

# Comparison of Effectiveness of Manual Therapy for Infant Crying: systematic review and meta-analysis of randomized controlled trials

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**Objectives:** The aim of this systematic review and meta-analysis is to assess and compare the effectiveness of manual therapy in alleviating infant crying, a common symptom of nocturnal crying (NC) and infantile colic (IC).

**Methods:** Total effective rate, crying time and adverse events were used as outcome indicators. To assess the quality, the risk of bias was determined for each study by two authors, using the Cochrane Collaboration's risk of bias tool. RevMan 5.0 was used for data analysis. A total of 98 articles were identified from 6 electronic databases.

**Results:** Among them, twenty-seven studies which included 13 NC and 14 IC were included. Meta-analysis showed favorable effects tuina therapy on total effective rate (TER) of NC (RR: 1.20 [95% CI 1.05 to 1.37],  $p = 0.007$ ), chiropractic therapy on crying time change of IC (SMD:  $-0.83$  [95% CI  $-1.61$  to  $-0.06$ ],  $p = 0.04$ ) and massage on total crying time of IC (SMD:  $-0.86$  [95% CI  $-1.09$  to  $-0.63$ ],  $p < 0.00001$ ). This systematic review compares different manual therapies for the treatment of NC and IC. While tuina, chiropractic, and massage show results in alleviating symptoms, the overall evidence remains limited due to the low quality and heterogeneity of the included studies.

**Conclusion:** Therefore, further high-quality research with unified control groups is needed to establish manual therapy as a recommended treatment option for NC and IC. Protocol registration number is CRD42022348143 01/08/2022.

**Keywords:** manual therapy, nocturnal crying, infantile colic, systematic review, meta-analysis

## INTRODUCTION

Crying is a typical and natural occurrence in healthy infants, nonetheless, it often prompts parents to seek medical care for their child. Inconsolable crying can be particularly challenging for parents as conventional soothing techniques may be ineffective, leading them to feel inadequate in their parenting skills and increasing their distress [1, 2]. Infant crying is often associated with a condition such as nocturnal crying (NC) or infantile colic (IC) and is rarely investigated as an independent symptom [3]. NC is defined as when infants and toddlers continue to cry intermittently at night. In severe cases, it can persist

throughout the night until dawn the next day, even though it is a normal symptom during the day. NC is a term used in traditional medicine, while in modern medicine, the occurrence can correspondingly define sleep disorders, behavioral disorders, or colic. Studies from the literature were identified by searching for "excessive crying," "nocturnal crying," and "night crying." Crying in infants has been studied mainly in relation to the presence of IC [4]. The prevalence of IC varies depending on the geography and definitions used and affects 4% to 28% of infants worldwide during their first months of life [5]. Most available definitions of IC focus on the length of time a baby cries and/or the impact it has on their caregivers [6]. The most commonly

used definitions of IC are Wessel's rule of three or the Rome criteria, of which the latest revisions emphasize the inconsolable nature of crying rather than the duration of crying [7]. NC and IC share similarities, such as unexplained inconsolable crying, but the former occurs exclusively at night. In modern medicine, IC is considered a behavioral condition that can be resolved on its own, while NC in traditional medicine is classified as a disorder that requires treatment [8-10].

Inconsolable crying of infants can cause significant stress and can have an adverse physiological, emotional, and psychological impact on both infants and their parents [7, 11, 12]. In traditional Chinese medicine (TCM), herbal medicine, tuina therapy, and acupuncture according to pattern identification are used for NC and most symptoms improve within 2 weeks during treatment [4, 13]. Modern medicine assumes that IC has multifactorial causes, with maternal, paternal, infant, and environmental factors all playing a role. Due to the multifactorial nature of IC, there is currently no established standard for its management and the available treatment options mainly focus on alleviating symptoms. Western medicine recommends interventions such as nursing, feeding, medication, or probiotic supplementation, but these therapies have not been widely recognized as having evidence-based support and have demonstrated limited efficacy [14-16].

As a safe approach to treating inconsolable crying, parents and families are increasingly accepting manual therapy and the approach has been integrated into the healthcare sector [17]. In traditional medicine, tuina or chuna (Korean) is a representative manual therapy. Tuina or chuna is a manipulation treatment that focuses on biomechanical function, diagnostics, pathology, and theories to balance orthopedic structure and function. This technique works by targeting the meridians throughout the body, correcting structural displacements, and recommending exercises based on symptoms and functional assessments. Based on these characteristics, tuina or chuna, which not only alleviates symptoms of NC but allows the growth and development of infants, has been used in NC [18, 19]. The applications of manual therapy in modern medicine are diverse and include techniques such as baby massage, chiropractic, osteopathy, spinal manipulation, and craniosacral therapy. While studies on manual therapy and IC have shown positive results that support its moderately safe use, there is currently no consensus on the most effective manual therapy approach for this condition [7].

To date, a total of three systematic reviews on manual therapy for crying infants, one examining NC and two IC have

been performed [4, 17, 20]. In the review of NC studies, only two randomized controlled trial (RCT) studies were included in the review. Both IC reviews have had a small number of RCT studies included; of these one was a review of crying with obvious causes, including colic and other aftereffects. Additionally, a meta-analysis was conducted using both IC reviews, and a limitation was raised such that the intervention was not subdivided to include manual therapy interventions in the studies in which the meta-analysis was performed.

The purpose of this systematic review was to examine and compare the efficacy of manual therapy in infant crying, a common symptom of NC and IC. We also provide a review of meta-analyses of studies evaluating the efficacy of manual therapy for the treatment of NC and IC. The meta-analysis stratified patients according to intervention to increase the precision of the review.

## MATERIALS AND METHODS

### 1. Inclusion and exclusion criteria

#### 1) Study types

Only parallel-group RCTs evaluating the efficacy of manual therapy for the treatment of NC and IC were included. We excluded cross-over studies to reduce the risk of potential bias. There were no limitations in the publication language of the study.

#### 2) Participant types

Studies involving infants and children who were assessed by clinicians as experiencing crying events, defined as 'nocturnal crying', 'crying excessively', 'night crying', or 'infantile colic', were included.

In the NC analysis, all definitions of unexplained crying were eligible for inclusion in this review. Children of all ages, especially infants and toddlers, were included. Children with colic were excluded unless the study indicated that the time of day at which the colic occurred was at night or during the night.

In IC, only infants with colic aged 0 to 25 weeks were included. The infants with colic were assessed by the physicians and were defined as 'crying excessively'. As there is no consensus on the criteria for excessive crying, we accepted all definitions of excessive unexplained crying for inclusion in this review.

### 3) Types and controls of intervention

For treatment interventions, studies that included active interventions consisting of manual therapies of tuina (or chuna), massage, chiropractic, osteopathy, and acupressure were included for the treatment of infants with NC and IC. As control interventions, all types of controls that included no treatments were included. However, studies using manual therapy as a control were excluded.

### 4) Outcomes measures

NC is a concept that appears mainly in Asian countries, and the total effective rate (TER) was selected as the outcome index because most of the related studies were conducted in China. In NC, the primary outcome was an improvement in the clinical symptoms of NC after treatment, measured using TER. In IC, the change in hours of crying per day and the mean crying time per day were the primary outcomes. The secondary outcome was the infantile colic score (ICS).

## 2. Literature search

We comprehensively searched the following six electronic databases from their inception date to July 2022: Medline (via PubMed), EMBASE (via Elsevier), Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Research Information Sharing Service, and Oriental Medicine Advanced Searching Integrated System. In addition, we reviewed the reference lists of the relevant studies and used Google Scholar to include as many eligible studies as possible. We set the search strategy as comprehensively as possible after consultation with pediatric specialists. The detailed search strategies for each database and the search results are presented in the [Supplementary Table S1-S6](#). Searches were performed without restriction by year.

## 3. Data selection and extraction

All studies identified from the databases and from other sources were imported into an Excel 2016 worksheet (Microsoft, Redmond, WA, USA). After the duplicates were removed, the titles and abstracts of the articles were reviewed for the first inclusion round. For the initially included studies, the full texts were retrieved and reviewed to confirm final inclusion. For the finally included studies, we extracted the following basic information (author and country, publication year, study setting),

sample size, details of participants, treatment and control intervention, details of the manual therapy used, outcome measures, and results. Study selection and data extraction were independently conducted by two researchers (UJ, HI) and any disagreement was resolved by discussions with another independent researcher (KH). If the data were ambiguous or insufficient, we contacted the authors of the included studies by email, if possible.

## 4. Quality/risk of bias assessment of the included studies

The quality of the included studies was evaluated using the Cochrane Collaboration risk of bias (ROB) tool; each domain was classified as high risk (H), low risk (L), or unclear (U). Two researchers (UJ, HI) assessed each study and discussed the results. If there was any disagreement, a third researcher (KH) made the final decision as an independent arbitrator. The following seven domains were evaluated: sequence generation, allocation concealment, blinding of participants and research personnel, blinding of outcome evaluation, completeness of outcome data, selective outcome reporting, and other biases. For blinding of participants and research personnel in the studies, considering that the participants receiving the intervention were infants or children and all interventions consisted of manual therapy, we evaluated the study as low risk when it clearly stated that the parents of the participants were blinded.

## 5. Data analysis

Descriptive analysis of the details of the participants, treatment and control interventions, and results of the included studies were conducted. In particular, the meta-analysis was performed using Review Manager software (version 5.4; Cochrane, London, United Kingdom) if two or more studies used the same type of treatment and control intervention with the same outcome measures. Continuous and binary outcomes were evaluated, and the data are presented as the mean difference or standardized mean difference (SMD) and risk ratio (RR) with their 95% confidence intervals (CI). Heterogeneity between the studies was assessed using both the  $\chi^2$  test and the  $I^2$  statistic; specifically,  $50\% \leq I^2 < 75\%$  and  $I^2 \geq 75\%$  were considered to indicate substantial and considerable heterogeneity, respectively.

## RESULTS

### 1. Study selection

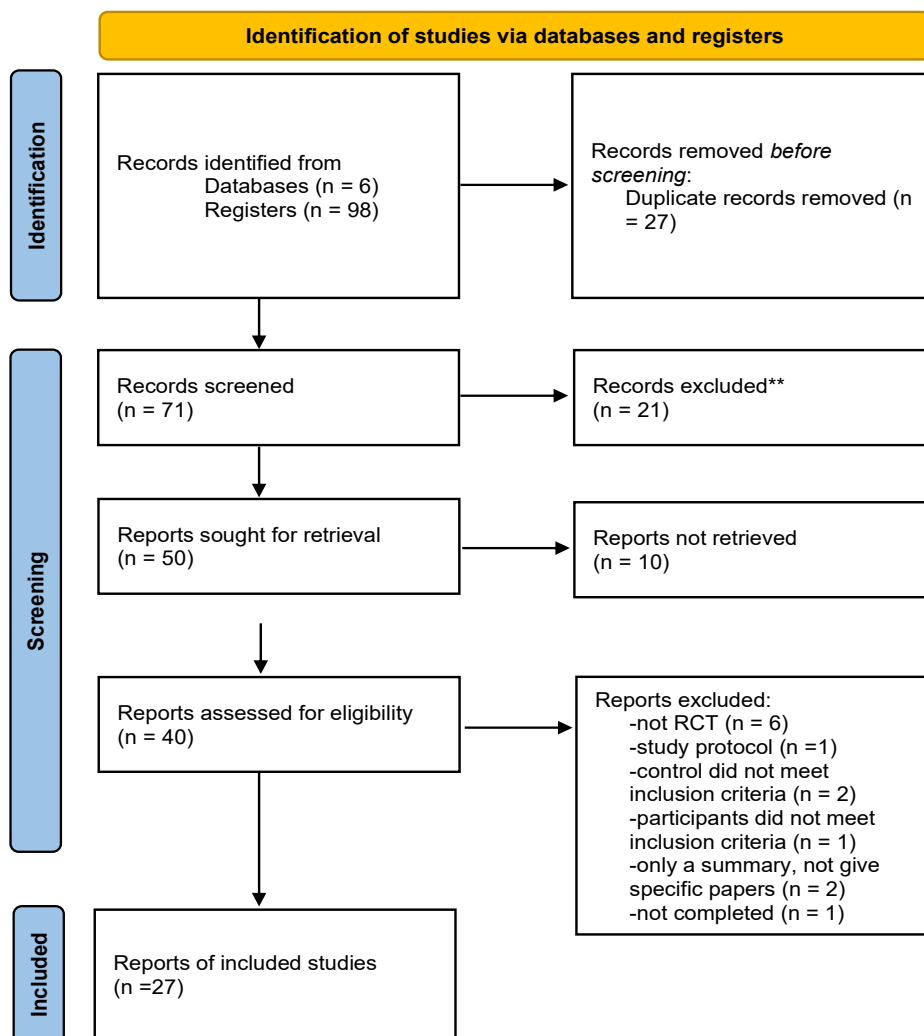
Initially, as the clear distinction between NC and IC was ambiguous, we conducted a literature search for both two simultaneously, and finally selected the RCT and then divided the participants into the NC and IC groups. Our search terms yielded 98 records: 25 from the Cochrane Library, five from EMBASE, and 41 from PubMed. Twenty-five patients were obtained from CNKI. Two studies were extracted from Korean databases. After removing duplicate studies, 27 records were screened. Based on the respective titles and abstracts, 31 records were excluded. We retrieved and reviewed 40 full articles. After a full-text review, 13 records were excluded. six articles were not randomized clinical trials, one article was a protocol, three did not meet

the inclusion criteria for several reasons, and only two studies provided a summary but did not publish a full paper, and one article was incomplete. In total, we included 27 RCTs (Chinese:  $n = 13$ ; English:  $n = 14$ ), comprising 13 NC and 14 IC studies (Fig. 1).

### 2. Study characteristics

#### 1) Study settings

In the NC group, all included studies were published in Chinese in China from 2005 to 2022. In the IC group, all included studies were published in English: four were conducted in Iran, three were conducted in Turkey, and two were conducted in Denmark and the UK, respectively. One study each was conducted in Spain, Norway, and Finland, respectively.



**Figure 1.** Flow chart showing the number of studies included and excluded from the systematic review.



**2) Participants**

In the NC group, the ages of the children ranged from 1 month to 6 years old. In the IC group, the ages of the infants ranged from 1 to 3 months. The mean age and duration of the disease were not calculated, as some studies did not provide the relevant information.

**3) Intervention**

In the NC group, several types of interventions were applied. Tuina was used in seven studies. Tuina was combined with TCM in five studies. Tuina with active controls such as chiropractic, moxibustion, patching, ear compression, and Western drugs were used in five studies. Only one study used chiropractic therapy alone as an intervention. In the control group, six studies with TCM were the most common. In two studies, western drugs were used in the control group. In the remaining studies, various controls such as abdominal hot compresses, patching, ear compression, psychological counseling, and moxibustion were used.

In the IC group, massage and chiropractic therapy were mainly used as an intervention in each of the five studies. Osteopathic therapy and reflexology were used in two studies, respectively. Acupressure was used in one study. Seven studies without treatment in the control group were the most common and three studies used rocking as a control intervention. Dimethicone, a crib vibrator, placebo, and routine training were used in one study each.

**4) Outcome measures**

In NC, with regard to the assessment of the outcomes, all studies reported the TER. For assessment with the TER, participants were classified according to the degree of improvement in crying symptoms as “cured” (N1), “markedly improved” (N2),

“improved” (N3), or “non-responder” after treatment. The TER was calculated using the following formula:  $TER = (N1 + N2 + N3)/total\ sample\ size$ . However, if “treated” (N1) was not mentioned, it was classified as N2, N3, and “non-responder”, and the TER formula was  $TER = (N2 + N3)/total\ sample\ size$ . In the IC group, except for one study, the crying time was used as an outcome index. Crying time was defined as the total crying time, the mean change, and the reduction rate of the crying time. Subsequently, sleeping time, ICS, and number of crying episodes were used.

**3. Quality/risk of bias for the included studies**

Fig. 2 and 3 shows the details of the ROB for all studies. Except for ten studies, all reported sequence generation using adequate methods such as computer program random sequencing, random number generators, and blocked randomization. With regard to the allocation concealment methods, only nine studies were performed using the sealed envelope method to determine the group, with a low ROB. However, in the NC group, the 13 studies did not report on the method of concealment of allocation. Regarding blinding of the participants’ parents, only four studies in the IC group were rated as low risk and all NC studies were rated as high risk. Seven RCTs only in the IC group clearly reported that the statistician was blinded and all NC studies did not describe blinding of outcome assessment. Regarding incomplete outcome data, 21 RCTs were evaluated as having low risk because they had no missing data or few missing data, and the number and reason for attrition were clearly reported in each group and were similar between the groups. The remaining studies were considered high-risk and were all IC studies. Regarding selective outcome reporting, if it was not possible to locate and examine the protocols of any of the selected studies,

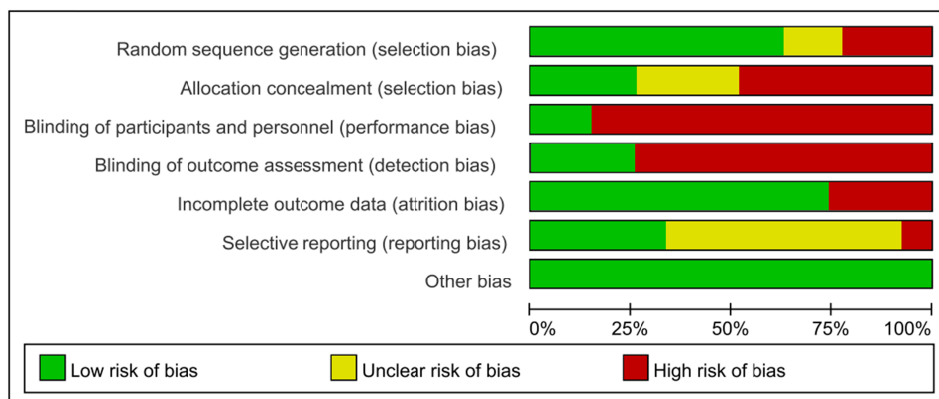


Figure 2. Risk of bias.

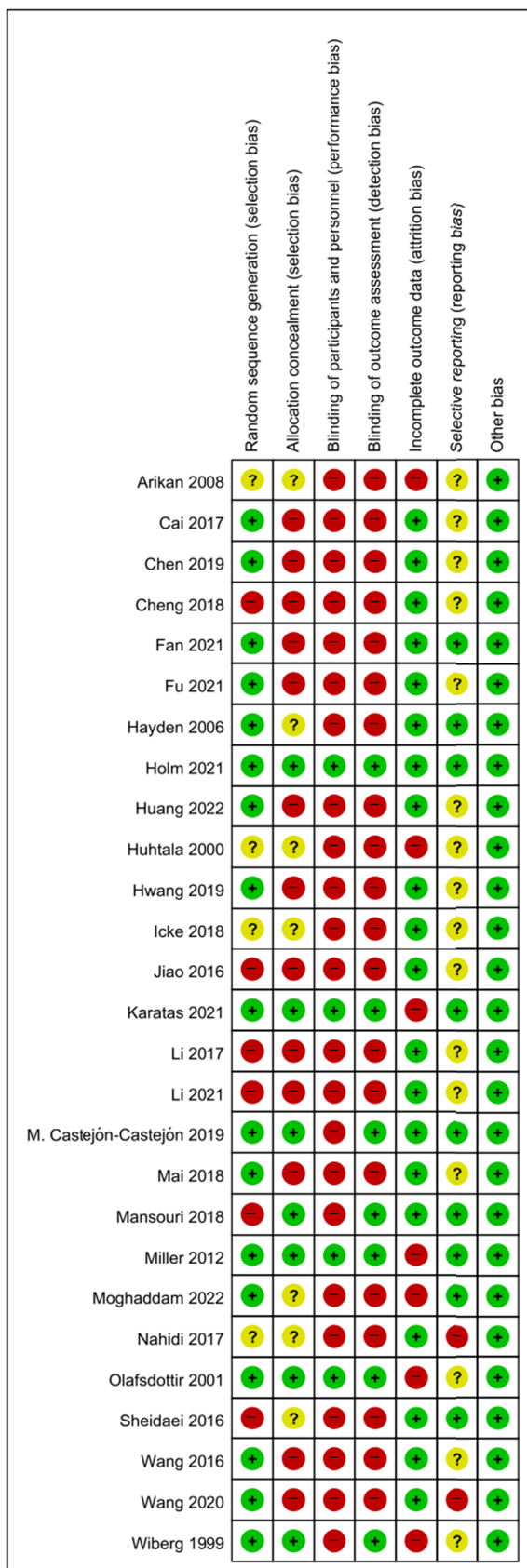


Figure 3. Risk of bias (graph).

in response, we discerned ROB by analyzing the methods that were reported in each study. A total of nine RCTs were rated as low risk. Other sources of bias, for all studies, were evaluated as low risk.

#### 4. Intervention effects

The main results of the included studies are summarized in Table 1 [21-33] and Table 2 [34-47]. For the 27 studies included in the table, the results of the intervention were classified into four categories: positive (P), negative (N), neutral (NS), and non-assessable. A meta-analysis was conducted on the effect of the sole interventions of tuina, chiropractic manipulation, and massage.

##### 1) Meta-analysis of the TER outcomes on tuina therapy

A total of 13 studies in NC investigated the effectiveness of tuina massage in NC TER. In six RCTs involving seven trials with 616 participants, the meta-analysis showed favorable effects of tuina therapy on NC TER outcomes compared to the control group (RR: 1.20 [95% CI 1.05 to 1.37],  $p = 0.007$ , Fig. 4). The  $I^2$  statistic showed substantial heterogeneity ( $I^2 = 61\%$ ).

##### 2) Meta-analysis of the change in crying time with the chiropractic intervention

A total of four studies in the IC investigated the effectiveness of chiropractic interventions in modifying crying time. In the four RCTs involving 351 participants, the meta-analysis showed favorable effects of chiropractic therapy on the change in IC crying time compared with the control group (SMD: -0.83 [95% CI -1.61 to -0.06],  $p = 0.04$ , Fig. 5). The statistic  $I^2$  showed substantial heterogeneity ( $I^2 = 66\%$ ).

##### 3) Meta-analysis of total crying time using the chiropractic intervention

A total of three IC studies investigated the effectiveness of chiropractic manipulation on total crying time. In the three RCTs involving 327 participants, a meta-analysis of the change in IC crying time showed that chiropractic therapy was more effective than that in the control group (SMD: -0.15 [95% CI -0.63 to 0.34],  $p = 0.55$ , Fig. 6). The  $I^2$  statistic did not indicate heterogeneity ( $I^2 = 0\%$ ). However, there was no statistically significant difference in the change in the overall crying time of the IC group.

**Table 1. Summary of the NC studies included in the review**

Author, year	Sample size (M/F)	Types of disease	Manual therapy group (No. of participants)	Control group (No. of participants)	Outcome measures	Results
Jiao 2016 [21]	132 (66/66)	Hyperactivity of heart-fire	Tuina (44)/tuina + patching (44)	Patching (44)	1) TER** 2) Tongue coating	1) P/P 2) N/P
Wang 2015 [22]	70 (35/35)	NR	Tuina + TCM (35)	TCM (35)	TER*	P
Cai 2017 [23]	60 (33/27)	NR	Tuina + western drugs (30)	Western drugs (30)	TER**	P
Li 2017 [24]	100 (52/48)	NR	Tuina (50)	TCM (50)	TER**	P
Cheng 2018 [25]	86 (41/45)	NR	Tuina + TCM (43)	TCM (43)	TER**	P
Mai 2018 [26]	200 (114/86)	NR	Tuina + TCM (100)	TCM (100)	1) TER* 2-1) Number of night crying 2-2) Total sleep time	1) P 2-1) P 2-2) P
Hwang 2019 [27]	58 (31/27)	NR	Tuina (29)	TCM (29)	1) TER* 2) TCM 2-1) Main symptom score 2-2) Secondary symptom score 3) BISQ 3-1) Sleep duration (night-time) 3-2) Sleep duration (day-time) 3-3) Night-time awakening 3-4) Number of night waking	1) P 2-1) P 2-2) P 3-1) P 3-2) P 3-3) P 3-4) P
Chen 2019 [28]	65 (31/34)	Nocturnal crying of stunted children	Tuina + ear compression (32)	Ear compression (33)	1) Sleep duration 2) Number of night crying 3) TER**	1) P 2) P 3) P
Wang 2020 [29]	60 (32/28)	Spleen cold qi stagnation	Tuina (20)/tuina + moxibustion (20)	Moxibustion (20)	1) Clinical efficacy 1-1) Cure rate 1-2) TER* 2) Main symptom score 3) Secondary symptom score	1-1) N/P 1-2) NS/P 2) N/P 3) N/P
Fan 2021 [30]	90 (45/45)	Spleen cold qi stagnation	Wenzhong Jianpi tuina (30)/conventional tuina (30)	Personal counselling (30)	1) TER* 2-1) The scores of overall symptoms 2-2) The scores of main symptoms 2-3) The scores of minor symptoms	1) P/P 2-1) P/P 2-2) P/P 2-3) P/P
Fu 2021 [31]	90 (47/43)	Spleen cold qi stagnation	Tuina + TCM (45)	TCM (45)	1) TER** 2) TCM 3) BISQ 3-1) Sleep duration (night-time) 3-2) Sleep duration (day-time) 3-3) Number of night waking 3-4) Night-time awakening	1) P 2) P 3-1) P 3-2) NS 3-3) P 3-4) P
Li 2021 [32]	42 (19/23)	NR	Tuina + TCM (21)	TCM (21)	TER**	P
Huang 2022 [33]	440 (218/222)	NR	Tuina (110)/chiropractic therapy (110)/tuina + chiropractic therapy (110)	Abdominal hot compress (110)	1) TER* 2-1) Modified PSQI 2-2) Modified SDSC 3-1) The spending time to fall asleep 3-2) Total sleep time 3-3) Number of night crying 4) TCM 4-1) Crying at night 4-2) Anorexia 4-3) Irritability	1) NS/NS/P 2-1) P/P/P 2-2) P/P/P 3-1) P/P/P 3-2) NS/NS/P 3-3) P/P/P 4-1) NS/NS/P 4-2) NS/NS/P 4-3) NS/NS/P

TCM, traditional Chinese medicine. \*TER = N1 + N2 + N3/total sample size, \*\*TER = N2 + N3/total sample size.

**Table 2. Summary of the IC studies included in the review**

Author, year	Sample size (M/F)	Manual therapy group (No. of participants)	Control group (No. of participants)	Outcome measures	Results (○/△)
Wiberg 1999 [34]	41	Chiropractic spinal manipulation (25)	Dimethicone (16)	Mean change in crying time	P
Huhtala 2000 [35]	58 (32/26)	Massage (28)	A crib vibrator (30)	Mean decrease total crying	NS
Olafsdottir 2001 [36]	72	Chiropractic spinal manipulation (41)	Placebo (31)	Length of crying	NS
Hayden 2006 [37]	25	Osteopathic therapy (13)	No treatment (12)	1) Mean change in crying time 2) Mean change in sleeping time	1) P 2) P
Arikan 2008 [38]	70 (42/28)	Chiropractic spinal manipulation (35)	No treatment (35)	Length of crying	P
Miller 2012 [39]	78	Chiropractic spinal manipulation (blinded) (30)/chiropractic spinal manipulation (unblinded) (26)	No treatment (22)	Mean change in crying time	1) P/P
Sheidaei 2016 [40]	100 (52/48)	Massage (50)	Rocking (50)	1) Length of crying 2) Length of sleep 3) Number of crying 4) Infant colic severity	1) P 2) P 3) P 4) P
Nahidi 2017 [41]	100 (52/48)	Massage (50)	Rocking (50)	1) Number of crying 2) Length of crying 3) Length of sleeping 4) Score of cry severity	1) P 2) P 3) P 4) P
Icke 2018 [42]	64 (43/30)	Reflexology (31)	No treatment (33)	ICS	P
Mansouri 2018 [43]	100 (48/52)	Massage (50)	Rocking (50)	1) Number of crying 2) Length of crying 3) Length of sleep	1) P 2) P 3) P
Castejón-Castejón 2019 [44]	54 (27/27)	Osteopathic therapy (29)	No treatment (25)	1) Lengths of crying 2) Lengths of sleep 3) Colic severity (ICSQ)	1) P 2) N 3) P
Holm 2021 [45]	185 (90/95)	Chiropractic spinal manipulation (96)	No treatment (89)	1) Length of crying (95% CI) 2) Numbers needed to treat based on improvement of at least 1 h of crying 3-1) Length of sleep (95% CI) 3-2) Hours when awake and content (95% CI)	1) NS 2) NS 3-1) NS 3-2) NS
Karatas 2021 [46]	40 (25/15)	Reflexology (20)	No treatment (20)	1) ICS 1-1) Cow's milk/soy protein intolerance 1-2) Immature gastrointestinal system 1-3) Immature central nervous system 1-4) Difficult infant temperament 1-5) Problem infant + parent-infant interaction 2) Length of crying	1-1) P 1-2) P 1-3) P 1-4) P 1-5) P 2) P
Moghaddam 2022 [47]	114 (59/55)	Massage (38)/acupressure (38)	The routine training (38)	1) ICS 2-1) Length of sleep 2-2) Length of crying	1) NS/P 2-1) P/P 2-2) P/P

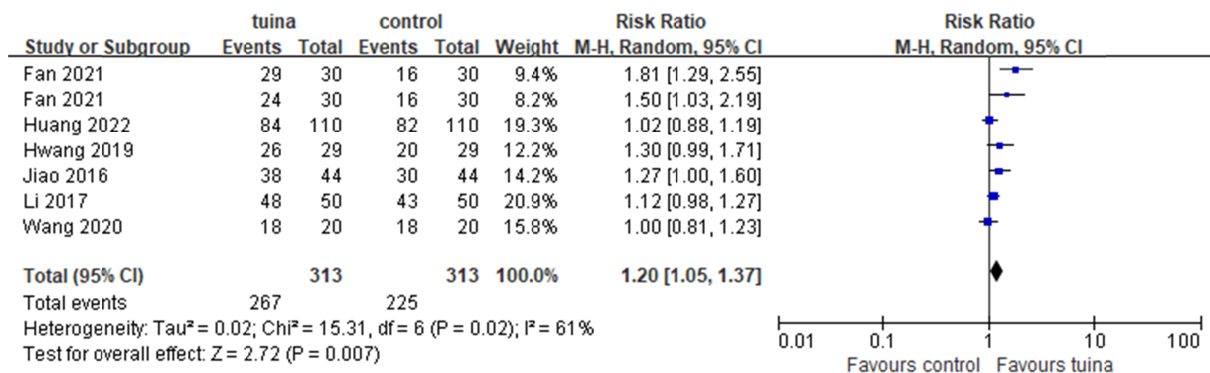


Figure 4. Meta-analysis of TER about tuina therapy.

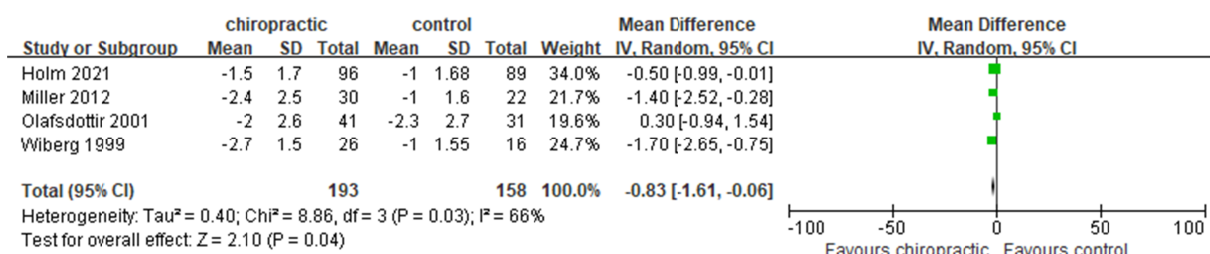


Figure 5. Meta-analysis of crying time change about chiropractic.

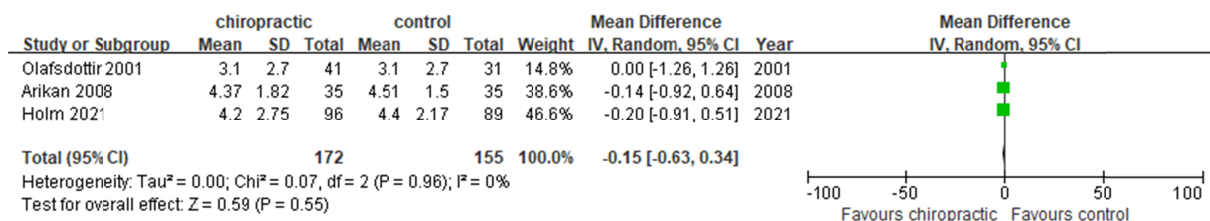


Figure 6. Meta-analysis of total crying time about chiropractic.

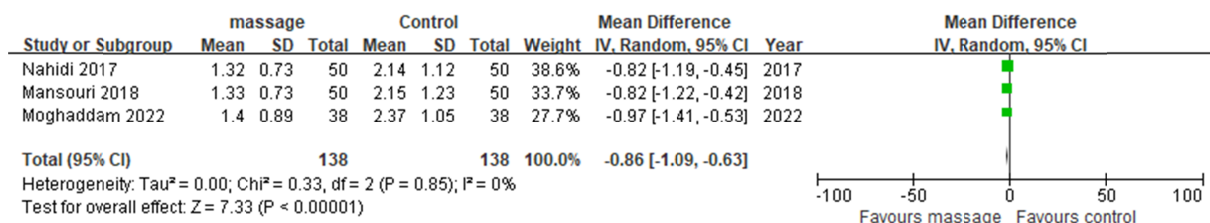


Figure 7. Meta-analysis of total crying time about massage.

4) Meta-analysis of total crying time following massage interventions

A total of three studies in the IC group investigated the effectiveness of massage on total crying time. In the three RCTs involving three trials with 276 participants, the meta-analysis

showed favorable effects of massage on the total crying time of IC compared with the control group (SMD: -0.86 [95% CI -1.09 to -0.63], p < 0.00001, Fig. 7). The I<sup>2</sup> statistic did not reveal heterogeneity (I<sup>2</sup> = 0%).

## 5. Adverse events

Only one study reported adverse effects (AEs) in infants with NC [33]. In a study by Huang, the four groups reported the occurrence of AE such as redness and swelling, skin erosion, pain, and fainting. In addition, the rate of AEs in the control group was higher than in the treatment group. Four studies reported that AEs occurred in the control group in infants with IC [34, 37, 39, 45]. These four studies reported AEs indicative of worsening symptoms, such as increased crying in the control group. No AEs were reported in three studies among infants with NC [21, 30, 31] and in the four studies evaluating IC [40, 43, 44, 46]. The other 15 studies (9 NC and 6 IC) did not mention any AEs.

## DISCUSSION

Crying is a natural and physiological phenomenon in the growth process of a child, although treatment is often recommended as excessive crying can not only affect the child's growth but also may reduce the quality of life of the parents who care for the child. Problems related to the crying of a child include NC and IC. The two are very similar in that the exact cause is unknown and unpredictable crying appears as the main symptom. However, NC is explained according to the theory of traditional medicine, which classifies it as a pathological disease that requires treatment. Furthermore, NC can manifest itself from newborns to children, with no specific age range, and is typically active at night. Conversely, IC, as described in modern medicine, occurs in newborns up to three months of age and is characterized by incessant crying at all times of day and night. Unlike NC, IC is considered a self-recovering behavior rather than a pathology.

In complementary alternative medicine, diseases can be treated with different interventions, including acupuncture and herbal medicine, as well as manual therapy, such as tuina, massage, and chiropractic maneuvers. In fact, previous studies have reported that several manual therapy approaches and the application of acupuncture have achieved significant results in alleviating crying symptoms in children [4, 48]. However, a systematic review on the effectiveness of tuina therapy in NC was included in only two RCTs, whereas most studies showed a limitation in terms of the risk of methodological distortion [4]. In addition, two systematic reviews evaluated the effectiveness of manual therapy on crying in infants in relation to IC, both

of which had a high risk of methodological distortion. Furthermore, one study included crying in children with identifiable causes such as irritable bowel syndrome and difficulty breast-feeding [17, 20]. Therefore, the objectives of our study were to provide an update on the evidence supporting the efficacy of manual therapy in NC and IC by supplementing the limitations of previous studies, and to compare studies evaluating patients with NC and IC.

The inclusion criteria for the participants in all IC studies were infants aged 1-3 months. However, in the NC studies, the age of the participants ranged from 1 month to 6 years and differed across studies. This difference can be attributed to the perspective of modern medicine, which considers crying episodes resolving when they begin at 15 days of age and naturally end at 3-4 months of age. Conversely, NC specifically refers to episodes of crying with unknown pathological etiology and the age limit varied between different studies. In two studies, there were no specific age inclusion criteria [22, 25], whereas some studies excluded infants aged 1-3 months from their group of participants [21, 33].

In the NC group, tuina therapy was used as an intervention in all 13 included RCTs. In the IC, infant massage therapy, such as chiropractic and nurturing touch, was used more often than tuina therapy. This difference stems from the difference in the theory underlying NC and IC. NC is a disease explained mainly by traditional medical theories in Eastern countries such as Korea and China, and tuina therapy is based on the same traditional medicine that has actively been used as a therapeutic intervention. IC is a symptom described in modern medicine, and massage, chiropractic, and osteopathic therapy are used instead of tuina therapy. Of note, tuina therapy and chiropractic manipulations share common features, such as manual treatment using hands or various devices without relying on treatments such as drugs, injections, or surgery. In the case of tuina therapy in China, this technique is rooted in meridians and acupuncture points and primarily involves massage that can be seamlessly combined with other physiotherapy or acupuncture practices. In contrast to chiropractic therapy, which focuses on spinal adjustments, this method is primarily centered around massage techniques, highlighting a distinctive approach. Chiropractic therapy involves the application of hands to the patient, followed by a rapid high velocity, with moderate amplitude aimed at the joints [49, 50].

In the outcome measures, NC adopted TER, a dichotomous outcome, in all studies. TER is calculated as a ratio of the total



number of people in each group who participated in the study, excluding those who did not achieve a therapeutic effect, and is the most commonly used outcome indicator in clinical studies of traditional medicine. However, this outcome index is a composite index; the criteria for evaluating effectiveness are often self-designed and have been described in the existing literature. Therefore, accurately assessing the effectiveness of a treatment becomes a challenge with this indicator. Conversely, IC relies on many continuous outcome indexes, such as crying time, number of crying episodes, sleep time, and ICS, and of these, the crying time was used as the most common outcome index. This is because the study applied Wagner's rule of three, which is the standard for the diagnosis of IC, or applied an empirical diagnosis of the severity of crying. This outcome index has the advantage of being able to objectively grasp the progress of IC. However, since the parents of the participating child directly recorded the crying time, there was a limitation on the possibility of bias in which blinding could not be achieved when collecting results.

AEs associated with manual therapy in the intervention group of the selected study were reported in only one study in the NC group. Symptoms of redness and swelling, broken skin, pain, and fainting were reported, and the AE ratio of the intervention group was lower than that of the control group. However, there were no reports of AE in 15 studies. In addition, if participants dropped out during the study and the cause was not accurately reported, a dropout due to side effects may be suspected, which may lead to an ROB. Therefore, it is difficult to reach a definitive conclusion about the safety of manual therapy for NC and IC.

This study had several limitations. First, it had a low level of evidence for many of the RCTs included in the review based on the Cochrane Collaboration assessment tool. Therefore, the reported data were likely to be overestimated. Second, performance bias when blinding of participants and research personnel was almost impossible due to the nature of the study whose participants were infants and children. Third, two of the four meta-analyses conducted showed statistical heterogeneity that was not low at 61% and 66%, respectively. Therefore, there was a limit to the effect size between each individual study that was somewhat inconsistent. Furthermore, compared to a previous systematic review, the interventions of the treatment group were classified in the same group given the common intervention involving manual therapy, although this allotment is limiting as it did not have a matching control group. This reduces

the internal validity of the meta-analysis results and may reduce the reliability of such results due to increased diversity.

Numerous studies were reviewed by comparing the effects on NC and IC. Manual therapy was effective for both the treatment of infants with NC and IC. However, given the inclusion of a small number of RCTs having low levels of evidence, and the lack of unity between the control interventions and the control groups, further research is required to address the impact of these limitations.

## CONCLUSION

This systematic review compared the inclusion criteria for participants, the type of manual therapy used as treatment interventions, and the outcome measures of infants with NC and IC. The review demonstrated the effectiveness of manual therapy, such as tuina, chiropractic, and massage therapy, for the treatment of infants with NC and IC. However, many of the included RCTs had a low level of evidence with no unified control group, the current evidence is insufficient to recommend manual therapy as an evidence-based treatment option at present. In the future, clinical studies must adopt a unified control group with a high level of evidence.

## DATA AVAILABILITY

The data will be made available upon reasonable request.

## AUTHORS' CONTRIBUTIONS

The study was conceptualized by UJ and HI. The study search, study screening, data extraction, and quality assessment were conducted by UJ and HI. The manuscript was drafted UJ and HI and revised by KH. All authors have read and approved the final manuscript.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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## SUPPLEMENTARY MATERIALS

Supplementary data is available at <https://doi.org/10.3831/KPI.2023.26.4.285>.

Supplementary Table S1. Search strategy in pubmed. Supplementary Table S2. Search strategy in cochrane library. Supplementary Table S3. Search strategy in embase. Supplementary Table S4. Search strategy in CNKI. Supplementary Table S5. Search strategy in RISS. Supplementary Table S6. Search strategy in OASIS.

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