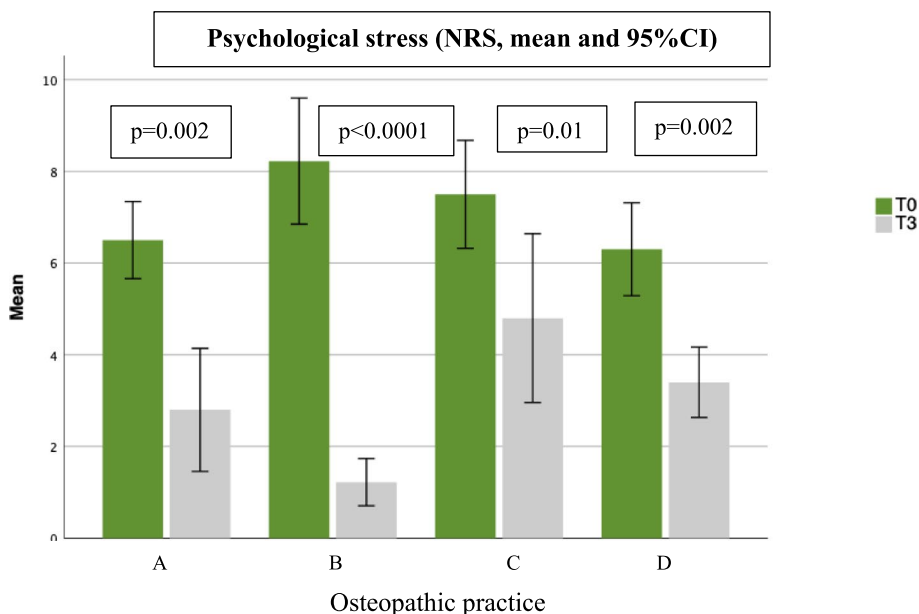
## Discussion

### Literature

Although IC/EC is classified as benign and self-limiting, there are 5 Cochrane reviews that address therapies for



**Fig. 2** Psychological stress of the parents (question 2): comparison of groups at baseline/end of study (mean and 95%CI)



**Fig. 3** Psychological stress of the parents (question 2): longitudinal changes in the osteopathy group by osteopathic practices treating at least 20 babies

this health disorder [17–20, 22], which indicates that IC/EC is of great importance to caregivers who confront it.

**Definitions**

The vast majority of studies on IC/EC have used the 1954 Wessel criteria. However, in the review by Zeevenhoven et al. [8], these criteria were found to be excessively

arbitrary, culture-dependent, and impractical to use, with insufficient focus on the insatiable nature of crying, and with inappropriate use of the word “paroxysmal”. Therefore, most recent studies used the Rome IV criteria for functional gastrointestinal disorders in infants. These criteria were introduced in 2016 and establish different diagnostic bases for clinical purposes (items 1–3) and



**Table 4** Longitudinal comparison of osteopathic treatments in intervention and control groups

	Baseline Mean $\pm$ SD	End of treatment Mean $\pm$ SD	Mean intragroup longitudinal changes, and 95% CI	<i>p</i> -value
<b>Psychological stress</b> (Suffering caused by infants crying), NRS (0-10)				
<b>Question 1:</b> Feeling of insecurity, helplessness				
Treatment phase, intervention group ( <i>n</i> =50)	5.4 $\pm$ 2.2	2.5 $\pm$ 2.0	-2.9 (-3.8 to -2.0)	< 0.001
Treatment phase, control group ( <i>n</i> =61)	5.7 $\pm$ 2.5	1.9 $\pm$ 1.5	-3.8 (-4.5 to -3.0)	< 0.001
<b>Question 2:</b> Level of stress				
Treatment phase, intervention group ( <i>n</i> =50)	7.0 $\pm$ 1.6	2.8 $\pm$ 2.0	-4.2 (-5.0 to -3.5)	< 0.001
Treatment phase, control group ( <i>n</i> =61)	6.7 $\pm$ 2.2	2.5 $\pm$ 1.8	-4.2 (-4.9 to -3.4)	< 0.001
<b>Question 3:</b> Limitation of daily activities				
Treatment phase, intervention group ( <i>n</i> =50)	7.1 $\pm$ 1.9	2.9 $\pm$ 2.1	-4.2 (-5.0 to -3.4)	< 0.001
Treatment phase, control group ( <i>n</i> =61)	6.9 $\pm$ 2.1	2.6 $\pm$ 2.0	-4.3 (-5.1 to -3.6)	< 0.001
<b>Intensity of crying</b> , NRS (0-10)				
Treatment phase, intervention group ( <i>n</i> =50)	7.5 $\pm$ 1.5	2.8 $\pm$ 2.3	-4.7 (-5.5 to -3.9)	< 0.001
Treatment phase, control group ( <i>n</i> =61)	7.2 $\pm$ 2.1	2.3 $\pm$ 2.0	-4.9 (-5.6 to -4.1)	< 0.001

SD Standard deviation, NRS Numeric Rating Scale, CI Confidence interval

research purposes (items 4–5). The new clinical criteria focus on symptoms that have been shown to cause high psychological stress in parents [25].

### Study design

For IC/EC, no standard therapy is convincingly evidence-based. In daily practice, the therapy of choice today is an interdisciplinary collaboration between several specialties (in this context referred to as “usual care”).

This is an open study in which the psychological stress of parents, rather than the symptoms of the infants, is the focus of interest. This is the decisive trigger for the parents’ decision to seek relief and thus for treatment of the infants. In this respect, quantification of the severity of this disorder differs from what is usually being evaluated in clinical medicine, namely the quantitative objectification of the problem itself or of a leading symptom. Consequently, for IC/EC, there are no established standard values or thresholds – how often, how long and/or with which “quality” the crying of an infant is to be classified as “non-pathological” or when an intervention is indicated from a medical point of view. From a methodological point of view, it seems ideal to let parents assess the symptoms of their babies without knowing whether treatment has taken place or not (focus on internal validity). However, convincing findings from other studies (e.g., Miller et al. [29]) as well as methodological considerations regarding the question investigated here suggest that blinding would be neither helpful nor goal-directing in this case.

Indeed, preventing parents from being present while a stranger performs physical therapy of more than 30 min duration on their infant could exacerbate symptoms,

provoke increased crying, and cause worry and irritation in parents. For this reason, pediatricians often advise against blinding parents during such a study [30]. Light touch as a sham treatment was also not a sensible option here since even light touch could induce relaxation, activate the parasympathetic nervous system, and thus influence colic symptoms. In contrast, the fact that parents were not blinded increases the external validity of the study results compared to a study design with blinding, as it reflects the treatment reality in Germany: parents would proactively decide to visit an osteopathic practice, which is “the measure of all things” in terms of (perceived) treatment success.

One difficulty (also concerning the willingness of practices to participate in this study) was that affected parents typically indicated extremely high psychological/emotional stress (they could not stand the crying and demanded immediate help). Therefore, it was feared that placing an infant in the control group to stay 3 weeks without complementary osteopathic therapy would not be accepted. In such a case, the osteopath was required to make an appointment for the first osteopathic treatment during the first visit but at the same time give the caregivers a guidebook on how to deal with crying infants. This was an arrangement that proved successful in the study.

### Methods

In the case of a negative outcome in clinical trials concerned with manual therapy or other interventions directly delivered by just one therapist, there is no way to determine whether the therapy itself or whether the therapist is to blame. In order to test the treatment approach and not the therapist, this study was performed in the

form of a “best practice” multicenter trial (well-trained and experienced osteopaths performed the treatments) with randomization stratified by therapist.

There are numerous well-reasoned recommendations in the literature for the primary outcome parameter we have chosen: (subjective) external evaluation by caregivers [31]. Accordingly, the psychological stress of caregivers was chosen as the main outcome of this study. Psychological stress refers to the subjective experience of suffering that has a significant negative impact on one's quality of life and well-being. Sufficiently high psychological stress is an important driving force for change and can prompt an affected person to seek help or accept the help offered [32]. In order to ask comprehensible questions to caregivers and to clarify how the psychological stress presents itself to them in concrete terms, a pilot survey was conducted with some 10 parents (unpublished material). The 3 most frequently mentioned answers were used phrase NRS questions.

To enable a comparison with other studies in which crying time is usually recorded as a primary outcome parameter, crying time was documented as a secondary parameter. The “crying diary” described by Barr is still used in most studies to document the daily crying time [33]. Since this mode of documentation requires great effort and is also prone to errors yet there is no practicable app that could be installed on a smartphone (such an app would probably also be prone to errors), we provided a so-called Likert scale that grades crying times/day in class widths of 30 min.

### Osteopathic diagnosis and treatment

Osteopathic practitioners rely on their understanding of the relationship between structure and function to optimize the body's self-regulation and self-healing capabilities. This approach to patient care and treatment is based on the core osteopathic concept that a human being is a dynamic functional unit in which all parts are inter-related and which possesses its own self-regulatory and self-healing mechanisms. Two essential components of osteopathic health care are a structural evaluation of the patient for diagnosis and an array of manipulative techniques for treatment [34]. The aim of the structural examination is to locate somatic dysfunctions that may contribute to the clinical presentation of the patient. Diagnostic criteria for somatic dysfunctions are focused on tissue texture abnormalities, asymmetry of bony landmarks and restriction of motion [35].

Osteopathic practitioners use a wide variety of therapeutic manual techniques to improve physiological function and restore homeostasis impaired by somatic dysfunction [34]. The practitioners assess and treat the “whole person” as a self-regulatory system, rather than

just focusing on specific symptoms or illnesses [36]. According to the principles of osteopathy, the location of dysfunction will not be restricted to the area of symptoms: dysfunctions can arise and be diagnosed throughout the body. Although osteopathic treatments typically involve a range of manual techniques, balanced ligamentous tension and cranial treatments (cranial osteopathy) are the treatment approaches of choice when treating infants. The Manual of Pediatric Osteopathy indicates that it seems difficult to prescribe a precise treatment modality because many different physical aspects may be present (restrictions in the meninges, thoracic tissues, and diaphragm; or in the ligamentous and muscular balance of the cervical spine) [37]. In keeping with the core principles of osteopathy [35] we did not specify a predefined array of techniques, but asked for documentation of techniques applied.

The selected number of osteopathic treatments was determined according to the results of the OSTINF study [24].

### Results

Analysis of the baseline data did not reveal relevant structural inequality between the groups nor that the study participants represented an atypical cohort for age and health disorder. The sex ratio was balanced. The mean age of the included infants was 39 days. History taking did not reveal any clear abnormalities that could explain the causes of the IC/EC health disorder. 92% of the mothers breastfed their infants at the beginning of the study. Thus the idea that a diet with cow's milk products may be an important cause of IC/EC could also be ruled out.

To determine parents' psychological stress, 3 questions were asked; it turned out that question 1 (a feeling of insecurity and helplessness) was not a suitable indicator or predictor of subjectively perceived psychological stress in contrast to nervous strain/stress (question 2) and limitation of daily activities (question 3). Substantial positive changes in the intervention group, i.e. the course of decrease in parents' psychological stress over the study period indicate that 3 osteopathic treatments probably served the purpose. The secondary outcome parameters (crying intensity, crying times, and parental self-confidence) consistently confirm the result of the primary outcome parameter.

In determining crying times, it became apparent that it is extremely difficult to accurately determine crying times and that crying duration is clearly a less suitable predictor than crying intensity.

At the end of the study, caregivers were asked the following questions: “*You have received three osteopathic treatments. Please tick what's your global impression of improvement in your baby's crying behavior*” and “*please*

*tick how satisfied you are with the osteopathic treatment.*" In the osteopathy group parents' ratings for questions 1 and 2 were 7.7 and 9.4, respectively, on an NRS of 0–10, reflecting high satisfaction of parents with the perceived effects of the treatment method.

A comparison of our results with the literature is difficult, as there are few studies on IC/EC with high quality. The meta-analysis by Ellwood et al. [2] contains the following statement: "More high-quality studies are needed to increase the level of certainty surrounding the findings about the effect of manual therapy for infantile colic." The Cochrane Review by Dobson et al [22]. comes to a similar conclusion.

The primary outcome parameter has been crying time in almost all studies. In their study on the impact of cranial osteopathy for the relief of infantile colic, Hayden et al. [23] come to a comparable reduction in crying times within 24 h (intervention group: change – 1.5 h, control group: change 0.5 h). Ellwood et al. [2] recommends that future studies should consider the effect of treatment on the parents to explore parenting confidence, and parent/infant bonding. We also believe that these aspects should be given greater consideration in future studies.

A recent study published by Carnes et al. [38] aimed to test the effectiveness of usual light touch osteopathic treatment against simple light touch without therapeutic intent for reducing crying time in infants with infantile colic. Sixty-six infants were recruited. Mean average daily crying time in the intervention group was 124 min over each 24-h period. However, as the control group (simple light touch without treatment intent) also showed an improvement in crying times of 115 min, there was no statistical significance between the groups. This shows the difficulty of choosing a sham group, where osteopaths, even without therapeutic intention, lay on their hands. This can lead to an improvement in crying time and may confirm that an untreated time interval in the control group chosen by us may be the better alternative.

### Limitations

In RCTs in which the waiting phase of the control group is compared with the therapy phase of the intervention group, effects triggered by expectation, in addition to therapy-specific effects, can come into play. In the present study, this should be irrelevant for objectifiable symptoms of the treated babies because, for crying infants, in the run-up to the therapy investigated here, everything possible was typically done by the caregivers (without reasonable success) to favorably influence the crying behavior. This cannot immediately be applied to the caregivers. It can, however, not be ruled out that the expectations of the therapy might have influenced the assessment of the caregivers in the control group.

This phenomenon is called the Hawthorne effect [39] and describes the positive effect on a participant in a study of the expectation of being treated particularly carefully and well.

A potential confounder may be the natural course of the problem. It is indeed well-known that excessive crying is a self-limiting problem [3]. As far as the explanatory (RCT) part of the study is concerned, longitudinal changes were compared between intervention and control group in parallel, so changes due to the natural course of the problem can be assumed to be comparable in both arms. We cannot exclude, however, the impact of the natural course in the nested observational part of the study. We tried, however, to compare the changes observed in this study with changes observed by other groups (historical controls), which may at least allow for a conservative qualitative conclusion.

In fact certain positive changes in both the primary and secondary outcome parameters were already observed in the control group during the waiting phase. These changes were much smaller in the control group than in the intervention group, which can be considered additional qualitative evidence that therapeutic intervention was the main causal factor for changes in the intervention group. Also, changes tended to be markedly larger than the natural course to be expected according to the literature. This gives rise to the assumption that the Hawthorne effect, if present, would probably have to be assumed in the caregivers of both groups and should not represent a source of bias.

### Conclusion

The demand for osteopathic treatment from parents of infants with IC/EC is clearly quite high and increasing in Germany, indicating that a really satisfactory conventional treatment option may not be available for this health disorder, or that the existing treatment options are evidently perceived to be unsatisfactory. In three osteopathic treatments performed by well-trained osteopaths with specific postgraduate training in the treatment of children, the psychological stress of the parents improved in a clinically relevant (and statistically highly significant) way, which can plausibly be explained as most likely being a consequence of clinically relevant effects of the treatment.

The results of this study were confirmed by the results of the downstream osteopathic intervention in the control group as well as by the results of other studies on this subject. In the observational study OSTINF [24], for instance, the level of stress parents perceived due to their baby's crying was assessed (using NRS; 0–10) in 219 infants with IC/EC before and after 3 osteopathic treatments. The results there showed an improvement of 67%,

(from 7.0 to 2.3), which is quantitatively matching the results of this study.

The answer to the question posed in the study (from the perspective of the affected parents): “A practical statement should be made as to whether or not parents in Germany should consult an osteopath for this health disorder of the infant” can be convincingly answered with yes.

Further studies, possibly with high numbers of cases, are desirable to corroborate the result of this study. Furthermore, studies on explanatory models of the clinical effectiveness of the osteopathic treatment of IC/EC would be worthwhile.

#### Abbreviations

EC	Excessive crying
IC	Infantile colic
NRS	Numeric Rating Scale
SD	Standard deviation
CI	Confidence interval
OMT	Osteopathic manipulative treatment
RCT	Randomized clinical trial

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#### Authors' contributions

FS and KLR contributed to the design and planning of the research. MZ, JG, PL and SL carried out the osteopathic treatments and the data collection. MR was involved in the analysis of results. FS and KLR drafted the initial manuscript, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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#### Data availability

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

#### Declarations

##### Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the German Academy of Osteopathy, Germany (EK006, July 2021). The Ethical Review Board gave us a positive approval. Written informed consent was obtained from all parents before their infants were enrolled in the study.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

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