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Adverse events associated with pediatric massage therapy: a systematic review

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Abbreviations:

AE – adverse events

EEG - electroencephalography

GA- Gestational age

MT- massage therapy

RCT- randomized controlled trial

VWM-Volvulus without malrotation

Table of contents summary:

Massage therapy is frequently used in children. To date, no study has systematically assessed its safety. This review reports safety of massage in children.

What is known:

- Massage therapy has been widely used for many different indications in children and adults.

- Several studies reports is efficacy, but adverse events of massage therapy is poorly investigated.

What this study adds:

-We identified a range of AEs associated with MT use, from mild to severe.

-No AE were reported when MT was provided by a registered massage therapist.

-Further research is needed to determine if the association of abdominal massage with volvulus without malrotation in preterm infants is causal.

Contribution statement: Dr Vohra and Dr Jou and Dryden conceptualized and designed the study, reviewed and critically reviewed the manuscript for important intellectual content.
Drs Karkhaneh and Zorzela and Funabashi designed the data collection instruments, collected data, carried out the initial analyses, and drafted the 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.

All data relevant to the study are included in the article or uploaded as supplementary information.

ABSTRACT

Introduction: Massage therapy (MT) is frequently used in children. No study has systematically assessed its safety in children and adolescents. We systematically review adverse events (AEs) associated with pediatric MT.

Methods: We searched seven electronic databases from inception to December 2018. We included studies if they: (i) were primary studies published in a peer-reviewed journal, (ii) involved children aged 0-18 years, and (iii) a type of MT was used for any indication. No restriction was applied to language, year of publication, and study design. AEs were classified based on their severity and association to the intervention.

Results: Literature searches identified 12,286 citations, of which 938 citations were retrieved for full-text evaluation and 60 studies were included. In the included studies, 31 (51.6%) did not report any information on AEs, 13 (21.6%) reported that no AE occurred, and 16 studies (26.6%) reported at least one AE after MT. There were 20 mild events (grade 1) that resolved with minimal intervention, 26 moderate events (grade 2-3) that required medical intervention, and 18 cases of severe AEs (grade 4-5) that resulted in hospital admission or prolongation of hospital stay; of these, 17 AE were volvulus in premature infants, four of which were ultimately fatal events.

Conclusion: We identified a range of AEs associated with MT use, from mild to severe. No AE were reported when MT was provided by a registered massage therapist. Further research is needed to determine if the association of abdominal massage with volvulus without malrotation in preterm infants is causal.

BACKGROUND

Massage therapy (MT) is one of the most popular complementary therapies in North America and has a long history of practice (1, 2). According to the College of Massage Therapists of Ontario, "Massage therapy consists primarily of hands-on manipulation of the soft tissues of the body, specifically, the muscles, connective tissue, tendons, ligaments and joints for the purpose of optimizing health. Massage therapy treatment has a therapeutic effect on the body and optimizes health and well-being by acting on the muscular, nervous and circulatory systems"(3).

Massage therapists press, rub and manipulate muscles and soft tissues of the body, often with their hands and fingers, to relieve physical dysfunction and pain, reduce stress, promote relaxation, reduce anxiety or depression, and improve general wellbeing(4, 5).

Various types of MTs have been practiced using specific techniques, including Swedish, Thai, shiatsu, tui na, connective tissue, deep tissue, myofascial, trigger point, etc. (6-8).

Massage is used in children around the world, including countries where massage is not part of their traditional medicine practices. Close to 1% of American children use MT (9). In Canada, a survey involving 979 families attending subspecialty clinics, demonstrated that the most common complementary therapy reported was massage, with 39.1% reporting use (10). In Europe, the frequency of massage use varies from 8.7 to 29% in a subpopulation of children with oncologic disorders (11). MT is frequently used in children with health problems and its use is as high as 47% in patients with neurologic disorders, 38% in patients with cardiac disorders and 34% in patients with respiratory disorders (12-14).

Despite MT's longstanding history and popularity, specific mechanisms by which massage exerts its therapeutic effects are not yet known(7, 15-17). Researchers have long been interested in MT for children's health and

wellbeing (18). A recent meta-analysis of clinical trials of MT on infants under six months of age found statistically significant effects on weight and height, improving head/arm/leg circumference, 24-hour sleep duration, lowering blood bilirubin level, and frequency of diarrhea (19). Among preterm infants, MT enhanced average weight gain and reduced hospital length of stay (20). In children 2-18 years old, MT has been shown to improve arthritis pain, muscle tone, and decrease anxiety (21). There is limited evidence supporting MT for cancer pain (22) and chronic pain in children (23).

Systematic reviews have focused on the effectiveness of pediatric MT with few attempts to investigate its safety (24, 25). While many complementary therapies are considered to be at low risk of harm, safety of health interventions should be measured, rather than assumed, especially in vulnerable populations, including children (26, 27).

The objective of this systematic review was to identify the evidence of adverse events associated with massage therapy in children.

METHODS

Searching Databases

A systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review (PRISMA) Statement and the PRISMA Harms (28, 29). In consultation with two massage therapists, a health research librarian designed a comprehensive search strategy. Seven electronic databases were searched from inception to December 2018. The databases included: Medline, EMBASE, CINAHL, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, Alt HealthWatch. No language restrictions were applied. The search strategy was adapted to follow recommendations by Golder & Loke to optimize for the retrieval of adverse effects data (30). The full Medline search strategy is available in

Appendix A.

Study Selection

Studies were eligible to be included if they: 1) were a primary study published in a peer-reviewed journal, 2) involved children from birth to 18 years of age, 3) used MT for any indication. The inclusion of studies was not limited by medical condition, training of massage provider, or the presence/absence of a comparison/control intervention. There was no restriction by study design or reporting AE. We excluded studies if they: 1) only applied light touch or 2) only used self-massage. Studies of reflexology and studies of massage for lacrimal duct obstruction were also excluded since those were not relevant to this review. Case reports were only included if they reported an AE. Two independent reviewers performed study selection and discrepancies were resolved by consensus or a third reviewer.

Data Extraction

A structured data extraction form was used to collect data from the articles. General characteristics of studies included country, study design, settings, population, age, and gender. Specific information included diagnosis/reason for seeking MT, type of MT, control group, outcome measures, AEs, time between massage and AE, MT provider, and clinical outcome after treating AE. Independent duplicate assessment was performed for both study selection and data extraction.

Data Synthesis

The data from studies were tabulated into general information and AEs tables. The Common Terminology Criteria for Adverse Events (CTCAE) scale was used to classify severity of AEs (31) (Table 1).

Table 1: Grading system for severity of adverse events (CTCAE)*

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

The severity was categorized into five *grades*, from *grade* 1 (mild, asymptomatic) to *grade* 5 (death), based on information provided by the studies. Duplicate assessment of CTCAE ratings were performed and discrepancies between two reviewers were resolved by consulting a senior reviewer.

We also classified the AEs as 'direct', if directly caused by the intervention, or 'indirect', if the intervention caused a delay in diagnosis or treatment which resulted in an adverse event (32).

Since this was a systematic review of AEs following MT, effectiveness/efficacy of MT was not assessed. We neither performed meta-analysis nor risk of bias assessment. We performed a subgroup analysis by study design

and severity of AE.

RESULTS

Comprehensive search in seven electronic databases yielded a total of 12,286 citations. Screening titles and abstracts identified 11,348 references irrelevant to the review question; 938 full text articles were retrieved for further evaluation. By using the pre-specified inclusion/exclusion criteria, 60 studies were included (Figure 1).

Included studies were published between 1991 and 2018, and were conducted in 11 countries including China (n=1), France (n=2), Germany (n=1), India (n=3), Iran (n=3), Madagascar (n=1), Malaysia (n=1), Poland (n=1), Russia (n=2), Singapore (n=1), Sweden (n=1) Switzerland (n=2), United States (n=1) and United Kingdom (n=2). Among 60 studies (n=3557), 29 studies (n=1520) were single arm experimental or case studies that received MT and 31 studies (n=2037) were controlled studies, of which almost half (n=972) have received MT and the rest (n=1065) were controls with no MT. Gestational age (GA) in the preterm infants having MT varied was from 23.5 to 37 weeks. Age of children ranged from 1 day to 18 years.

Reports of Adverse Events

Of 60 included studies, 16 (26.6%) reported AE(s), 31 (51.6%) did not mention if an AE occurred or not, and 13 (21.6%) reported that no AE occurred. Figure 1 illustrates the PRISMA flow diagram.

Of 16 studies (n=438) reporting AEs, 13 were published in English, one in Russian, and two in French. Table 2 reports the different populations and kind of MT used in each study.

Table 2: characteristics of the included studies reporting adverse effects after massage therapy

First author (Year, descending) location	Objective	Design/Setting	Population	Age	Sex, grouping	Intervention/Exposure	Control	Outcome measures	Adverse events	Reported conclusion
Patel, GM (2017), USA	A case of bruise and dry parches on face	Case report/Hospital	1 patient	6 wk	1M	Craniosacral massage for reflux	NA	NA	Bruising & bleeding from dry facial patches & multiple firm occipital subcutaneous lesions	Massage therapy was the cause of superficial bleeding. All newborns should be given prophylactic vitamin K1 shortly after birth.
Li, Z. (2015), China	A case of multiple bruises on the body	Case report/Forensic office	1 patient	5 yr	1M	Traditional Chinese massage "Ba Sha" involves pinching skins between thumb and index finger on the neck, chest, and back	NA	NA	Bruising	Traditional Chinese massage therapy may result in striking lesions of the skin which may raise concern about child abuse.
Mass, C. (2014), Germany	Assessing risk factors of volvulus without malrotation (VWM) in pre-term infants	Case-control/ University hospital	5 extreme preterm infants/25 controls	37-52 d	5F with VWM and small for GA in case; 13M with VLBW, 12 F in control	Abdominal massage on preterm infants to stimulate peristalsis	Matched infants but not exposed to massage	Last meconium evacuation, number of enemas, number of manipulation with rectal tubes, frequency of abdominal massage, number of stools	Intestinal volvulus	Infants with volvulus had significantly more frequency of rectal tube manipulations but no difference in enema, abdominal massage or defecation, massage did not show to be a risk factor for VWM.
Massodi, T. (2014), India	Assessing prevalence and risk factors of neonatal mastitis	Case series/Hospital	32	6-48 d	NS, only 15 of 32 babies had received massage	Breast massage to express the secretions and downsize breast hypertrophy	NA	NA	Mastitis	Parental counselling to prevent breast massage in babies for breast hypertrophy which is benign and settled spontaneously in most babies.
Zweifel, N. (2013), Switzerland	Case series of preterm infants with intestinal volvulus with necrotic small intestine	Case series/Hospital	3 preterm infants	26, 27, 32 d	NS, 3 had volvulus without malrotation	Abdominal massage or pelvic rotation to stimulate peristalsis by nurses	NA	NA	Intestinal volvulus	Long-lasting rotary forces generated by massaging can reach to small bowel through very thin abdominal wall leading to volvulation: "manufactured" volvulus.
Rudnicki, J. (2012), Poland	Assessing direct effects of massage on physiological	Single-arm experime	39 preterm infants	18-24 days	NS, 22 infants 28-37 wk, and 17 infants >32 wk	Shantal massage (stroking & rubbing) in entire body for	NA	aEEG, SaO2, Pulse Rate, CCFM, and cerebral blood flow	Oxygen desaturation <85%	Monitoring aEEG, SaO2, and pulse increases the safety of massage in preterm infants

	parameters of preterm Infants	ntal /Hospital			GA	~17 minutes		assessed by the Doppler technique		one might be desaturation below 85%.
Guilbert J. et al. (2007), France	A case of severe epilepsy after pediatric massage with topical oil containing Camphor	Case report/Hospital	1	4 mo	1F	Abdominal massage with anti-flatulence solution containing Camphor	NA	NA	Status epilepticus	Topical lotions should be free of any toxic chemicals such as Camphor; clinicians must keep this in mind examining similar cases.
Razafimahandry, H.J. (2007), Madagascar	Reporting series of humeral osteomyelitis due to Staphylococcus aureus infection expanded by massage	Case series/University hospital	4	5-11 yr	2M, 2F	Local traditional massage	NA	NA	Spreading local infection	Traditional massage can spread the local infection and delay of treatment can lead to severe functional sequelae.
Paraskevopoulos, E. (2006), Switzerland	Two cases of intestinal volvulus in preterm infants	Case series/Hospital	2	19d,32 d	2F, both infants 27 wk GA	Intensive abdominal massage for stimulating peristalsis	NA	NA	Intestinal volvulus	Repeated intensive abdominal massage can be a risk factor for intestinal volvulus.
Solanki, K. (2005), India	Assessing transcutaneous absorption of topical oil in neonatal massage	RCT/ hospital	118 infants in 3 groups of 39, 40, 39.	Range 1-4 days; mean (SD)=1.5 (0.7)	Mean=35 wk GA	Whole body massage with 5 ml oil (Safflower and coconut) for 10 minutes 4 times a day, for 5 days by a trained person	Same massage with no oil	Serum triglycerides, fatty acids (Linoleic acid, Arachidonic acid , Alpha Linolenic acid, Docosa- hexaenoic acid)	Skin rash	Fatty acid in oil can be absorbed from the skin and change fatty acid profiles of babies. Safflower oil may cause rash in babies' skin.
Sankaranarayanan, K. (2005), India	Assessing the effects of massage with coconut or mineral oil on growth, neuro-behavior, and side effects on preterm and term infants	RCT/Tertiary care center	224 infants into 3 groups of 76, 74, and 74	2 days old	In 3 coconut, mineral and no-oil groups babies were half term (≥37 wk) and half preterm (<37 wk)	Whole body massage using mineral and coconut oil by trained person from day 2 until discharge and thereafter by trained mother until 31 days	Same massage with baby powder only	Weight, head circumference, and length of infants were measured daily until discharge and every week until 31 days	Skin rash	Massage with coconut oil improves weight gain velocity in preterm and term babies. Mild transient skin rash was observed in babies in three groups of coconut, mineral and placebo over the course of the trial.
Cullen, L.A. (2005), UK	Exploring effects of touch between parents and children with autism	Single-arm experimental/community	15 Autistic children with parents	1-9 yr, median =3	13M, 2F	1-hour whole body touch with gentle stroking weekly/8 wk by therapist and daily by parents	NA	Children response to touch	Hyperactivity	Parents consistently expressed a "sense of closeness" with their autistic children after 16-week of practice.
Bildemaz, K. (2001), France	Case series of intestinal volvulus in preterm infants	Case series/Hospital	7 preterm infants	27-29 wk	1M, 6F	Abdominal massage with lubricants/3 hours to stimulate	NA	NA	Intestinal volvulus	Abdominal wall massage identified as a risk factor for intestinal volvulus in preterm

						peristalsis				infants.
Kalinga, M.J. (1996), Singapore	A case of popliteal artery pseudo-aneurysm in a patient with multiple osteochondroma	Case report/Clinic	1 patient	16 yr	1M	Local massage on bone lesion by a traditional Chinese healer for 5 times	NA	NA	Popliteal artery pseudo-aneurysm	No massage therapy recommended over osteochondroma on distal medical aspect of femur.
Ram, S.P. (1994), Malaysia	A case of bilateral hematoma testes	Case report/Clinic	1 patient	1 d	1M, born at home	Local traditional massage and warm sand bag on hydrocele	NA	NA	Hematoma/swelling of testicles	Any manipulation of infant scrotum can traumatize the testes or blood vessels.
Medvedev, E. (1994), Russia	A case of acute unilateral neurosensory hearing loss after massage therapy	Case report/Clinic	1 patient	14 yr	1M with autonomic nervous system dysfunction	Local massage on neck area and trapezius muscle	NA	NA	Acute unilateral neurosensory hearing loss	Massage of trapezius muscle may have initiated vascular spasm through autonomic nervous system which caused low blood perfusion to Cochlea and acute hearing loss.

Footnote: GA: gestational age; HR: heart rate; BP: blood pressure; RR: respiratory rate; NA: not applicable; NS: not stated; RCT: randomized controlled trial; VWM: volvulus without malrotation; VLBW: very low birth weight; aEEG: amplitude-integrated electroencephalography; CCFM: color cerebral function monitor; RISS: Rice infant sensorimotor stimulation is eye-to-eye contact, auditory stimulation, cephalocaudal massage for 10 minutes, rocking or vestibular stimulation for 5 minutes; F: female; M:male; yr: year; mo: month, wk: week; d: day; TSP: Training and Support Program.

In total, 11 different types of AEs occurred in 64 individuals. Of 16 studies reporting an AE, five did not state who performed the massage therapy. Of the 11 that reported, MT was provided by trained nurses (n=2), parents/grandparents (n=1), paramedic personnel (n=1), nanny (n=1), traditional massage practitioner (n=1), and trained massage practitioner (n=5). Of all, only one study described the providers' experience or qualifications regarding massage therapy (33). In some cases, a nurse or trained massage practitioner started MT, and a parent continued the massage. None of the studies reported any AE associated with MT when it was provided by a licensed or registered massage therapist (Tables 3-5).

Indirect Adverse Event

One publication identified an indirect AE, i.e., a delay in diagnosis and/or treatment. A case report documented four children with *Staphylococcus aureus* osteomyelitis, which presented as upper arm swelling (34). The authors considered the use traditional MT for swelling a cause for delay in the diagnosis and treatment, leading to progression of the infection (Grade 3).

Adverse Events and severity

Serious AE (Grades 4-5)

Five included studies reported 18 cases of serious AEs after MT (35-39).

Seventeen pre term infants (15 females and two males) were diagnosed with intestinal volvulus without malrotation after abdominal massage. The MT were usually performed 4-8 times per day by nurses to stimulate peristalsis in preterm (27-31 week gestational age), and extremely preterm (>23.5 and <27 weeks gestational age) infants. The intestinal volvulus occurred from 13 days to 52 days after birth. Four infants died (Grade 5) and 13 survived after bowel resection surgery (Grade 4). A retrospective case control study done by Maas (28), reports five extremely pre term infants (GA 24.4 weeks) with volvulus without malrotation. Each case was

matched with five other pre term infants with similar birth weight, GA and birth year. Three of the five patients with volvulus died. Maas reports that MT was not found to be risk factor for the volvulus, as both cases and controls received massage similarly.

In addition, a serious AE also occurred in a 4-month old female who had status epilepticus due to camphor intoxication, following abdominal massage with camphor-containing lotion. She was hospitalized for 72 hours for uncontrolled seizures, where she was intubated, mechanically ventilated, and given seizure treatment (Grade 4) (Table 3).

Table 3: Severe adverse events (Grade 4-5) in pediatric massage therapy (n=18)

First author (Year), location	Indication for treatment	AE	N of events	Age/weight	Age at AE	Gender	Type of MT	MT practitioner	Outcome	Notes from the authors
Case-control										
Maas, C. (2014), Germany	To stimulate peristalsis in extremely preterm infants	VWM	5	23.6-25.4 weeks GA; 370-630 grams	37-52 d after birth	5 F	Abdominal massage 4-6 times/day	NS	3 Died (Grade 5) 2 Survived after surgery (Grade 4)	Data did not support the hypothesis that abdominal massage was a risk factor for VWM
Case series										
Zweifel, N. et al. (2013), Switzerland	To stimulate peristalsis in preterm infants	VWM	3	27-31 weeks GA; 880 grams	NS	2 F 1 M	Repeated abdominal massage multiple times a day	Nurse	3 survived after surgery (Grade 4)	There may be a causal relationship between abdominal massage and VWM; no further cases were diagnosed after the practice was discontinued
Paraskevopoulos E. et al. (2006), Switzerland	To stimulate peristalsis	VWM	2	27 weeks GA	At 19th and 32nd day after birth	2 F	Intensive abdominal massage every 3 hours	Nurse	2 survived after surgery (Grade 4)	The infants had no other risk factors other than the abdominal massage; the practice was discontinued with no further cases since
Billiemaz, K. (2001), France	To stimulate peristalsis	VWM	7	27-29 weeks GA: 660-1100 grams	Day 13-33	6 F 1 M	Abdominal massage	Health care provider	1 died (Grad 5) 6 survived after surgery (Grade 4)	No new cases of VWM were seen after the practice was discontinued
Case report										
Guilbert J. et al. (2007), France	Flatulence	Status epilepticus	1	4 months	72 hours	1 F	Abdominal massage with camphor-containing lotion	Caregiver	Hospitalized, intubated, treated for status epilepticus (Grade 4)	Other investigations were normal; the infant was extubated after three days and later discharged home with a normal neurological examination

Footnote: AE: adverse event; MT: massage therapy; VWM: volvulus without malrotation; GA: gestational age; wk: week; NS: not stated; F: female; M: male.

Moderate AEs (Grade 2-3)

There was one trial (CCT) (40), two case series (34, 41) and four case reports(42-45) from 1994 to 2017 reporting on 27 children, aged from 1-day to 16 years old. All children experienced moderate AEs including infant mastitis/abscess, osteomyelitis, popliteal artery pseudo-aneurysm, acute unilateral neurosensory hearing loss, scrotal hematoma, and oxygen desaturation. The CCT (40) assessed physiological measurements including amplitude-integrated electroencephalography (aEEG), oxygen saturation (SaO2), pulse rate, and cerebral blood flow in 39 preterm infants following whole body Shantal (stroking and rubbing whole body) massage by a therapist and the mother. They reported four cases of oxygen desaturation (<85%) requiring withdrawal from the experiment (Grade 2); no further details were provided. One case series (41) described 15 cases of neonatal mastitis following repeated massage in 15 infants aged 6-48 days; all cases needed antibiotic therapy with or without abscess drainage (Grade 3).

Three case reports of MT AE were also published: (i) a popliteal artery pseudo aneurysm after leg MT on an osteochondroma in a 16-year old male (43); (ii) acute unilateral neurosensory hearing loss after MT on the neck and trapezius muscle in a 14-year old male diagnosed with autonomic nervous system dysfunction (44); and (iii) scrotal hematoma after traditional MT with a warm sand bag on hydrocele of a 1-day old baby boy (45). The first and third cases resolved after hospitalization and appropriate surgery and second case resolved after intensive treatment plan at a hospital for 15 days and at home for seven days (Grade 3) (Table 4).

Table 4: Moderate adverse events (Grade 2-3) in pediatric massage therapy (n=26)

First author (Year), location	Indication for treatment	AE	N of events	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome	Notes from the authors
CCT										
Rudnicki, J. (2012), Poland	Assessing the physiologic effects* of MT in preterm infants	Arterial oxygen desaturation <85%	4/39	39 preterm infants, 22 <32 weeks GA and 17 ≥32 weeks GA	18 days (n=17), 24 days (n=22)	5 F	Shantal (stroking and rubbing whole body)	Therapist/mother	Withdrawn from the study (Grade 2)	No other information was given by the authors about management or resolution of this AE
Case series										
Masoodi, T. (2014), India	Breast hypertrophy (12 mastitis and 20 abscess)	Mastitis and breast abscesses	15/30 received MT to express secretions for breast hypertrophy	6-48 days	NS	NS	Repeated breast massage	NS	Resolved after antibiotic therapy/drainage of abscess (Grade 3)	Massage for neonatal breast hypertrophy should not be performed
Razafimahandry, H.J. (2007), Madagascar	Upper arms osteomyelitis (Staphylococcus aureus)	Severe infection due to delayed diagnosis (20-60 days)	4	5-11 years	NS	2 F 2 M	Traditional massage	NS	3 cases resolved after hospitalization and antibiotic therapy (Grade 3)	One case was a severely cachectic 11 year old boy diagnosed with pulmonary tuberculosis and died of septic shock five days later; no other details regarding his death was described
Case report										
Kalinga, M.J. (1996), Singapore	Swelling of right thigh due to osteochondroma	Popliteal artery pseudo-aneurysm	1	16 years	3rd session of massage	M	MT with herbal medicine (5 sessions)	Traditional Chinese Medicine practitioner	Resolved after hospitalization and surgery (Grade 3)	Diagnosis was right popliteal artery pseudo-aneurysm after the 5th session of MT. At surgery femoral artery defect was found adjacent to the osteochondroma
Medvedev, E. (1994), Russia	Autonomic nervous system dysfunction	Acute unilateral neurosensory hearing loss	1	14 years	During treatment	M	Tonic MT of the neck including trapezius muscle	NS	Recovered with hospitalization; medications plus "5 sessions of TENS** for 8th cranial nerve" (Grade 3)	The boy with ANS dysfunction received MT and developed acute unilateral neurosensory hearing loss with noise. MT stimulated the ANS and caused vascular spasm leading to decreased blood flow to the cochlea and subsequent hearing impairment
Ram, S.P. (1994), Malaysia	Hydrocele	Scrotal hematoma	1	1 day	1st day	M	Traditional MT to testes with warm sand bag	NS	Resolved after surgery (Grade 3)	None

Footnote: AE: adverse event; CCT: controlled clinical trial; MT: massage therapy; GA: gestational age; NS: not stated; F: female; M: male; TENS: transcutaneous electrical nerve stimulation; ANS: autonomic nervous system; * amplitude-integrated electroencephalography (aEEG), oxygen saturation (SaO2), pulse rate, and cerebral blood flow.

Mild AE (Grade 1)

Two RCTs (46, 47) described skin rashes after whole body massage with various oils (almond, mineral, coconut, or safflower) examining the effects of MT on growth measurements (weight, height, etc.) in 17 infants with age from 1-day to 3-days old. These mild reactions occurred in 2.5% in the first (46) and 6% in the second (47) study populations; all resolved spontaneously without discontinuation of MT or the oils (Grade 1). Two almost identical RCTs (48, 49) examined the immunogenicity of mild rubbing massage on vaccination sites among 808 and 328 infants 2-6 months old, respectively. AEs included crying, anorexia, drowsiness, vomiting, irritability, fever, pain, redness, and induration; all were mild and did not need an intervention except general health advice for vaccinated children (Grade 1). Two single-arm experimental studies, one by Cullen et al., (33) described mild hyperactivity (n=1) and the other by Beaver et al., (50) reported increased blood pressure/heart rate and decreased transcutaneous oxygen saturation (n=8) following MT. One case report by Li et al., (51) described a mild skin bruising after a MT technique involving pinching skin. All of these interventions needed minimal intervention for resolution (Grade 1) (Table 5).

Unclassified AEs

Due to insufficient information, we were unable to properly assess and rate the severity of AE reported by a CCT. Goncharove et al (52) assessed the effect of MT with a mixture of aromatic oils on CNS rehabilitation among 31 infants aged 4-18 months with perinatal hypoxic central nervous system (CNS) injury. One child (age and sex not provided) developed an "allergic reaction" (oil product not specified) and dropped out of the study (no further details were provided to allow for severity rating). The manuscript was written in Russian and author's contact information was not available (Table 5).

Table 5: Mild adverse events (Grade 1) in pediatric massage therapy +unclassified severity (n=20)

First author (Year), location	Indication for treatment	AE	N of events	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome	Notes
RCT										
Solanki, K. (2005), India	Examining MT with oil on growth and fatty acid profile of the infant	skin rash	3/118	1-3 days	3rd and 4th days	47 F 71 M	Massage with safflower oil for 10 min, 4 times/day over 5 days	Trained massager	Resolved spontaneously (Grade 1)	The rash resolved without treatment in 1-2 days despite continuing the oil massage
Sankaranarayanan, K. (2005), India	Examining MT with oil on weight and growth and AE	skin rash	14/224	2 days	NS	NS	Massage 5 minutes 4/day with coconut/mineral oil or no oil	Trained person and mother	Resolved spontaneously (Grade 1)	Massage in hospital and home continued for 30 days; mild rash occurred equally in all groups, coconut oil (n=5), mineral oil (n=5), and placebo (n=4), and did not require discontinuation of massage
Single-arm experimental										
Cullen, L.A.(2005), UK	Examining MT on communication of autistic child	Worsened hyperactivity	1	NS	After 24 hours	M	1-hour weekly MT for 8 times by massager and daily by parent	Therapist and parents	No major complication (Grade 1)	Eight other participants (2-13 years old, all with autism) who completed the study over eight weeks reported “no obvious negatives”
Case report										
Patel, GM (2017), USA	Examining of MT for reflux	Bruising and dry patches on face	1	6 weeks	3 days after MT	M	Craniosacral massage	Not reported	No major complication (Grade 1)	Vitamin K deficiency bleeding was confirmed after rapid elevation of International correction ratio (INR); the craniosacral massage therapy was the cause of his superficial bleeding
Li, Z. (2015), China	Vomiting (repeated)	Bruising	1	5 years	NS	M	Traditional Chinese massage therapy (Ba sha)	Grandmother/mother	Bruising was mild (Grade 1); (patient died due to strangulation)	An incidental case with multiple bruises over the chest, neck, and shoulders resulting from traditional Chinese MT (ba sha), involving pinching the skin between thumb and index finger, for vomiting. Injuries resulting from ba sha were not the cause of death

Footnote: AE: adverse event; CCT: controlled clinical trial; RCT: randomized controlled trial; MT: massage therapy; NS: not stated; F: female; M: male. * Aromatic oils included sweet marjoram, frankincense, German camomile, myrrh, benzoin, Litsea cubeba, spike lavender, and red thyme.

DISCUSSION

To the best of our knowledge, this is the first systematic review to primarily assess AEs associated with pediatric MT.

Of serious AE identified, abdominal massage to stimulate peristalsis in preterm infants has been associated with multiple reports of volvulus without malrotation. No AE were identified in association with registered or licensed MT; in trained hands, pediatric MT appears to be safe.

Volvulus without malrotation (VWM) is considered a rare event (35, 36).In an epidemiological survey in Germany, found 26 cases of VWM were identified in very low birth weight infants (VLBW) estimating a rate if 1.08 to 1.5/1000 VLBW (53). We identified 17 events of volvulus without malrotation in pre term infants on this review, mostly VLBW. In 5 VWM, the authors did not considered MT as a risk factor for the volvulus, while for the remaining 12 events, MT was considered a risk factor by authors (35). The identified cases of VWM led to a routine change in their centers to avoid abdominal massage in preterm infants due the risk of volvulus. All the authors report that changing their practice to avoid abdominal massage in preterm neonates generated no further events of VWM in their centers (35). Volvulus without malrotation is a rare condition, but seems to be associated with preterm birth (<30weeks GA) and low birth weight (<1000 g) (36, 38, 54-56). The large majority of the events reported in this review occurred in infants born at <30 weeks GA and weighted <1000g, which may be a confounder, since VLBW is consider a risk factor for VWM.

MT appears to be a common non-standardized practice in many NICUs and it remains unclear whether or not it can cause an uncommon condition such as VWM.

Others have reported findings of VWM in pre term infants. Horsch has reviewed cases of volvulus in surgical referral center over 8 years in Germany and found 3 preterm infants with VWM, of these, 1 received properistaltic abdominal massage (57). Yarkin after reviewing 2 years of data from an epidemiological survey identified that 12 of 15 cases of low birth weight (<1500g) pre term infants with VWM had abdominal

massages prior to the event, although due the uncontrolled study design they were unable to determine abdominal massage as a direct risk factor (58). Horsch and Yarkin were not included in this review because they did not look into MT specifically.

Several authors (35, 57, 59, 60) have speculated on other risk factors for VWM, including immaturity of the intestine resulting in prolonged transit times and stool retention, use of continuous positive airway pressure (CPAP) or other intensive respiratory support, and female gender. Several of these risk factors were also identified in the included reports and it makes difficult to assure causality of MT in the development of VWM, suggesting caution in the use of abdominal MT in preterm infants until further investigation can be performed.

Strengths and limitations

This review was inclusive in searching peer-reviewed publications in seven databases from inception onwards, and did not limit by language. We minimized subjective errors by independent duplicate screening, study selection, and data extraction. This SR meticulously collected data from included studies and classified severities of AEs according to well-established criteria.

We have incorporated to this reviews all relevant studies, including case reports, case series, and clinical trials in an effort to be comprehensive. In addition, we reported studies that reported if AEs occurred or not, whether they mentioned if AEs were assessed or not, except for case reports which were only included if an event was reported.

As any study, this review has limitations. The majority of the AEs, including 4 out of 5 severe AE, were described in case series/reports. Although case studies are well-recognized sources of reports on severe, unusual, and/or rare AEs, conclusions drawn from such sources are limited and do not necessarily warrant increased perception of risk unless supported by controlled studies. Additionally, given the limited information and heterogeneity of the data reported in the included studies, it was not possible to identify any conclusive association between MT and specific AEs, except for *ba sha* massage which caused a characteristic bruising

pattern in one case report (51). Lastly, we found that much of the data was inadequately collected and/or reported, contributing to difficulties in accurately assessing risk. These include lack of detailed information about MT provider training/qualifications and details about MT treatments and management of AEs. It is important to highlight that none of the studies reported AEs associated with MT provided by a licensed or registered massage therapist, although only one study reported the therapist training and qualifications.

CONCLUSIONS

We were able to identify a range of AEs associated with MT use, from mild to severe. No AE were reported when MT was provided by a registered massage therapist. Further research is needed to determine if the association of abdominal massage with volvulus without malrotation in preterm infants is causal.

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Figure 1. Prisma flow diagram

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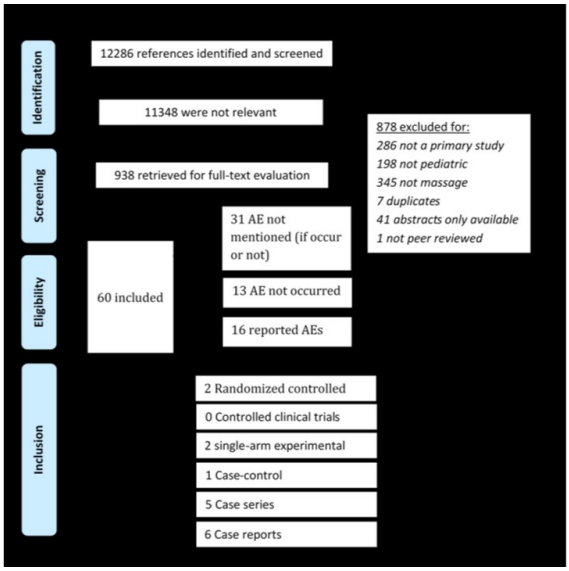
Appendix A: search strategy



338x190mm (96 x 96 DPI)

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Keywords:	Musculo-Skeletal

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Adverse events associated with pediatric massage therapy: a systematic review

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Abbreviations:

AE – adverse events

EEG - electroencephalography

GA- Gestational age

MT- massage therapy

RCT- randomized controlled trial

VWM-Volvulus without malrotation

Table of contents summary:

Massage therapy is frequently used in children. To date, no study has systematically assessed its safety. This review reports safety of massage in children.

What is known:

- Massage therapy has been widely used for many different indications in children and adults.

- Several studies reports its efficacy, but adverse events of massage therapy is poorly investigated.

What this study adds:

-We identified a range of AEs associated with MT use, from mild to severe.

- We identified an association between abdominal MT in preterm neonates and volvulus without malrotation, the causality of this association is yet to be determined, but until further data are identified this should warrant extreme causation on the use of abdominal massage in preterm neonates.

Contribution statement: Dr Vohra and Dr Jou and Dryden conceptualized and designed the study, reviewed and critically reviewed the manuscript for important intellectual content.
Drs Karkhaneh and Zorzela and Funabashi designed the data collection instruments, collected data, carried out the initial analyses, and drafted the 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.

All data relevant to the study are included in the article or uploaded as supplementary information.

ABSTRACT

Introduction: Massage therapy (MT) is frequently used in children. No study has systematically assessed its safety in children and adolescents. We systematically review adverse events (AEs) associated with pediatric MT.

Methods: We searched seven electronic databases from inception to December 2018. We included studies if they: (i) were primary studies published in a peer-reviewed journal, (ii) involved children aged 0-18 years, and (iii) a type of MT was used for any indication. No restriction was applied to language, year of publication, and study design. AEs were classified based on their severity and association to the intervention.

Results: Literature searches identified 12,286 citations, of which 938 citations were retrieved for full-text evaluation and 60 studies were included. In the included studies, 31 (51.6%) did not report any information on AEs, 13 (21.6%) reported that no AE occurred, and 16 studies (26.6%) reported at least one AE after MT. There were 20 mild events (grade 1) that resolved with minimal intervention, 26 moderate events (grade 2-3) that required medical intervention, and 18 cases of severe AEs (grade 4-5) that resulted in hospital admission or prolongation of hospital stay; of these, 17 AE were volvulus in premature infants, four of which were ultimately fatal events.

Conclusion:

We identified a range of AEs associated with MT use, from mild to severe. Unfortunately, the majority of included studies did not report if an adverse event occurred or not, leading to publication bias. This review reports an association between abdominal massage with volvulus without malrotation in preterm infants, it is still to be defined if this is casual or not, but our findings warrant caution in the use of abdominal massage in preterm infants until further investigation is done in the subject.

BACKGROUND

Massage therapy (MT) is one of the most popular complementary therapies in North America and has a long history of practice.[1, 2] According to the College of Massage Therapists of Ontario, "Massage therapy consists primarily of hands-on manipulation of the soft tissues of the body, specifically, the muscles, connective tissue, tendons, ligaments and joints for the purpose of optimizing health. Massage therapy treatment has a therapeutic effect on the body and optimizes health and well-being by acting on the muscular, nervous and circulatory systems".[3]

Massage therapists press, rub and manipulate muscles and soft tissues of the body, often with their hands and fingers, to relieve physical dysfunction and pain, reduce stress, promote relaxation, reduce anxiety or depression, and improve general wellbeing.[4, 5]

Various types of MTs have been practiced using specific techniques, including Swedish, Thai, shiatsu, tui na, connective tissue, deep tissue, myofascial, trigger point, etc.[6-8]

Massage is used in children around the world, including countries where massage is not part of their traditional medicine practices. Close to 1% of American children use MT.[9] In Canada, a survey involving 979 families attending subspecialty clinics, demonstrated that the most common complementary therapy reported was massage, with 39.1% reporting use.[10] In Europe, the frequency of massage use varies from 8.7 to 29% in a subpopulation of children with oncologic disorders.[11] MT is frequently used in children with health problems and its use is as high as 47% in patients with neurologic disorders, 38% in patients with cardiac disorders and 34% in patients with respiratory disorders.[12-14]

Despite MT's longstanding history and popularity, specific mechanisms by which massage exerts its therapeutic effects are not yet known.[7, 15-17] Researchers have long been interested in MT for children's health and wellbeing.[18] A recent meta-analysis of clinical trials of MT on infants under six months of age found statistically significant effects on weight and height, improving head/arm/leg circumference, 24-hour sleep duration, lowering blood bilirubin level, and frequency of diarrhea.[19] Among preterm infants, MT enhanced average weight gain and reduced hospital length of stay.

[20] In children 2-18 years old, MT has been shown to improve arthritis pain, muscle tone, and decrease anxiety.[21] There is limited evidence supporting MT for cancer pain.[22] and chronic pain in children.[23]

Most systematic reviews of pediatric massage therapy have focused on the effectiveness of MT rather than its safety.[18-21, 24-30] One systematic review included two case reports of AEs among children[8, 31]; one infant with scrotal hematoma associated with MT of a hydrocele[32] and a teenager with a popliteal artery pseudoaneurysm after MT overlying an exostosis.[33] AEs reported for adults were more diverse, including: cerebrovascular accidents, disc herniation/spinal cord injury, thromboembolism (renal, pulmonary), soft tissue trauma, leg ulcer, and genitourinary injuries.[8, 31, 34, 35] These studies demonstrated that the nature and circumstances of MT AEs for adults are quite different from pediatrics. While many complementary therapies are considered to be at low risk of harm, safety of health interventions should be measured, rather than assumed, especially in vulnerable populations, including children.[36, 37]

The objective of this systematic review was to identify the evidence of adverse events associated with massage therapy in children.

METHODS

Searching Databases

A systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review (PRISMA) Statement and the PRISMA Harms.[38, 39] In consultation with two massage therapists, a health research librarian designed a comprehensive search strategy. Seven electronic databases were searched from inception to December 2018. The databases included: Medline, EMBASE, CINAHL, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, Alt HealthWatch. We identified search terms by using key words including Massage, Adverse Effects, and Pediatrics and a combination of subject terms selected from the controlled vocabulary or thesaurus (e.g. MeSH - Medical Subject Headings, Emtree for Embase, CINAHL Headings and PsycINFO Thesaurus) with a wide range of free-text terms.

No language restrictions were applied. The search strategy was adapted to follow recommendations by Golder & Loke to

optimize for the retrieval of adverse effects data.[40] The full Medline search strategy is available in Appendix A.

Study Selection

Studies were eligible to be included if they:

1) were a primary study published in a peer-reviewed journal, primary study was defined as "*study reported directly by the researcher that conducted the study"*, rather than depending on data collected from previously done research.

2) involved children from birth to 18 years of age, 3) used MT for any indication, studies were not excluded based on conditions leading to MT. The inclusion of studies was not limited by medical condition, training of massage provider, or the presence/absence of a comparison/control intervention. There was no restriction by study design or reporting AE. We excluded studies if they: 1) only applied light touch or 2) only used self-massage, 3) grey literature. Studies of reflexology and studies of massage for lacrimal duct obstruction were also excluded since those were not relevant to this review. Case reports were only included if they reported an AE. Two reviewers performed study selection, independent and in duplicate, and discrepancies were resolved by consensus or a third reviewer.

Data Extraction

A structured data extraction form was used to collect data from the articles. General characteristics of studies included country, study design, settings, population, age, and gender. Specific information included: indication for treatment, AE severity, N of event, age, (age/weight and age at AE for newborn babies), gender, type of MT, MT practitioner, outcome with severity grade, and notes from the authors. Independent duplicate assessment was performed for both study selection and data extraction.

Adverse events were defined as per the Cochrane handbook as: ´adverse event is an unfavorable or harmful outcome that occurs during, or after, the use of a drug or other intervention, but is not necessarily caused by it'.[41]

Data Synthesis

The data from studies were tabulated into general information and AEs tables. The Common Terminology Criteria for Adverse Events (CTCAE) scale was used to classify severity of AEs.[42] (Table 1)

Table 1: Grading system for severity of adverse events (CTCAE)*	
Grading	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
*CTCAE: Common Terminology Criteria for Adverse Events	

The severity was categorized into five *grades*, from *grade* 1 (mild, asymptomatic) to *grade* 5 (death), based on information provided by the studies. Duplicate assessment of CTCAE ratings were performed and discrepancies between two reviewers were resolved by consulting a senior reviewer.

We also classified the AEs as 'direct', if directly caused by the intervention, or 'indirect', if the intervention caused a delay in diagnosis or treatment which resulted in an adverse event.[43]

Since this was a systematic review of AEs following MT, effectiveness/efficacy of MT was not assessed. We neither performed meta-analysis nor risk of bias assessment. Subgroup analysis was done separating study designs by severity of adverse events to assess if any specific type of massage would lead to more severe events.

RESULTS

Comprehensive search in seven electronic databases yielded a total of 12,286 citations. Screening titles and abstracts identified 11,348 references irrelevant to the review question; 938 full text articles were retrieved for further evaluation. By using the pre-specified inclusion/exclusion criteria, 60 studies were included (Figure 1).

The discrepancies were discussed, and consensus was reached between the two reviewers. There were no residual

discrepancies.

Included studies were published between 1991 and 2018, and were conducted in 11 countries including China (n=1), France (n=2), Germany (n=1), India (n=3), Iran (n=3), Madagascar (n=1), Malaysia (n=1), Poland (n=1), Russia (n=2), Singapore (n=1), Sweden (n=1) Switzerland (n=2), United States (n=1) and United Kingdom (n=2). Among 60 studies with a total population of (n=3557), 29 studies (n=1520) were single arm experimental or case studies that received MT and 31 studies (n=2037) were studies a comparator/control group, of which almost half (n=972) have received MT and the rest (n=1065) were controls with no MT. Gestational age (GA) in the preterm infants having MT varied was from 23.5 to 37 weeks. Age of children ranged from 1 day to 18 years.

Studies not reporting on AE

There were 13 studies (10 RCT, 1 CCT, 2 single-arm experiments) that did not report if an AE occurred, or not, after receiving MT. Of total 878, 436 children (0 to 18 years) received MT for various reasons including infantile colic, childhood eczema, weight gain in preterm babies, soothing pain for heel stick, improving neurological diseases, and helping urinary tract and HIV infection.

Reports of Adverse Events

Of 60 included studies, 16 (26.6%) reported AE(s), 31 (51.6%) did not mention if an AE occurred or not, and 13 (21.6%) reported that no AE occurred. Figure 1 illustrates the PRISMA flow diagram. Of 16 studies (n=438) reporting AEs, 13 were published in English, one in Russian, and two in French. In total, 11 different types of AEs occurred in 64 individuals. Of 16 studies reporting an AE, five did not state who performed the massage therapy. Of the 11 that reported, MT was provided by trained nurses (n=2), parents/grandparents (n=1), paramedic personnel (n=1), nanny (n=1), traditional massage practitioner (n=1), and trained massage practitioner (n=5). In some cases, a nurse or trained massage practitioner started MT, and a parent continued the massage. None of the studies reported any AE associated with MT when it was provided by a licensed or registered massage therapist.

Indirect Adverse Event

One publication identified an indirect AE, i.e., a delay in diagnosis and/or treatment. A case report documented four children with *Staphylococcus aureus* osteomyelitis, which presented as upper arm swelling.[44] The authors considered the use traditional MT for swelling a cause for delay in the diagnosis and treatment, leading to progression of the infection (Grade 3).

Risk of Bias Assessment

Risk of bias was not assessed for two reasons: (i) the large majority of included studies (11 of 16) were case reports and case series, for which there is no universally accepted tool to assess bias; and (ii) with regards to RCTs, there is evidence that existing ROB tools are developed with efficacy as their main focus and that other factors should be considered for assessment of adverse events.[41]Until an appropriate tool is developed, we opt to not proceed with an assessment that may itself lead to bias. At present, there is no clear guidance on how to proceed with ROB assessment on studies reporting adverse events data.[37, 41, 45-48]

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Adverse Events and severity

Serious AE (Grades 4-5)

Five included studies reported 18 cases of serious AEs after MT.[49-53]

Seventeen preterm infants (15 females and two males) were diagnosed with intestinal volvulus without malrotation after abdominal massage. The MT were usually performed 4-8 times per day by nurses to stimulate peristalsis in preterm (27-31-week gestational age), and extremely preterm (>23.5 and <27 weeks gestational age) infants. The intestinal volvulus

occurred from 13 days to 52 days after birth. Four infants died (Grade 5) and 13 survived after bowel resection surgery (Grade 4). A retrospective case control study done by Maas,[49] reports five extremely preterm infants (GA 24.4 weeks) with volvulus without malrotation. Each case was matched with five other preterm infants with similar birth weight, GA and birth year. Three of the five patients with volvulus died. Maas reports that MT was not found to be risk factor for the volvulus, as both cases and controls received massage similarly.

In addition, a serious AE also occurred in a 4-month old female who had status epilepticus due to camphor intoxication, following abdominal massage with camphor-containing lotion. She was hospitalized for 72 hours for uncontrolled seizures, where she was intubated, mechanically ventilated, and given seizure treatment (Grade 4) (Table 2).

Table 2: Volvulus without malrotation in pediatric massage therapy (n=17)

First author (Year), location Study design	Indication for treatment	AE Severity	n event /N population	Age/weight	Age at AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Maas, C. (2014), Germany Case-control	To stimulate peristalsis in extremely preterm infants	VWM Severe	5/2	23.6-25.4 weeks GA; 370-630 grams	37-52 d after birth	5 F	Abdominal massage 4-6 times/day	NS	3 Died (Grade 5) 2 Survived after surgery (Grade 4)	Data did not support the hypothesis that abdominal massage was a risk factor for VWM; no further cases were diagnosed after the practice was discontinued
Zweifel, N. et al. (2013), Switzerland Case series	To stimulate peristalsis in preterm infants	VWM Severe	3/3	27-31 weeks GA; 880 grams	NS	2 F 1 M	Repeated abdominal massage multiple times a day	Nurse	3 survived after surgery (Grade 4)	There may be a causal relationship between abdominal massage and VWM; no further cases were diagnosed after the practice was discontinued
Paraskevopoulos E. et al. (2006), Switzerland Case series	To stimulate peristalsis	VWM Severe	2/2	27 weeks GA	At 19th and 32nd day after birth	2 F	Intensive abdominal massage every 3 hours	Nurse	2 survived after surgery (Grade 4)	The infants had no other risk factors other than the abdominal massage; the practice was discontinued with no further cases since
Billiemaz, K. (2001), France Case series	To stimulate peristalsis	VWM Severe	7/7	27-29 weeks GA: 660-1100 grams	Day 13-33	6 F 1 M	Abdominal massage	Health care provider	1 died (Grad 5) 6 survived after surgery (Grade 4)	No new cases of VWM were seen after the practice was discontinued

Footnote: AE: adverse event; MT: massage therapy; VWM: volvulus without malrotation; GA: gestational age; wk: week; NS: not stated; F: female; M: male.

Moderate AEs (Grade 2-3)

There was one non-randomized controlled trial (NRCT),[54] two case series[44, 55] and four case reports[32, 33, 56, 57] from 1994 to 2017 reporting on 27 children, aged from 1-day to 16 years old. Those children experienced moderate AEs including infant mastitis/abscess, osteomyelitis, popliteal artery pseudo-aneurysm, acute unilateral neurosensory hearing loss, scrotal hematoma, and oxygen desaturation. The NRCT[54] assessed physiological measurements including amplitude-integrated electroencephalography (aEEG), oxygen saturation (SaO2), pulse rate, and cerebral blood flow in 39 preterm infants following whole body Shantal (stroking and rubbing whole body) massage by a therapist and the mother. They reported four cases of oxygen desaturation (<85%) requiring withdrawal from the experiment (Grade 2); no further details were provided. One case series[55] described 15 cases of neonatal mastitis following repeated massage in 15 infants aged 6-48 days; all cases needed antibiotic therapy with or without abscess drainage (Grade 3).

Three case reports of MT AE were also published: (i) a popliteal artery pseudo aneurysm after leg MT on an osteochondroma in a 16-year old male;[33] (ii) acute unilateral neurosensory hearing loss after MT on the neck and trapezius muscle in a 14-year old male diagnosed with autonomic nervous system dysfunction;[57] and (iii) scrotal hematoma after traditional MT with a warm sand bag on hydrocele of a 1-day old baby boy.[32] The first and third cases resolved after hospitalization and appropriate surgery and second case resolved after intensive treatment plan at a hospital for 15 days and at home for seven days (Grade 3) (Table 3).

Table 3: Moderate to Severe adverse events in pediatric massage therapy (n=27)

First author (Year), location Study design	Indication for treatment	AE Severity	n event/N population	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Rudnicki, J. (2012), Poland CCT	Assessing the physiologic effects* of MT in preterm infants	Arterial oxygen desaturation <85% Moderate	4/39	39 preterm infants, 22 <32 weeks GA and 17 ≥32 weeks GA	18 days (n=17), 24 days (n=22)	5 F	Shantal (stroking and rubbing whole body)	Therapist/ mother	Withdrawn from the study (Grade 2)	No other information was given by the authors about management or resolution of this AE
Masoodi, T. (2014), India Case series	Breast hypertrophy (12 mastitis and 20 abscess)	Mastitis and breast abscesses Moderate	15/32 received MT to express secretions for breast hypertrophy	6-48 days	NS	NS	Repeated breast massage	NS	Resolved after antibiotic therapy/drainage of abscess (Grade 3)	Massage for neonatal breast hypertrophy should not be performed
Razafimahandry, H.J. (2007), Madagascar Case series	Upper arms osteomyelitis (Staphylococcus aureus)	Severe infection due to delayed diagnosis (20-60 days) Moderate	4/4	5-11 years	NS	2 F 2 M	Traditional massage	NS	3 cases resolved after hospitalization and antibiotic therapy (Grade 3)	One case was a severely cachectic 11-year old boy diagnosed with pulmonary tuberculosis and died of septic shock five days later; no other details regarding his death was described
Guilbert J. et al. (2007), France Case series	Flatulence	Status epilepticus Severe	1/1	4 months	72 hours	1 F	Abdominal massage with camphor-containing lotion	Caregiver	Hospitalized, intubated, treated for status epilepticus (Grade 4)	Other investigations were normal; the infant was extubated after three days and later discharged home with a normal neurological examination
Kalinga, M.J. (1996), Singapore Case report	Swelling of right thigh due to osteochondroma	Popliteal artery pseudo-aneurysm Moderate	1/1	16 years	3rd session of massage	M	MT with herbal medicine (5 sessions)	Traditional Chinese Medicine practitioner	Resolved after hospitalization and surgery (Grade 3)	Diagnosis was right popliteal artery pseudo-aneurysm after the 5th session of MT. At surgery femoral artery defect was found adjacent to the osteochondroma
Medvedev, E. (1994), Russia Case report	Autonomic nervous system dysfunction	Acute unilateral neurosensory hearing loss Moderate	1/1	14 years	During treatment	M	Tonic MT of the neck including trapezius muscle	NS	Recovered with hospitalization; medications plus "5 sessions of TENS** for 8th cranial nerve" (Grade 3)	The boy with ANS dysfunction received MT and developed acute unilateral neurosensory hearing loss with noise. MT stimulated the ANS and caused vascular spasm leading to decreased blood flow to the cochlea and subsequent hearing impairment
Ram, S.P. (1994), Malaysia Case report	Hydrocele	Scrotal hematoma Moderate	1/1	1 day	1st day	M	Traditional MT to testes with warm sand bag	NS	Resolved after surgery (Grade 3)	None

Footnote: AE: adverse event; MT: massage therapy; CCT: controlled clinical trial (non-randomized controlled trial); GA: gestational age; NS: not stated; F: female; M: male; TENS: transcutaneous electrical nerve stimulation; ANS: autonomic nervous system.

Mild AE (Grade 1)

Two RCTs[58, 59] described skin rashes after whole body massage with various oils (almond, mineral, coconut, or safflower) examining the effects of MT on growth measurements (weight, height, etc.) in 17 infants with age from 1-day to 3-days old. These mild reactions occurred in 2.5% in the first[58] and 6% in the second[59] study populations; all resolved spontaneously without discontinuation of MT or the oils (Grade 1). Two almost identical RCTs[60, 61] examined the immunogenicity of mild rubbing massage on vaccination sites among 808 and 328 infants 2-6 months old, respectively. AEs included crying, anorexia, drowsiness, vomiting, irritability, fever, pain, redness, and induration; all were mild and did not need an intervention except general health advice for vaccinated children (Grade 1). Two single-arm experimental studies, one by Cullen et al.,[62] described mild hyperactivity (n=1) and the other by Beaver et al.,[63] reported increased blood pressure/heart rate and decreased transcutaneous oxygen saturation (n=8) following MT. One case report by Li et al.,[64] described a mild skin bruising after a MT technique involving pinching skin. All these interventions needed minimal intervention for resolution (Grade 1) (Table 4).

Unclassified AEs

Due to insufficient information, we were unable to properly assess and rate the severity of AE reported by a NRCT. Goncharov et al.,[65] assessed the effect of MT with a mixture of aromatic oils on CNS rehabilitation among 31 infants aged 4-18 months with perinatal hypoxic central nervous system (CNS) injury. One child (age and sex not provided) developed an “allergic reaction” (oil product not specified) and dropped out of the study (no further details were provided to allow for severity rating). The manuscript was written in Russian and author’s contact information was not available.

Table 4: Mild adverse events in pediatric massage therapy (n=20)

First author (Year), location Design	Indication for treatment	AE Severity	n event /N population	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Patel, GM (2017), USA Case-report	Examining of MT for reflux	Bruising and dry patches on face Mild	1/1	6 weeks	3 days after MT	M	Craniosacral massage	Not reported	No major complication (Grade 1)	Vitamin K deficiency bleeding was confirmed after rapid elevation of International correction ratio (INR); the craniosacral massage therapy was the cause of his superficial bleeding
Li, Z. (2015), China Case-report	Repeated vomiting	Bruising Mild	1/1	5 years	NS	M	Traditional Chinese massage therapy (Ba sha)	Grandmother/mother	Bruising was mild (Grade 1); (patient died due to strangulation)	An incidental case with multiple bruises over the chest, neck, and shoulders resulting from traditional Chinese MT (ba sha), involving pinching the skin between thumb and index finger, for vomiting. Injuries resulting from ba sha were not the cause of death
Solanki, K. (2005), India RCT	Examining MT with oil on growth and fatty acid profile of the infant	skin rash Mild	3/118	1-3 days	3rd and 4th days	47 F 71 M	Massage with safflower oil for 10 min, 4 times/day over 5 days	Trained massager	Resolved spontaneously (Grade 1)	The rash resolved without treatment in 1-2 days despite continuing the oil massage
Sankaranarayanan, K. (2005), India RCT	Examining MT with oil on weight and growth and AE	skin rash Mild	14/224	2 days	NS	NS	Massage 5 minutes 4/day with coconut/mineral oil or no oil	Trained person and mother	Resolved spontaneously (Grade 1)	Massage in hospital and home continued for 30 days; mild rash occurred equally in all groups, coconut oil (n=5), mineral oil (n=5), and placebo (n=4), and did not require discontinuation of massage
Cullen, L.A. (2005), UK Single-arm experiment	Examining MT on communication of autistic child	Worsened hyperactivity Mild	1/15	NS	After 24 hours	M	1-hour weekly MT for 8 times by massager and daily by parent	Therapist and parents	No major complication (Grade 1)	Eight other participants (2-13 years old, all with autism) who completed the study over eight weeks reported “no obvious negatives”

Footnote: AE: adverse event; RCT: randomized controlled trial; MT: massage therapy; NS: not stated; F: female; M: male.

DISCUSSION

To the best of our knowledge, this is the first systematic review to primarily assess AEs associated withpediatric MT.

After extensive search in multiple databases and including non-English studies we identified 64 adverse events associated with pediatric massage. These events were further classified in mild, moderate and severe by our team. Moderate events were the most frequently identified, closely followed by mild and severe adverse events. Of serious AE identified, abdominal massage to stimulate peristalsis in preterm infants was identified as been associated with multiple reports of volvulus without malrotation.

Volvulus without malrotation (VWM) is considered a rare event, often associated with preterm birth (<30weeks GA) and low birth weight (<1000 g)[49, 50, 52, 66-69] We identified 17 events of volvulus without malrotation in preterm infants on this review, mostly very low birth weight (VLBW). In five VWM, the authors did not considered MT as a risk factor for the volvulus while for the remaining 12 events, MT was considered a risk factor by authors.[49] The identified cases of VWM led to a routine change in their centers to avoid abdominal massage in preterm infants due the risk of volvulus. All the authors report that changing their practice to avoid abdominal massage in preterm neonates generated no further events of VWM in their centers.[49] The large majority of the events reported in this review occurred in infants born at <30 weeks GA and weighted <1000g, which may be a confounder, since VLBW is consider a risk factor for VWM. Others have reported findings of VWM in preterm infants. Horsch has reviewed cases of volvulus in surgical referral center over 8 years in Germany and found 3 preterm infants with VWM, of these, 1 received properistaltic abdominal massage.[70] Yarkin after reviewing 2 years of data from an epidemiological survey identified that 12 of 15 cases of low birth weight (<1500g) pre term infants with VWM had abdominal massages prior to the event, although due the uncontrolled study design they were unable to determine abdominal massage as a direct risk factor.[71] Horsch and Yarkin were not included this review because they did not look into MT specifically. Several authors[49, 70, 72, 73] have speculated on other risk factors for VWM, including immaturity of the intestine resulting in

prolonged transit times and stool retention, use of continuous positive airway pressure (CPAP) or other intensive respiratory support, and female gender. Several of these risk factors were also identified in the included reports and it makes difficult to assure causality of MT in the development of VWM.

Massage therapy has been studied in children, but with the main focus of assessing efficacy, very little has been reported on adverse events.[18-21, 24-30] In contrast, adults report a wide range of adverse events associated with massage, from mild events to severe, including: cerebrovascular accidents, thromboembolism (renal, pulmonary), skin injury, leg ulcer, genitourinary injuries disc herniation, soft tissue trauma, neurologic compromise, spinal cord injury, dissection of the vertebral arteries".[8, 34, 35] Although, it is difficult to compare the different populations and co-morbidities associated with each.

Similar to other studies,[74] this review reveals a lack of adverse events reporting. The majority of included studies did not report if the intervention was associated with any adverse event or not, leading to significant reporting bias from the primary studies and carried into the review level, confirming the true magnitude of adverse events related to massage in pediatrics remains unknown.

Similar to other studies this review reveals a lack of adverse events reporting in general. The majority of included studies did not report if the intervention was associated with any adverse event or not, leading to significant reporting bias from the primary studies and carried into the review level, unknowing the true magnitude of adverse events related to massage in pediatrics.[74]

Strengths and limitation

This review was inclusive in searching peer-reviewed publications in seven databases from inception onwards, not limiting by language. We minimized subjective errors by independent duplicate screening, study selection, and data extraction. This SR meticulously collected data from included studies and classified severities of AEs according to well-established criteria. We have incorporated to this review all relevant studies, including case reports, case series, and clinical trials in an effort to be comprehensive. In addition, we reported studies that reported if AEs occurred or not, whether they mentioned if AEs were assessed

or not, except for case reports which were only included if an event was reported.

As any study, this review has limitations. The majority of the AEs, were described in case series/reports. Although case studies are well-recognized sources of reports on severe, unusual, and/or rare AEs, conclusions drawn from such sources are limited and subject t of confounding factors. Additionally, given the limited information and heterogeneity of the data reported in the included studies, it was not possible to identify any conclusive association between MT and specific AEs, except for ba sha massage which caused a characteristic bruising.

Risk of bias was not performed due the nature of included studies.

Clinical relevance of review findings:

The most significant review finding warranting clinical surveillance is the association between abdominal massage and VWM in pre term infants. There are several confounder s impeding this review to define a causal relationship between neonatal abdominal massage and VWM, but the reports should be taken into careful consideration and abdominal massage should be consider with caution on this population.

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CONCLUSIONS

We were able to identify a range of AEs associated with MT use, from mild to severe. Unfortunately, the majority of included studies did not report if an adverse event occurred or not, leading to publication bias. This review reports an association between abdominal massage with volvulus without malrotation in preterm infants, it is still to be defined if this is casual or not, but our findings warrant caution in the use of abdominal massage in pre term infants until further investigation is done in the subject.

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case-control-study. BMC Pediatrics. 2014;14:287.
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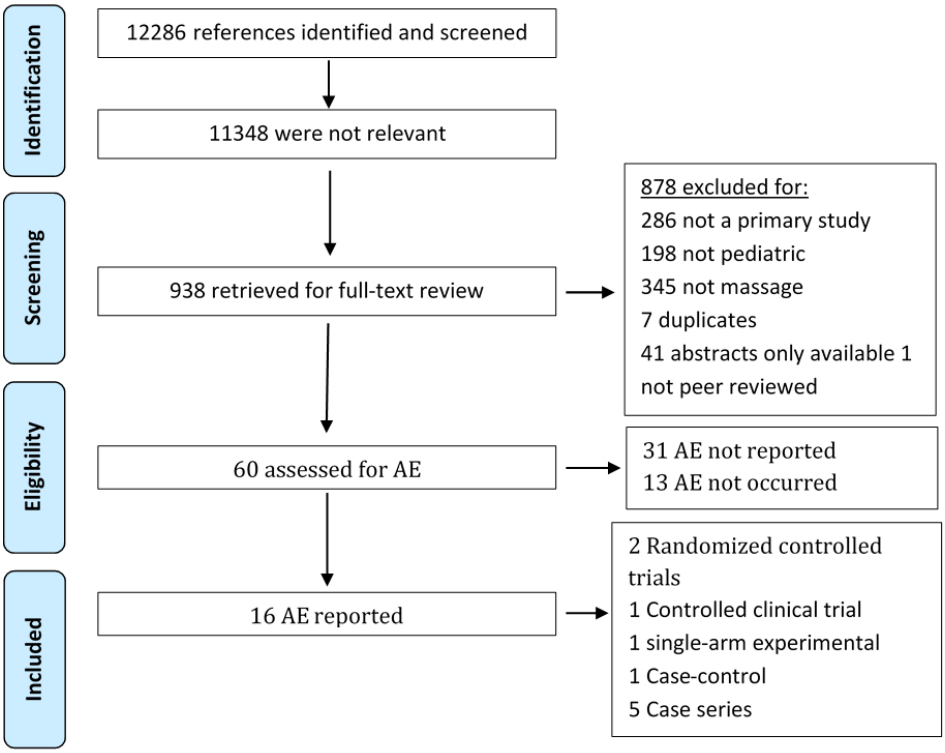
controlled trials of antiepileptic drugs in children over a 10-year period. Arch Dis Child. 2010;95(9):731-8.

Figure 1: PRISMA diagram for systematic review of pediatric massage therapy adverse events (AE)



Appendix: Medline search strategy for pediatric massage therapy adverse events

1. abhyanga.tw.
2. acupressure.tw.
3. acupressure/
4. Amma.tw.
5. Anma.tw.
6. Anmo.tw.
7. Aromatherapy massage.tw.
8. ashiatsu oriental bar therap$.tw.
9. aston pattern$.tw.
10. augmented soft tissue mobilization.tw.
11. augmented soft-tissue mobilization.tw.
12. balinese massage.tw.
13. belavi facelift massage.tw.
14. bindegewebsmassage.tw.
15. bindegewebs massage.tw.
16. bodywork.tw.
17. (bowen adj1 (therap$ or technique or work)).mp. [mp=ti, ot, ab, nm, hw]
18. budzek medical massage.tw.
19. chih ya.tw.
20. classical massage.tw.
21. connective tissue massage.tw.
22. (craniosacral adj1 (massage or therap$)).tw.
23. deep-tissue massage.tw.
24. deep tissue massage.tw.
25. Esalen.mp. [mp=ti, ot, ab, nm, hw]
26. foot reflexion massage.tw.
27. four-hand massage.tw.
28. generic massage.tw.
29. hellerwork.tw.
30. hoshino therap$.tw.
31. hot stone massage.tw.
32. huna kane.tw.
33. ice massage.tw.
34. ingham method.tw.
35. jamu.tw.

36. Jin Shin Do.tw.
37. korean martial therap$.tw.
38. lomilomi.tw.
39. looyen work.tw.
40. Lymphatic drainage.tw.
41. lypposage.tw.
42. manual lymph drainage.tw.
43. manual stimulat$.tw.
44. marma massage.tw.
45. exp massage/
46. massage.tw.
47. massotherapy.tw.
48. medical massage.tw.
49. Meridian massage.tw.
50. muscle energy technique$.tw.
51. (myofascial adj1 (mobilization or release)).tw.
52. Myomassolog$.tw.
53. myopathic muscular therap$.tw.
54. Myotherap$.tw.
55. naprapath$.tw.
56. (neuromuscular adj1 (facilitat$ or therap$ or technique$ or massage)).tw.
57. nuad bo rarn.tw.
58. nuat thai.tw.
59. oil massage.tw.
60. onsen technique.tw.
61. oncology massage.tw.
62. oriental bodywork.tw.
63. orthopedic massage.tw.
64. pfrimmer deep muscle therap$.tw.
65. *physical stimulation/
66. physical stimulat$.tw.
67. phytotherapy.tw.
68. point holding.tw.
69. process accupressure.tw.
70. rebalancing.tw.
71. reflex zone massage.tw.
72. reflexognosy.tw.

73. reflexology.tw.
74. reposturing dynamics.tw.
75. rolfing.tw.
76. (Rosen adj1 (method$ or massage)).tw.
77. russian massage.tw.
78. Shiatsu.tw.
79. shiatzu.tw.
80. exp shiatsu/
81. (soft tissue adj1 (manipulat$ or mobilizat$ or release)).tw.
82. sport$ massage.tw.
83. (strain-counterstrain adj1 (therap$ or massage or technique)).tw.
84. structural integrat$.tw.
85. swedish massage.tw.
86. tactile stimulat$.tw.
87. thai massage.tw.
88. tibetan massage.tw.
89. tibetan point holding.tw.
90. (trager adj1 (approach or technique or therap$ or massage)).tw.
91. triggerpoint massage.tw.
92. Tuina.tw.
93. tui na.tw.
94. zero balanc$.tw.
95. zhi ya.tw.
96. zhiya.tw.
97. zone therap$.tw.
98. or/1-97
99. (exp massage/ or massage.tw.) adj3 (carotid body/ or exp carotid arteries/ or carotid.tw. or heart.tw. or cardiac.tw. or sinus.tw. or uterine.tw. or udder.tw. or prostatic.tw. or prostate.tw. or cornea.tw. or ocular.tw. or intraocular pressure/ or glaucoma/ or decubitus ulcer.mp. or vagal.mp.)
100. 98 not 99
101. (ae or co or et).fs.
102. ((Side or Advers$) adj3 (effect$ or affect$ or reaction$ or event$)).tw.
103. (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$ or complicat$).tw.
104. exp risk/
105. (risk-benefit adj5 (analy$ or ratio$ or assess$)).mp.
106. exp causality/

107. significant event.tw.
108. exp Safety/
109. safe$.tw.
110. aggravation$.tw.
111. consequences.tw.
112. injury.tw.
113. exp "Wounds and Injuries"/
114. case report$.tw.
115. or/101-114
116. anemia.tw.
117. bruising.tw.
118. exp Hematoma/ or exp Purpura/ or exp Contusions/ or exp Hemorrhage/ or exp Ecchymosis/
119. bruise.tw.
120. carotid artery stenosis.tw.
121. exp Dislocations/
122. dilocation$.tw.
123. exp Hearing Loss/
124. hearing loss.tw.
125. hearing deterioration.tw.
126. abscess.tw.
127. abscess/
128. displacement of stent.tw.
129. stent displacement.tw.
130. eczema.tw.
131. eczema/
132. embolization.tw.
133. exp Embolization, Therapeutic/ or exp Pulmonary Embolism/
134. fetal haemorrhage.tw.
135. fracture.tw.
136. fracture/
137. haematoma.tw.
138. hematoma.tw.
139. infection.tw.
140. nerve damage.tw.
141. pain.tw.
142. exp Pain/
143. posterior interosseous syndrome.tw.

144. pseudoaneurysm.tw.
145. exp Aneurysm, False/
146. exp Pulmonary Embolism/
147. ruptured colon.tw.
148. ruptured uterus.tw.
149. swell$.tw.
150. strangulation.tw.
151. exp Asphyxia/ or exp Neck Injuries/
152. exp Thyrotoxicosis/
153. thyrotoxicosis.tw.
154. ulceration.tw.
155. exp Ulcer/
156. weak$.tw.
157. or/116-156
158. 115 or 157
159. exp infant, newborn/
160. infant/
161. exp child, preschool/
162. child/
163. exp puberty/
164. minors/
165. adolescent/
166. (newborn$ or new-born$ or infan$ or baby$ or babies$ or preemie$ or prematur$).tw.
167. toddler$.tw.
168. (preschool$ or pre-school$).tw.
169. nursery school$.tw.
170. (kindergarten$ or kindergarden$).tw.
171. (child$ or kid or kids or boy$ or girl$).tw.
172. elementary school$.tw.
173. (schoolchild$ or "school child$").tw.
174. (schoolage$ or school age$).tw.
175. ("junior high$" or "middle school$").tw.
176. youth$.tw.
177. (teen$ or adolescen$ or juvenil$ or "young adult$" or pubert$ or underage$ or "under age$").tw.
178. (pubescen$ or pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$).tw.
179. secondary school$.tw.
180. (high school$ or highschool$).tw.

181. exp Pediatrics/

182. pediatric$.tw.

183. paediatric.tw.

184. or/159-183

185. 100 and 158 and 184

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Adverse events associated with pediatric massage therapy: a systematic review

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Abbreviations:

AE – adverse events

EEG - electroencephalography

GA- Gestational age

MT- massage therapy

RCT- randomized controlled trial

VWM-Volvulus without malrotation

Table of contents summary:

Massage therapy is frequently used in children. To date, no study has systematically assessed its safety. This review reports safety of massage in children.

What is known:

- Massage therapy has been widely used for many different indications in children and adults.

- Several studies report its efficacy, but adverse events of massage therapy is poorly investigated.

What this study adds:

- A range of AEs associated with MT use, from mild to severe.

- An association between abdominal MT in preterm neonates and volvulus without malrotation, the causality of this association is yet to be determined

Until further data are identified extreme causation on the use of abdominal massage in preterm neonates is warranted

Contribution statement: Dr Vohra and Dr Jou and Dryden conceptualized and designed the study, reviewed and critically reviewed the manuscript for important intellectual content.
Drs Karkhaneh and Zorzela and Funabashi designed the data collection instruments, collected data, carried out the initial analyses, and drafted the 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.

All data relevant to the study are included in the article or uploaded as supplementary information.

ABSTRACT

Introduction: Massage therapy (MT) is frequently used in children. No study has systematically assessed its safety in children and adolescents. We systematically review adverse events (AEs) associated with pediatric MT.

Methods: We searched seven electronic databases from inception to December 2018. We included studies if they: (i) were primary studies published in a peer-reviewed journal, (ii) involved children aged 0-18 years, and (iii) a type of MT was used for any indication. No restriction was applied to language, year of publication, and study design. AEs were classified based on their severity and association to the intervention.

Results: Literature searches identified 12,286 citations, of which 938 citations were retrieved for full-text evaluation and 60 studies were included. In the included studies, 31 (51.6%) did not report any information on AEs, 13 (21.6%) reported that no AE occurred, and 16 studies (26.6%) reported at least one AE after MT. There were 20 mild events (grade 1) that resolved with minimal intervention, 26 moderate events (grade 2-3) that required medical intervention, and 18 cases of severe AEs (grade 4-5) that resulted in hospital admission or prolongation of hospital stay; of these, 17 AE were volvulus in premature infants, four of which were ultimately fatal events.

Conclusion:

We identified a range of AEs associated with MT use, from mild to severe. Unfortunately, the majority of included studies did not report if an adverse event occurred or not, leading to publication bias. This review reports an association between abdominal massage with volvulus without malrotation in preterm infants, it is still to be defined if this is casual or not, but our findings warrant caution in the use of abdominal massage in preterm infants.

BACKGROUND

Massage therapy (MT) is one of the most popular complementary therapies in North America and has a long history of practice.[1, 2] According to the College of Massage Therapists of Ontario, "Massage therapy consists primarily of hands-on manipulation of the soft tissues of the body, specifically, the muscles, connective tissue, tendons, ligaments and joints for the purpose of optimizing health. Massage therapy treatment has a therapeutic effect on the body and optimizes health and well-being by acting on the muscular, nervous and circulatory systems".[3]

Massage therapists press, rub and manipulate muscles and soft tissues of the body, often with their hands and fingers, to relieve physical dysfunction and pain, reduce stress, promote relaxation, reduce anxiety or depression, and improve general wellbeing.[4, 5]

Various types of MTs have been practiced using specific techniques, including Swedish, Thai, shiatsu, tui na, connective tissue, deep tissue, myofascial, trigger point, etc.[6-8]

Massage is used in children around the world, including countries where massage is not part of their traditional medicine practices. Close to 1% of American children use MT.[9] In Canada, a survey involving 979 families attending subspecialty clinics, demonstrated that the most common complementary therapy reported was massage, with 39.1% reporting use.[10] In Europe, the frequency of massage use varies from 8.7 to 29% in a subpopulation of children with oncologic disorders.[11] MT is frequently used in children with health problems and its use is as high as 47% in patients with neurologic disorders, 38% in patients with cardiac disorders and 34% in patients with respiratory disorders.[12-14]

Despite MT's longstanding history and popularity, specific mechanisms by which massage exerts its therapeutic effects are not yet known.[7, 15-17] Researchers have long been interested in MT for children's health and wellbeing.[18] A recent meta-analysis of clinical trials of MT on infants under six months of age found statistically significant effects on weight and height, improving head/arm/leg circumference, 24-hour sleep duration, lowering blood bilirubin level, and frequency of diarrhea.[19] Among preterm infants, MT enhanced average weight gain and reduced hospital length of stay.[20] In children 2-18 years old, MT has been shown to improve arthritis pain, muscle tone, and decrease anxiety.[21]

There is limited evidence supporting MT for cancer pain.[22] and chronic pain in children.[23]

Most systematic reviews of pediatric massage therapy have focused on the effectiveness of MT rather than its safety.[18-21, 24-30] One systematic review included two case reports of AEs among children[8, 31]; one infant with scrotal hematoma associated with MT of a hydrocele[32] and a teenager with a popliteal artery pseudoaneurysm after MT overlying an exostosis.[33] AEs reported for adults were more diverse, including: cerebrovascular accidents, disc herniation/spinal cord injury, thromboembolism (renal, pulmonary), soft tissue trauma, leg ulcer, and genitourinary injuries.[8, 31, 34, 35] These studies demonstrated that the nature and circumstances of MT AEs for adults are quite different from pediatrics. While many complementary therapies are considered to be at low risk of harm, safety of health interventions should be measured, rather than assumed, especially in vulnerable populations, including children.[36, 37]

The objective of this systematic review was to identify the evidence of adverse events associated with massage therapy in children.

METHODS

Searching Databases

A systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Review (PRISMA) Statement and the PRISMA Harms.[38, 39] In consultation with two massage therapists, a health research librarian designed a comprehensive search strategy. Seven electronic databases were searched from inception to December 2018. The databases included: Medline, EMBASE, CINAHL, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, Alt HealthWatch. We identified search terms by using key words including Massage, Adverse Effects, and Pediatrics and a combination of subject terms selected from the controlled vocabulary or thesaurus (e.g. MeSH - Medical Subject Headings, Emtree for Embase, CINAHL Headings and PsycINFO Thesaurus) with a wide range of free-text terms.

No language restrictions were applied. The search strategy was adapted to follow recommendations by Golder & Loke to optimize for the retrieval of adverse effects data.[40] The full Medline search strategy is available in Appendix A.

Study Selection

Studies were eligible to be included if they:

1) were a primary study published in a peer-reviewed journal, primary study was defined as "*study reported directly by the researcher that conducted the study"*, rather than depending on data collected from previously done research.

2) involved children from birth to 18 years of age, 3) used MT for any indication, studies were not excluded based on conditions leading to MT. The inclusion of studies was not limited by medical condition, training of massage provider, or the presence/absence of a comparison/control intervention. There was no restriction by study design or reporting AE. We excluded studies if they: 1) only applied light touch or 2) only used self-massage, 3) grey literature. Studies of reflexology and studies of massage for lacrimal duct obstruction were also excluded since those were not relevant to this review. Case reports were only included if they reported an AE. Two reviewers performed study selection, independent and in duplicate, and discrepancies were resolved by consensus or a third reviewer.

Data Extraction

A structured data extraction form was used to collect data from the articles. General characteristics of studies included country, study design, settings, population, age, and gender. Specific information included: indication for treatment, AE severity, N of event, age, (age/weight and age at AE for newborn babies), gender, type of MT, MT practitioner, outcome with severity grade, and notes from the authors. Independent duplicate assessment was performed for both study selection and data extraction.

Adverse events were defined as per the Cochrane handbook as: ´adverse event is an unfavorable or harmful outcome that occurs during, or after, the use of a drug or other intervention, but is not necessarily caused by it'.[41]

Data Synthesis

The data from studies were tabulated into general information and AEs tables. The Common Terminology Criteria for Adverse Events (CTCAE) scale was used to classify severity of AEs.[42] (Table 1)

Table 1: Grading system for severity of adverse events (CTCAE)*

Grading	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

*CTCAE: Common Terminology Criteria for Adverse Events

The severity was categorized into five *grades*, from *grade* 1 (mild, asymptomatic) to *grade* 5 (death), based on information provided by the studies. Duplicate assessment of CTCAE ratings were performed and discrepancies between two reviewers were resolved by consulting a senior reviewer.

We also classified the AEs as 'direct', if directly caused by the intervention, or 'indirect', if the intervention caused a delay in diagnosis or treatment which resulted in an adverse event.[43]

Since this was a systematic review of AEs following MT, effectiveness/efficacy of MT was not assessed. We neither performed meta-analysis nor risk of bias assessment. Subgroup analysis was done separating study designs by severity of adverse events to assess if any specific type of massage would lead to more severe events.

RESULTS

Comprehensive search in seven electronic databases yielded a total of 12,286 citations. Screening titles and abstracts identified 11,348 references irrelevant to the review question; 938 full text articles were retrieved for further evaluation. By using the pre-specified inclusion/exclusion criteria, 60 studies were included (Figure 1).

The discrepancies were discussed, and consensus was reached between the two reviewers. There were no residual discrepancies.

Included studies were published between 1991 and 2018, and were conducted in 11 countries including China (n=1), France (n=2), Germany (n=1), India (n=3), Iran (n=3), Madagascar (n=1), Malaysia (n=1), Poland (n=1), Russia (n=2), Singapore (n=1), Sweden (n=1) Switzerland (n=2), United States (n=1) and United Kingdom (n=2). Among 60 studies with a total population of (n=3557), 29 studies (n=1520) were single arm experimental or case studies that received MT and 31 studies (n=2037) were studies a comparator/control group, of which almost half (n=972) have received MT and the rest (n=1065) were controls with no MT. Gestational age (GA) in the preterm infants having MT varied was from 23.5 to 37 weeks. Age of children ranged from 1 day to 18 years.

Studies not reporting on AE

There were 13 studies (10 RCT, 1 CCT, 2 single-arm experiments) that did not report if an AE occurred, or not, after receiving MT. Of total 878, 436 children (0 to 18 years) received MT for various reasons including infantile colic, childhood eczema, weight gain in preterm babies, soothing pain for heel stick, improving neurological diseases, and helping urinary tract and HIV infection.

Reports of Adverse Events

Of 60 included studies, 16 (26.6%) reported AE(s), 31 (51.6%) did not mention if an AE occurred or not, and 13 (21.6%) reported that no AE occurred. Figure 1 illustrates the PRISMA flow diagram. Of 16 studies (n=438) reporting AEs, 13 were published in English, one in Russian, and two in French. In total, 11 different types of AEs occurred in 64 individuals. Of 16 studies reporting an AE, five did not state who performed the massage therapy. Of the 11 that reported, MT was provided by trained nurses (n=2), parents/grandparents (n=1), paramedic personnel (n=1), nanny (n=1), traditional massage practitioner (n=1), and trained massage practitioner (n=5). In some cases, a nurse or trained massage practitioner started MT, and a parent continued the massage. None of the studies reported any AE associated with MT when it was provided by a licensed or registered massage therapist.

Indirect Adverse Event

One publication identified an indirect AE, i.e., a delay in diagnosis and/or treatment. A case report documented four children with *Staphylococcus aureus* osteomyelitis, which presented as upper arm swelling.[44] The authors considered the use traditional MT for swelling a cause for delay in the diagnosis and treatment, leading to progression of the infection (Grade 3).

Risk of Bias Assessment

Risk of bias was not assessed for two reasons: (i) the large majority of included studies (11 of 16) were case reports and case series, for which there is no universally accepted tool to assess bias; and (ii) with regards to RCTs, there is evidence that existing ROB tools are developed with efficacy as their main focus and that other factors should be considered for assessment of adverse events.[41]Until an appropriate tool is developed, we opt to not proceed with an assessment that may itself lead to bias. At present, there is no clear guidance on how to proceed with ROB assessment on studies reporting adverse events data.[37, 41, 45-48]

Studies not reporting on AE

There were 13 studies (10 RCT, 1 CCT, 2 single-arm experiments) not reporting if an AE occurred, or not, after receiving MT. Of total 878, 436 children (0 to 18 years) received MT for various reasons including infantile colic, childhood eczema, weight gain in preterm babies, soothing pain for heel stick, improving neurological diseases, urinary tract infection and HIV infection.

Adverse Events and severity

Serious AE (Grades 4-5)

Five included studies reported 18 cases of serious AEs after MT.[49-53]

Seventeen preterm infants (15 females and two males) were diagnosed with intestinal volvulus without malrotation after abdominal massage. The MT were usually performed 4-8 times per day by nurses to stimulate peristalsis in preterm (27-31-week gestational age), and extremely preterm (>23.5 and <27 weeks gestational age) infants. The intestinal volvulus occurred from 13 days to 52 days after birth. Four infants died (Grade 5) and 13 survived after bowel resection surgery

(Grade 4). A retrospective case control study done by Maas,[49] reports five extremely preterm infants (GA 24.4 weeks) with volvulus without malrotation. Each case was matched with five other preterm infants with similar birth weight, GA and birth year. Three of the five patients with volvulus died. Maas reports that MT was not found to be risk factor for the volvulus, as both cases and controls received massage similarly.

In addition, a serious AE also occurred in a 4-month old female who had status epilepticus due to camphor intoxication, following abdominal massage with camphor-containing lotion. She was hospitalized for 72 hours for uncontrolled seizures, where she was intubated, mechanically ventilated, and given seizure treatment (Grade 4) (Table 2).

Table 2: Volvulus without malrotation in pediatric massage therapy (n=17)

First author (Year), location Study design	Indication for treatment	AE Severity	n event /N population	Age/weight	Age at AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Maas, C. (2014), Germany Case-control	To stimulate peristalsis in extremely preterm infants	VWM Severe	5/2	23.6-25.4 weeks GA; 370-630 grams	37-52 d after birth	5 F	Abdominal massage 4-6 times/day	NS	3 Died (Grade 5) 2 Survived after surgery (Grade 4)	Data did not support the hypothesis that abdominal massage was a risk factor for VWM; no further cases were diagnosed after the practice was discontinued
Zweifel, N. et al. (2013), Switzerland Case series	To stimulate peristalsis in preterm infants	VWM Severe	3/3	27-31 weeks GA; 880 grams	NS	2 F 1 M	Repeated abdominal massage multiple times a day	Nurse	3 survived after surgery (Grade 4)	There may be a causal relationship between abdominal massage and VWM; no further cases were diagnosed after the practice was discontinued
Paraskevopoulos E. et al. (2006), Switzerland Case series	To stimulate peristalsis	VWM Severe	2/2	27 weeks GA	At 19th and 32nd day after birth	2 F	Intensive abdominal massage every 3 hours	Nurse	2 survived after surgery (Grade 4)	The infants had no other risk factors other than the abdominal massage; the practice was discontinued with no further cases since
Billiemaz, K. (2001), France Case series	To stimulate peristalsis	VWM Severe	7/7	27-29 weeks GA: 660-1100 grams	Day 13-33	6 F 1 M	Abdominal massage	Health care provider	1 died (Grad 5) 6 survived after surgery (Grade 4)	No new cases of VWM were seen after the practice was discontinued

Footnote: AE: adverse event; MT: massage therapy; VWM: volvulus without malrotation; GA: gestational age; wk: week; NS: not stated; F: female; M: male.

Moderate AEs (Grade 2-3)

There was one non-randomized controlled trial (NRCT),[54] two case series[44, 55] and four case reports[32, 33, 56, 57] from 1994 to 2017 reporting on 27 children, aged from 1-day to 16 years old. Those children experienced moderate AEs including infant mastitis/abscess, osteomyelitis, popliteal artery pseudo-aneurysm, acute unilateral neurosensory hearing loss, scrotal hematoma, and oxygen desaturation. The NRCT[54] assessed physiological measurements including amplitude-integrated electroencephalography (aEEG), oxygen saturation (SaO2), pulse rate, and cerebral blood flow in 39 preterm infants following whole body Shantal (stroking and rubbing whole body) massage by a therapist and the mother. They reported four cases of oxygen desaturation (<85%) requiring withdrawal from the experiment (Grade 2); no further details were provided. One case series[55] described 15 cases of neonatal mastitis following repeated massage in 15 infants aged 6-48 days; all cases needed antibiotic therapy with or without abscess drainage (Grade 3).

Three case reports of MT AE were also published: (i) a popliteal artery pseudo aneurysm after leg MT on an osteochondroma in a 16-year old male;[33] (ii) acute unilateral neurosensory hearing loss after MT on the neck and trapezius muscle in a 14-year old male diagnosed with autonomic nervous system dysfunction;[57] and (iii) scrotal hematoma after traditional MT with a warm sand bag on hydrocele of a 1-day old baby boy.[32] The first and third cases resolved after hospitalization and appropriate surgery and second case resolved after intensive treatment plan at a hospital for 15 days and at home for seven days (Grade 3) (Table 3).

Table 3: Moderate to Severe adverse events in pediatric massage therapy (n=27)

First author (Year), location Study design	Indication for treatment	AE Severity	n event/N population	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Rudnicki, J. (2012), Poland CCT	Assessing the physiologic effects* of MT in preterm infants	Arterial oxygen desaturation <85% Moderate	4/39	39 preterm infants, 22 <32 weeks GA and 17 ≥32 weeks GA	18 days (n=17), 24 days (n=22)	5 F	Shantal (stroking and rubbing whole body)	Therapist/ mother	Withdrawn from the study (Grade 2)	No other information was given by the authors about management or resolution of this AE
Masoodi, T. (2014), India Case series	Breast hypertrophy (12 mastitis and 20 abscess)	Mastitis and breast abscesses Moderate	15/32 received MT to express secretions for breast hypertrophy	6-48 days	NS	NS	Repeated breast massage	NS	Resolved after antibiotic therapy/drainage of abscess (Grade 3)	Massage for neonatal breast hypertrophy should not be performed
Razafimahandry, H.J. (2007), Madagascar Case series	Upper arms osteomyelitis (Staphylococcus aureus)	Severe infection due to delayed diagnosis (20-60 days) Moderate	4/4	5-11 years	NS	2 F 2 M	Traditional massage	NS	3 cases resolved after hospitalization and antibiotic therapy (Grade 3)	One case was a severely cachectic 11-year old boy diagnosed with pulmonary tuberculosis and died of septic shock five days later; no other details regarding his death was described
Guilbert J. et al. (2007), France Case series	Flatulence	Status epilepticus Severe	1/1	4 months	72 hours	1 F	Abdominal massage with camphor-containing lotion	Caregiver	Hospitalized, intubated, treated for status epilepticus (Grade 4)	Other investigations were normal; the infant was extubated after three days and later discharged home with a normal neurological examination
Kalinga, M.J. (1996), Singapore Case report	Swelling of right thigh due to osteochondroma	Popliteal artery pseudo-aneurysm Moderate	1/1	16 years	3rd session of massage	M	MT with herbal medicine (5 sessions)	Traditional Chinese Medicine practitioner	Resolved after hospitalization and surgery (Grade 3)	Diagnosis was right popliteal artery pseudo-aneurysm after the 5th session of MT. At surgery femoral artery defect was found adjacent to the osteochondroma
Medvedev, E. (1994), Russia Case report	Autonomic nervous system dysfunction	Acute unilateral neurosensory hearing loss Moderate	1/1	14 years	During treatment	M	Tonic MT of the neck including trapezius muscle	NS	Recovered with hospitalization; medications plus "5 sessions of TENS** for 8th cranial nerve" (Grade 3)	The boy with ANS dysfunction received MT and developed acute unilateral neurosensory hearing loss with noise. MT stimulated the ANS and caused vascular spasm leading to decreased blood flow to the cochlea and subsequent hearing impairment
Ram, S.P. (1994), Malaysia Case report	Hydrocele	Scrotal hematoma Moderate	1/1	1 day	1st day	M	Traditional MT to testes with warm sand bag	NS	Resolved after surgery (Grade 3)	None

Footnote: AE: adverse event; MT: massage therapy; CCT: controlled clinical trial (non-randomized controlled trial); GA: gestational age; NS: not stated; F: female; M: male; TENS: transcutaneous electrical nerve stimulation; ANS: autonomic nervous system.

Mild AE (Grade 1)

Two RCTs[58, 59] described skin rashes after whole body massage with various oils (almond, mineral, coconut, or safflower) examining the effects of MT on growth measurements (weight, height, etc.) in 17 infants with age from 1-day to 3-days old. These mild reactions occurred in 2.5% in the first[58] and 6% in the second[59] study populations; all resolved spontaneously without discontinuation of MT or the oils (Grade 1). Two almost identical RCTs[60, 61] examined the immunogenicity of mild rubbing massage on vaccination sites among 808 and 328 infants 2-6 months old, respectively. AEs included crying, anorexia, drowsiness, vomiting, irritability, fever, pain, redness, and induration; all were mild and did not need an intervention except general health advice for vaccinated children (Grade 1). Two single-arm experimental studies, one by Cullen et al.,[62] described mild hyperactivity (n=1) and the other by Beaver et al.,[63] reported increased blood pressure/heart rate and decreased transcutaneous oxygen saturation (n=8) following MT. One case report by Li et al.,[64] described a mild skin bruising after a MT technique involving pinching skin. All these interventions needed minimal intervention for resolution (Grade 1) (Table 4).

Unclassified AEs

Due to insufficient information, we were unable to properly assess and rate the severity of AE reported by a NRCT. Goncharov et al.,[65] assessed the effect of MT with a mixture of aromatic oils on CNS rehabilitation among 31 infants aged 4-18 months with perinatal hypoxic central nervous system (CNS) injury. One child (age and sex not provided) developed an “allergic reaction” (oil product not specified) and dropped out of the study (no further details were provided to allow for severity rating). The manuscript was written in Russian and author’s contact information was not available.

Table 4: Mild adverse events in pediatric massage therapy (n=20)

First author (Year), location Design	Indication for treatment	AE Severity	n event /N population	Age	Time of AE	Gender	Type of MT	MT practitioner	Outcome (Grade)	Notes from study authors
Patel, GM (2017), USA Case-report	Examining of MT for reflux	Bruising and dry patches on face Mild	1/1	6 weeks	3 days after MT	M	Craniosacral massage	Not reported	No major complication (Grade 1)	Vitamin K deficiency bleeding was confirmed after rapid elevation of International correction ratio (INR); the craniosacral massage therapy was the cause of his superficial bleeding
Li, Z. (2015), China Case-report	Repeated vomiting	Bruising Mild	1/1	5 years	NS	M	Traditional Chinese massage therapy (Ba sha)	Grandmother/mother	Bruising was mild (Grade 1); (patient died due to strangulation)	An incidental case with multiple bruises over the chest, neck, and shoulders resulting from traditional Chinese MT (ba sha), involving pinching the skin between thumb and index finger, for vomiting. Injuries resulting from ba sha were not the cause of death
Solanki, K. (2005), India RCT	Examining MT with oil on growth and fatty acid profile of the infant	skin rash Mild	3/118	1-3 days	3rd and 4th days	47 F 71 M	Massage with safflower oil for 10 min, 4 times/day over 5 days	Trained massager	Resolved spontaneously (Grade 1)	The rash resolved without treatment in 1-2 days despite continuing the oil massage
Sankaranarayanan, K. (2005), India RCT	Examining MT with oil on weight and growth and AE	skin rash Mild	14/224	2 days	NS	NS	Massage 5 minutes 4/day with coconut/mineral oil or no oil	Trained person and mother	Resolved spontaneously (Grade 1)	Massage in hospital and home continued for 30 days; mild rash occurred equally in all groups, coconut oil (n=5), mineral oil (n=5), and placebo (n=4), and did not require discontinuation of massage
Cullen, L.A. (2005), UK Single-arm experiment	Examining MT on communication of autistic child	Worsened hyperactivity Mild	1/15	NS	After 24 hours	M	1-hour weekly MT for 8 times by massager and daily by parent	Therapist and parents	No major complication (Grade 1)	Eight other participants (2-13 years old, all with autism) who completed the study over eight weeks reported “no obvious negatives”

Footnote: AE: adverse event; RCT: randomized controlled trial; MT: massage therapy; NS: not stated; F: female; M: male.

DISCUSSION

To the best of our knowledge, this is the first systematic review to primarily assess AEs associated withpediatric MT.

After extensive search in multiple databases and including non-English studies we identified 64 adverse events associated with pediatric massage. These events were further classified in mild, moderate and severe by our team. Moderate events were the most frequently identified, closely followed by mild and severe adverse events. Of serious AE identified, abdominal massage to stimulate peristalsis in preterm infants was identified as been associated with multiple reports of volvulus without malrotation.

Volvulus without malrotation (VWM) is considered a rare event, often associated with preterm birth (<30weeks GA) and low birth weight (<1000 g)[49, 50, 52, 66-69] We identified 17 events of volvulus without malrotation in preterm infants on this review, mostly very low birth weight (VLBW). In five VWM, the authors did not considered MT as a risk factor for the volvulus while for the remaining 12 events, MT was considered a risk factor by authors.[49] The identified cases of VWM led to a routine change in their centers to avoid abdominal massage in preterm infants due the risk of volvulus. All the authors report that changing their practice to avoid abdominal massage in preterm neonates generated no further events of VWM in their centers.[49] The large majority of the events reported in this review occurred in infants born at <30 weeks GA and weighted <1000g, which may be a confounder, since VLBW is consider a risk factor for VWM. Others have reported findings of VWM in preterm infants. Horsch has reviewed cases of volvulus in surgical referral center over 8 years in Germany and found 3 preterm infants with VWM, of these, 1 received properistaltic abdominal massage.[70] Yarkin after reviewing 2 years of data from an epidemiological survey identified that 12 of 15 cases of low birth weight (<1500g) pre term infants with VWM had abdominal massages prior to the event, although due the uncontrolled study design they were unable to determine abdominal massage as a direct risk factor.[71] Horsch and Yarkin were not included this review because they did not look into MT specifically. Several authors[49, 70, 72, 73] have speculated on other risk factors for VWM, including immaturity of the intestine resulting in

prolonged transit times and stool retention, use of continuous positive airway pressure (CPAP) or other intensive respiratory support, and female gender. Several of these risk factors were also identified in the included reports and it makes difficult to assure causality of MT in the development of VWM.

Massage therapy has been studied in children, but with the main focus of assessing efficacy, very little has been reported on adverse events.[18-21, 24-30] In contrast, adults report a wide range of adverse events associated with massage, from mild events to severe, including: cerebrovascular accidents, thromboembolism (renal, pulmonary), skin injury, leg ulcer, genitourinary injuries disc herniation, soft tissue trauma, neurologic compromise, spinal cord injury, dissection of the vertebral arteries".[8, 34, 35] Although, it is difficult to compare the different populations and co-morbidities associated with each.

Similar to other studies,[74] this review reveals a lack of adverse events reporting. The majority of included studies did not report if the intervention was associated with any adverse event or not, leading to significant reporting bias from the primary studies and carried into the review level, confirming the true magnitude of adverse events related to massage in pediatrics remains unknown.

Strengths and limitation

This review was inclusive in searching peer-reviewed publications in seven databases from inception onwards, not limiting by language. We minimized subjective errors by independent duplicate screening, study selection, and data extraction. This SR meticulously collected data from included studies and classified severities of AEs according to well-established criteria. We have incorporated to this review all relevant studies, including case reports, case series, and clinical trials in an effort to be comprehensive. In addition, we reported studies that reported if AEs occurred or not, whether they mentioned if AEs were assessed or not, except for case reports which were only included if an event was reported.

As any study, this review has limitations. The majority of the AEs, were described in case series/reports. Although case studies are well-recognized sources of reports on severe, unusual, and/or rare AEs, conclusions drawn from such sources are limited and subject t of confounding factors. Additionally, given the limited

information and heterogeneity of the data reported in the included studies, it was not possible to identify any conclusive association between MT and specific AEs, except for ba sha massage which caused a characteristic bruising.

Risk of bias was not performed due the nature of included studies.

Clinical relevance of review findings:

The most significant review finding warranting clinical surveillance is the association between abdominal massage and VWM in pre term infants. There are several confounder s impeding this review to define a causal relationship between neonatal abdominal massage and VWM, but the reports should be taken into careful consideration and abdominal massage should be consider with caution on this population.

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CONCLUSIONS

We were able to identify a range of AEs associated with MT use, from mild to severe. Unfortunately, the majority of included studies did not report if an adverse event occurred or not, leading to publication bias. This review reports an association between abdominal massage with volvulus without malrotation in preterm infants, it is still to be defined if this is casual or not, but our findings warrant caution in the use of abdominal massage in pre term infants.

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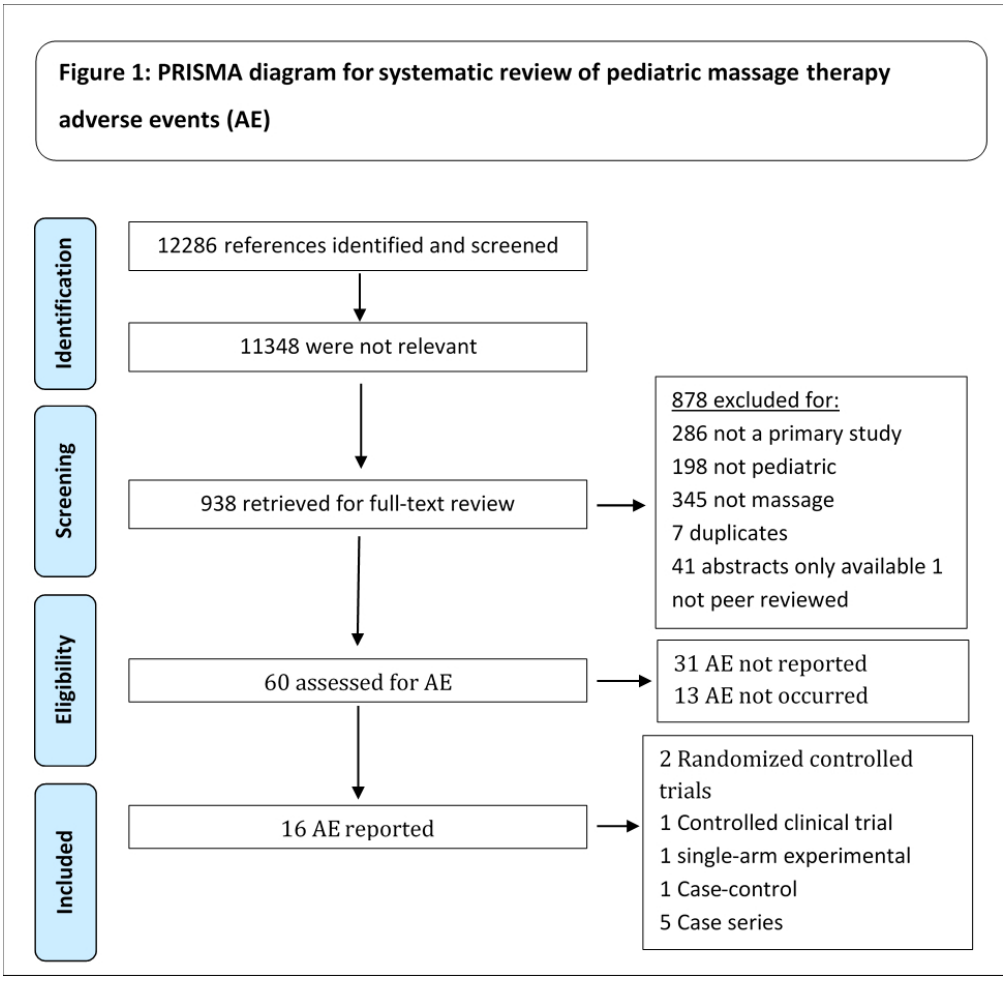
Figure 1: PRISMA diagram for systematic review of pediatric massage therapy adverse events (AE)
Identification
Screening
Eligibility
Included
12286 references identified and screened
11348 were not relevant
938 retrieved for full-text review
878 excluded for:
286 not a primary study
198 not pediatric
345 not massage
7 duplicates
41 abstracts only available 1 not peer reviewed
60 assessed for AE
31 AE not reported
13 AE not occurred
16 AE reported
2 Randomized controlled trials
1 Controlled clinical trial
1 single-arm experimental
1 Case-control
5 Case series

Appendix: Medline search strategy for pediatric massage therapy adverse events

1. abhyanga.tw.
2. acupressure.tw.
3. acupressure/
4. Amma.tw.
5. Anma.tw.
6. Anmo.tw.
7. Aromatherapy massage.tw.
8. ashiatsu oriental bar therap$.tw.
9. aston pattern$.tw.
10. augmented soft tissue mobilization.tw.
11. augmented soft-tissue mobilization.tw.
12. balinese massage.tw.
13. belavi facelift massage.tw.
14. bindegewebsmassage.tw.
15. bindegewebs massage.tw.
16. bodywork.tw.
17. (bowen adj1 (therap$ or technique or work)).mp. [mp=ti, ot, ab, nm, hw]
18. budzek medical massage.tw.
19. chih ya.tw.
20. classical massage.tw.
21. connective tissue massage.tw.
22. (craniosacral adj1 (massage or therap$)).tw.
23. deep-tissue massage.tw.
24. deep tissue massage.tw.
25. Esalen.mp. [mp=ti, ot, ab, nm, hw]
26. foot reflexion massage.tw.
27. four-hand massage.tw.
28. generic massage.tw.
29. hellerwork.tw.
30. hoshino therap$.tw.
31. hot stone massage.tw.
32. huna kane.tw.
33. ice massage.tw.
34. ingham method.tw.
35. jamu.tw.

36. Jin Shin Do.tw.
37. korean martial therap$.tw.
38. lomilomi.tw.
39. looyen work.tw.
40. Lymphatic drainage.tw.
41. lypposage.tw.
42. manual lymph drainage.tw.
43. manual stimulat$.tw.
44. marma massage.tw.
45. exp massage/
46. massage.tw.
47. massotherapy.tw.
48. medical massage.tw.
49. Meridian massage.tw.
50. muscle energy technique$.tw.
51. (myofascial adj1 (mobilization or release)).tw.
52. Myomassolog$.tw.
53. myopathic muscular therap$.tw.
54. Myotherap$.tw.
55. naprapath$.tw.
56. (neuromuscular adj1 (facilitat$ or therap$ or technique$ or massage)).tw.
57. nuad bo rarn.tw.
58. nuat thai.tw.
59. oil massage.tw.
60. onsen technique.tw.
61. oncology massage.tw.
62. oriental bodywork.tw.
63. orthopedic massage.tw.
64. pfrimmer deep muscle therap$.tw.
65. *physical stimulation/
66. physical stimulat$.tw.
67. phytotherapy.tw.
68. point holding.tw.
69. process accupressure.tw.
70. rebalancing.tw.
71. reflex zone massage.tw.
72. reflexognosy.tw.

73. reflexology.tw.
74. reposturing dynamics.tw.
75. rolfing.tw.
76. (Rosen adj1 (method$ or massage)).tw.
77. russian massage.tw.
78. Shiatsu.tw.
79. shiatzu.tw.
80. exp shiatsu/
81. (soft tissue adj1 (manipulat$ or mobilizat$ or release)).tw.
82. sport$ massage.tw.
83. (strain-counterstrain adj1 (therap$ or massage or technique)).tw.
84. structural integrat$.tw.
85. swedish massage.tw.
86. tactile stimulat$.tw.
87. thai massage.tw.
88. tibetan massage.tw.
89. tibetan point holding.tw.
90. (trager adj1 (approach or technique or therap$ or massage)).tw.
91. triggerpoint massage.tw.
92. Tuina.tw.
93. tui na.tw.
94. zero balanc$.tw.
95. zhi ya.tw.
96. zhiya.tw.
97. zone therap$.tw.
98. or/1-97
99. (exp massage/ or massage.tw.) adj3 (carotid body/ or exp carotid arteries/ or carotid.tw. or heart.tw. or cardiac.tw. or sinus.tw. or uterine.tw. or udder.tw. or prostatic.tw. or prostate.tw. or cornea.tw. or ocular.tw. or intraocular pressure/ or glaucoma/ or decubitus ulcer.mp. or vagal.mp.)
100. 98 not 99
101. (ae or co or et).fs.
102. ((Side or Advers$) adj3 (effect$ or affect$ or reaction$ or event$)).tw.
103. (risk$ or harm$ or aetiolog$ or etiolog$ or cause or causation or causing or causal$ or complicat$).tw.
104. exp risk/
105. (risk-benefit adj5 (analy$ or ratio$ or assess$)).mp.
106. exp causality/

107. significant event.tw.
108. exp Safety/
109. safe$.tw.
110. aggravation$.tw.
111. consequences.tw.
112. injury.tw.
113. exp "Wounds and Injuries"/
114. case report$.tw.
115. or/101-114
116. anemia.tw.
117. bruising.tw.
118. exp Hematoma/ or exp Purpura/ or exp Contusions/ or exp Hemorrhage/ or exp Ecchymosis/
119. bruise.tw.
120. carotid artery stenosis.tw.
121. exp Dislocations/
122. dilocation$.tw.
123. exp Hearing Loss/
124. hearing loss.tw.
125. hearing deterioration.tw.
126. abscess.tw.
127. abscess/
128. displacement of stent.tw.
129. stent displacement.tw.
130. eczema.tw.
131. eczema/
132. embolization.tw.
133. exp Embolization, Therapeutic/ or exp Pulmonary Embolism/
134. fetal haemorrhage.tw.
135. fracture.tw.
136. fracture/
137. haematoma.tw.
138. hematoma.tw.
139. infection.tw.
140. nerve damage.tw.
141. pain.tw.
142. exp Pain/
143. posterior interosseous syndrome.tw.

144. pseudoaneurysm.tw.
145. exp Aneurysm, False/
146. exp Pulmonary Embolism/
147. ruptured colon.tw.
148. ruptured uterus.tw.
149. swell$.tw.
150. strangulation.tw.
151. exp Asphyxia/ or exp Neck Injuries/
152. exp Thyrotoxicosis/
153. thyrotoxicosis.tw.
154. ulceration.tw.
155. exp Ulcer/
156. weak$.tw.
157. or/116-156
158. 115 or 157
159. exp infant, newborn/
160. infant/
161. exp child, preschool/
162. child/
163. exp puberty/
164. minors/
165. adolescent/
166. (newborn$ or new-born$ or infan$ or baby$ or babies$ or preemie$ or prematur$).tw.
167. toddler$.tw.
168. (preschool$ or pre-school$).tw.
169. nursery school$.tw.
170. (kindergarten$ or kindergarden$).tw.
171. (child$ or kid or kids or boy$ or girl$).tw.
172. elementary school$.tw.
173. (schoolchild$ or "school child$").tw.
174. (schoolage$ or school age$).tw.
175. ("junior high$" or "middle school$").tw.
176. youth$.tw.
177. (teen$ or adolescen$ or juvenil$ or "young adult$" or pubert$ or underage$ or "under age$").tw.
178. (pubescen$ or pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$).tw.
179. secondary school$.tw.
180. (high school$ or highschool$).tw.

181. exp Pediatrics/
182. pediatric$.tw.
183. paediatric.tw.
184. or/159-183
185. 100 and 158 and 184