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REVIEW

Non-Pharmacological Management for Vaccine-Related Pain in Children in the Healthcare Setting: A Scoping Review

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Purpose: To examine how research was conducted on non-pharmacological management in children with vaccine-related pain in the healthcare setting, so as to provide reference for the relief of vaccine-related pain in children.

Methods: This study conducted a scoping review guided by the methodological framework of Arksey and O'Malley. MEDLINE, Cochrane Library, EMBASE, CINAHL, PubMed databases were searched in detail, and search strategy included the keyword "vaccine", the keyword "pain", and the keyword "children". Two researchers conducted literature screening and data extraction independently, and any disagreements were resolved through team consultation.

Results: This study retrieved 1017 literatures, of which 22 were finally included, including 18 randomized controlled studies, 3 quasi-experimental studies and 1 cohort study. Non-pharmacological management measures were summarized in the study, mainly involving taste, tactile, olfactory, visual, exercise, and postural interventions and injection technique. All the above non-pharmacological management were effective in mitigating vaccine-related pain in children. The study population in the included literatures was mainly neonates and infants. Regarding the analgesic effects of taste intervention, breastfeeding was better than sweeteners, and sweeteners were better than sterile water or non-nutritive sucking. However, there was a lack of comparative studies on the analgesic effects of other non-pharmacological management.

Conclusion: There are many non-pharmacological management measures with varying analgesic effects. Diversified non-pharmacological management measures can provide more analgesic choices for children. For reducing vaccine-related pain in newborns and infants, breastfeeding is recommended first, then sweeteners, and then non-nutritious sucking. In addition to the taste intervention, the analgesic effects of other non-pharmacological management measures need further comparative studies. Moreover, medical staff can use a combination of non-pharmacological analgesic measures to maximize the analgesic effect, and medical staff should also fully consider the analgesia willingness of children and parents.

Keywords: vaccine-related pain, non-pharmacological management, vaccination, children, scoping review

Introduction

Vaccines reduce the risk of disease by building a natural defense with the body, which prevent 2 to 3 million deaths from disease each year.[1] The Centers for Disease Control and Prevention (CDC) recommends that children aged 0–18 should complete routine vaccinations according to the immunization schedule.[2] Moreover, children 5 years and older need to be additionally vaccinated Covid-19 vaccine.[3] That means more than a dozen vaccines should be vaccinated in childhood. However, the current prevalence of vaccination is not optimal in children. The National Health Commission of China proposed in the "Healthy Children Action Improvement Plan (2021–2025)" that routine vaccination coverage of children should be kept above 90%.[4] In fact, World Health Organization (WHO) data shows that as of October 4, 2021, the global

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vaccination rates range from 42% to 87%.[5] In other words, there is still a long way to go to increase vaccination rates among children.

Children develop at different levels, both physically and psychologically, and are susceptible to pain. The adverse effects of pain on children can be divided into short-term effects and long-term effects, short-term effects such as vaccine hesitancy and needle fear,[6] and long-term effects such as pain sensitivity, excessive anxiety, social disorders and avoidance behavior.[7] Vaccine-related pain is an important cause of low vaccination rates.[8] Most parents believe in the safety of vaccines, vaccine-related pain and the number of vaccinations were key reasons for vaccine hesitancy.[9] Therefore, alleviating vaccine-related pain is an integral part in preventing vaccine hesitancy. Vaccine-related pain management is advocated by children, parents, and clinicians,[10] and access to pain management is a fundamental human right,[11] so there is an urgent need for pain relief in children.

A variety of reasons, such as clinicians' neglect of pain management in children, family members' concerns about pharmacological addiction and side effects, the increased economic cost of pharmacological analgesia and the long response time of oral medication, all lead to the limited use of pharmacological management.[12] In contrast, non-pharmacological analgesia can reduce the dose of analgesics,[13] improve medical compliance,[14] and have low cost of use,[15] showing great advantages in children's analgesia. Therefore, the use of non-pharmacological interventions to relieve vaccine-related pain in children may be a reliable approach.

In a patient-focused review,[16] analgesic measures were divided into site-specific interventions and patient-led interventions. The review[16] found the dose of pharmacological management and the degree of participation in non-pharmacological management affected analgesic efficacy. Children's participation in non-pharmacological management is determined by their own interests. There are many non-pharmacological interventions with different effects, so it is necessary to list as many non-pharmacological interventions as possible in order to meet the analgesic needs and interests of different children. The purpose of the scoping review was to examine how research was conducted on non-pharmacological management in children with vaccine-related pain in the healthcare setting, so as to provide reference for the relief of vaccine-related pain in children.

Methods

Based on the methodological framework proposed by Arksey and O'Malley,[17] this scoping review was performed. In summary, this methodological framework involves 6 corn stages: (a) identifying the research question; (b) identifying relevant studies; (c) study selection; (d) charting the data; (e) collating, summarizing and reporting the results; (f) consultations with consumers, stakeholders and policymakers to retrieve relevant references and insights beyond the literature. Before the literature search, we identified research questions: "What types of non-pharmacological interventions have been reported in vaccine-related pain in children in the healthcare setting, and are there differences between the non-pharmacological management measures?"

Literature Search

Literature search was conducted in January 2022 in the following databases: MEDLINE, Cochrane Library, EMBASE, CINAHL, and PubMed. Search strategy included the keyword "vaccine", the keyword "pain", and the keyword "children" . The above keywords use the Boolean operator "AND" in combination. The Inclusion and exclusion criteria were formulated by the PCC mnemonic, which was proposed by Joanna Briggs Institute.[18] The PCC mnemonic consists of 3 parts: P for participants, C for concept, and C for context. Regarding participants, this scoping review included all children who experienced vaccine-related pain. Children with oral vaccine formulations were excluded because oral vaccine formulations do not cause any pain. The concept in the study refers to non-pharmacological management. Pain relief measures include pharmacological and non-pharmacological management, the study clarifies as many non-pharmacological management measures as possible for vaccine-related pain. As for context, any healthcare setting is included. There was no restriction on study design or publication date, but the language was limited to English only.

Study Selection

All retrieved literatures were imported into NoteExpress, through which duplicate literatures were deleted. Then, manual screening was performed based on inclusion and exclusion criteria, which mainly consisted of two steps. First, two authors read the title and abstract to preliminarily exclude literatures, and then read the full text to eliminate the

literatures that do not meet the requirements. If there was any disagreement regarding literature screening, the research team discussed and determined it. In order to improve the accuracy of literature selection, all members of the research team had studied evidence-based nursing courses and were familiar with the literature screening process.

Data Extraction

Data were extracted by two independent researchers using data extraction tools developed by the research team. Extracted data included general information (year, country, methodology, aim, population, and sample size) and effects of non-pharmacological interventions (control group, experimental group, duration of intervention, pain outcomes and findings). The data were extracted by one researcher and checked by another researcher, and if necessary, the discrepancy was resolved through negotiation with the third member of the research team.

Results

A total of 1017 literatures were retrieved from the preliminary search. After step-by-step screening, 22 literatures met the inclusion criteria. The literature screening process is shown in Figure 1.

Characteristics of the Included Studies

Of the 22 literatures, more than four-fifths (18/22) were published in the last 10 years. Most studies were conducted in Turkey (n=8) and Iran (n=4), followed by China (n=2). Regarding study types, there were 18 randomized controlled studies, 3 quasi-experimental studies, and 1 cohort study. The sample size for this study ranged from 60 to 537, and the primary study population was infants. The details of the general information are presented in Table 1, and the effects of non-pharmacological interventions are presented in Table 2.

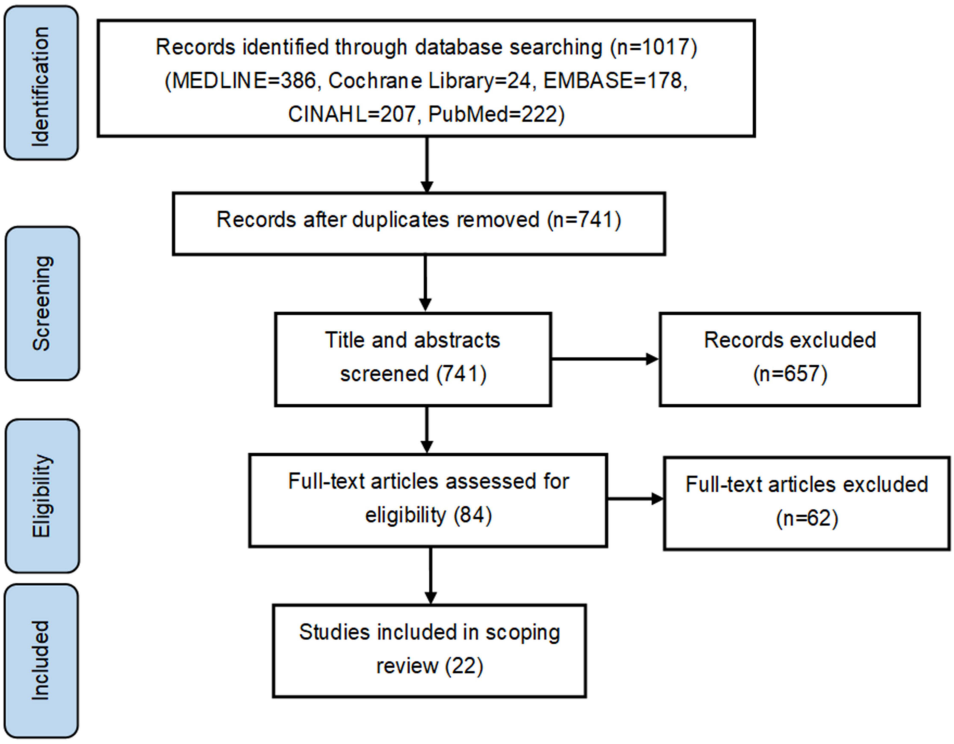

Figure 1 Flow chart of literature screening.

Table 1 Details of the General Information

Author	Year	Country	Methodology	Aim	Population	Sample Size
Rad ZA[38]	2021	Iran	Randomized controlled trial	To compare the effects of maternal breast milk odor with that of another mother's breast milk odor.	Preterm infants 28–37 weeks of gestation	90
Ueki S[29]	2021	Japan	Randomized controlled trial	To assess whether BUZZY can relieve the pain.	Healthy children under 6 years old	118
Sapci E[30]	2021	Turkey	Randomized controlled trial	To assess the effects of Buzzy on pain, fear, and anxiety.	First grade students	90
Gungor T[32]	2021	Turkey	Randomized controlled trial	To investigate the effects of local heat and cold.	Infants aged 2–6 months	96
Althumairi A[40]	2021	Saudi Arabia	Quasi-experimental study	To assess the effects of VR on pain and fear.	Children aged 4–6 years	104
Khanjari S[31]	2021	Iran	Randomized controlled trial	To assess the effects of Buzzy on pain and anxiety.	7-year-old children	105
Hatami BZ[26]	2018	Iran	Randomized controlled trial	To compare the effects of breast milk and powdered milk on pain.	1-day-old neonates	100
Lee VY[41]	2018	Australia	Randomized controlled trial	To examine the effects of exercise on vaccine-related pain, anxiety and fear.	Children aged 11–13 years	116
Gajbhiye M[24]	2018	India	Quasi-experimental study	To study the status of pain and the effects of breastfeeding and oral sucrose.	Full term vaginally delivered healthy newborns	150
Lima AG[19]	2017	Brazil	Randomized controlled trial	To compare the effects of 25% glucose and non-nutritive sucking.	Newborns	78
Göl İ[45]	2017	Turkey	Randomized controlled trial	To compare the effects of rapid injection without aspiration and 10-second manual pressure before injection.	Infants aged 4–6 months	128
Caglar S[34]	2017	Turkey	Randomized controlled trial	To assess the effects of ShotBlocker on pain.	Full-term neonates	100
Erkul M[25]	2017	Turkey	Randomized controlled trial	To compare the effects of breastfeeding.	Full-term neonates	100
Yin H[43]	2017	China	Cohort study	To compare the effects of supine position and upright position for pain relief.	Infants aged 6–12 weeks	282
Fallah R[27]	2017	Iran	Randomized controlled trial	To compare the effects of breastfeeding, kangaroo mother care (KMC), and swaddling.	Term neonates	120
Karaca CE[35]	2016	Turkey	Randomized controlled trial	To assess the effects of flick on pain.	Term neonates	70
Koç T[36]	2015	Turkey	Randomized controlled trial	To assess the effects of foot reflexology on pain.	Infants aged 1–12 month	60
Yilmaz G[20]	2014	Turkey	Randomized controlled trial	To compare the effects of 75% sucrose, 25% sucrose, and sterile water.	Infants aged 16–19 month	537
Liaw J[21]	2011	China	Randomized controlled trial	To compare the effects of non-nutritive sucking, 20% oral sucrose, and routine care.	Infants aged 36 weeks or older	165
Hatfield LA[22]	2008	America	Randomized controlled trial	To compare the effects of sterile water and oral sucrose.	Infants aged 2 months or 4 months	100
Thyr M[23]	2007	Sweden	Quasi-experimental study	To compare the effects of sterile water and 30% glucose.	Infants at 3, 5 and 12 months	110
Ipp M[46]	2007	Canada	Randomized controlled trial	To compare the pain levels of the two injection techniques.	Infants aged 4–6 month	113

Taste Intervention

The most frequent non-pharmacological management for vaccine-related pain was taste intervention (n=9). Most of the studies performed the intervention 2 minutes before the vaccination, and some continued intervention during the vaccination until the end. Combined with the findings of the taste intervention, breastfeeding was superior to sweeteners, and sweeteners were superior to sterile water or non-nutritive sucking in terms of analgesic effects for newborns and

Table 2 The Effects of Non-Pharmacological Interventions

Author	Intervention				
	Control Group	**Experimental Group**	**Duration**	**Pain Outcome**	**Finding**
Rad ZA[38]	Distilled water	Maternal breast milk odor (MBMO); Another mother's breast milk odor (BMO)	3 min before vaccination until the end	SaO_2, BP, HR and PIPP	MBMO greatly affected HR as well as pain scores compared with another intervention, but in terms of BP and SaO_2, there were no significant differences in the three groups.
Ueki S[29]	No intervention	BUZZY	15–20 s before vaccination and lasted 1–2 min	FLACC and Faces Pain Scale-Revised	No differences were observed in the researchers' assessments. However, significant differences were found in the parents' assessments.
Sapci E[30]	No intervention	BUZZY	30 s before vaccination until the end	WBFPRS	BUZZY could relieve the pain.
Gungor T[32]	No intervention	Local heat application; Local cold application	2 min before vaccination	FLACC	Local cold and heat application could relieve the pain, while local heat application was more effective.
Althumairi A[40]	No intervention	Virtual reality	2 min during vaccination	WBFPRS	Virtual reality could relieve the pain.
Khanjari S[31]	No intervention	BUZZY; Placebo (off BUZZY device without cold)	During vaccination	WBFPRS	Pain in the BUZZY group was significantly lower than the placebo and control groups.
Hatami BZ[26]	No feeding	Breastfed group; Bottle-fed mother's milk group; Powdered formula group	Feeding for 2 min in a calm environment and for at least 2 min during vaccination	Crying duration, behavioral variations (sound, face and limb) and physiological criteria (HR and SaO_2)	All the pain outcomes were significantly lower in breastfed group compared to the control, bottle-fed mother's milk, and powdered formula groups.
Lee VY[41]	No intervention	Elastic resistance bands	Exercise 15 min before vaccination	WBFPRS	Female in the exercise group reported significantly less pain than those in the control group. Females in the control group reported greater pain scores than males but not in the exercise group.
Gajbhiye M[24]	No intervention	Oral sucrose; Breastfeeding	1 mL of 25% oral sucrose was given 2 min before vaccination; Breast feeding was started 2 min before vaccination until the end	HR, SaO_2, crying duration and PIPP	The analgesic effects of breastfeeding were better than that of oral sucrose. HR, SpO2, and crying duration of oral sucrose group were significantly lower than that of control group, while the changes of physiological parameters of breastfeeding group were lower than that of control group. the changes of physiological parameters of oral sucrose group and breastfeeding group were not significant.
Lima AG[19]	25% glucose	Non-nutritive sucking	2 mL of 25% glucose was orally administered 2 min before vaccination; 2 min before and during the vaccination	NIPS, SaO_2, HR and crying time	NIPS scores and crying time in 25% glucose group were lower than those in non-nutritive sucking group.
Göl İ[45]	No intervention	10 s manual pressure, rapid injection without aspiration; 10s manual pressure combined with rapid injection without aspiration	During vaccination	NIPS, crying time, SaO2 and HR	Manual pressure and rapid injection without aspiration were effective in pain relief.
Caglar S[34]	No intervention	ShotBlocker	20 s before vaccination until the end	NIPS, HR and RR	ShotBlocker could reduce NIPS scores and heart rates.
Erkul M[25]	No intervention	Breastfeeding	5 min before vaccination	NIPS, crying time, SaO_2 and HR	Breastfeeding could reduce NIPS scores, crying time, and heart rates. Breastfeeding could also maintain SaO_2.

(*Continued*)

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Table 2 (Continued).

Author	Intervention				
	Control Group	**Experimental Group**	**Duration**	**Pain Outcome**	**Finding**
Yin H[43]	Supine position	Upright position	During vaccination	Crying, irritability and facial expression	At 30s after vaccination, crying, irritability, and pained facial expression were reduced more in supine infants than in upright infants. However, there was no significant difference in pain response between the two groups at 180 s after intervention.
Fallah R[27]	Breastfeeding	Kangaroo mother care; Swaddling	10 min before and 1 min after vaccination	NIPS and crying time	Breastfeeding was more effective than kangaroo mother care and swaddling in terms of pain relief.
Karaca CE[35]	No intervention	Flick	Flick once before vaccination	NIPS and crying time	Flick could reduce pain scores during and after vaccination. Flick could also shorten the crying time.
Koç T[36]	No intervention	Foot Reflexology	20–30 min before vaccination	FLACC, HR, SaO_2 and crying time	Babies in the foot reflexology group had less pain, lower heart rates, higher oxygen saturation and shorter crying time than those in the control group.
Yilmaz G[20]	Sterile water	75% sucrose solution; 25% sucrose solution	2 min before vaccination	Crying time and CHEOPS	75% sucrose solution group could reduce pain and crying time more than the other two groups.
Liaw J[21]	No intervention	Non-nutritive sucking; 20% oral sucrose	2 min before vaccination	NFCS, HR, RR and crying time	Crying time of 20% oral sucrose group was significantly shorter than those in the other groups.
Hatfield LA[22]	Sterile water	24% disaccharide solution	2 min before vaccination	University of Wisconsin Children's Hospital (UWCH) Pain Scale	At 2, 5, 7 and 9 min after vaccination, the pain scores in 24% disaccharide solution group were lower than that in sterile water group.
Thyr M[23]	Sterile water	30% glucose	30 s before, during and 10–30 s after the vaccination	Crying time	In the 30% glucose group, average crying time decreased by 22% at 3 months, 62% at 5 months, and 52% at 12 months. At 5 and 12 months, crying time was shorter in the 30% glucose group than that in the sterile water group.
Ipp M[46]	Slow aspiration prior to injection, slow injection and slow withdrawal	No aspiration, rapid injection and rapid withdrawal	During vaccination	Modified Behavior Pain Scale (MBPS), crying time and visual analogue scale (VAS).	Vaccination using a pragmatic rapid injection technique was less painful than a slow standard of care technique.

Abbreviations: SaO_2, blood oxygen saturation; BP, blood pressure; HR, heart rate; PIPP, premature infant pain profiles; FLACC, Face, Legs, Activity, Cry, and Consolability scale; WBFPRS, Wong-Baker Faces Pain Rating Scale; VAS, visual analogue scale; NIPS, Neonatal Infant Pain Scale; RR, respiratory rate; CHEOPS, Children's Hospital of Eastern Ontario Pain Scale scores; NFCS, Neonatal Facial Coding System.

infants.[19–25] When it comes to the method of feeding, further research showed that breastfed was better than bottle-fed and powdered formula for analgesia.[26] Furthermore, the concentration of glucose affects the analgesic effects, 75% glucose group had lower pain scores and less time crying compared to the 25% glucose group.[20] As for the comparison between taste intervention and tactile intervention, one study[27] implemented the intervention 10 minutes before and 1 minute after vaccination, the results showed that taste intervention (breastfeeding) was more effective in reducing pain than tactile intervention (kangaroo care, swaddling).

Tactile Intervention

BUZZY® is a battery powered plastic vibrating tool, measuring about 8 cm x 5 cm x 2.5 cm, shaped like a bee, the disposable or reusable ice pack is the bee's wings, which can achieve cooling and vibration function.[28] The analgesic effects of BUZZY had been confirmed in infants, preschoolers, and school-aged children,[29–31] but they were all compared to standard care, and the application effects in different age groups could not be known. In addition, a study[32] showed that topical cold application alone can also reduce pain in infants. Another tool suitable for tactile intervention is Shotblocker, a horseshoe-shaped tool with a thickness of about 2 mm, the lower surface of the tool is a short, blunt skin contact point, and the center of the tool is a hole that exposes the injection site.[33] A study[34] found that ShotBlocker can reduce NIPS scores and heart rates in term neonates, compared to standard care. The other two tactile interventions without any tools are flick and foot reflexology. Flicking once before vaccination is an extremely simple action, but it can reduce NIPS scores and crying time.[35] Compared with flick, foot reflexology takes longer time. Foot reflexology involves applying appropriate pressure to specific areas of the feet. A study[36] showed that implementing foot reflexology on 1-year-old infants means less pain, lower heart rates, higher oxygen saturation and shorter crying time.

Olfactory and Visual Intervention

Breast milk is a natural pain reliever containing beta endorphins, especially colostrum, which contains twice the concentration of beta endorphins as plasma.[37] In a randomized controlled study,[38] breast milk, another mother's breast milk, and distilled water were placed 3 cm in front of the nose of premature infants. Compared with the other two groups, there were statistically significant differences in heart rates and pain scores in breast milk group. Virtual reality (VR) is a computer technology that synthesizes a simulated environment, which mobilizes multiple senses through immersive experience, enabling users to gain immersion in a simulated three-dimensional space.[39] According to a study,[40] children wear VR glasses to watch a 3D animated adventure story, and nurses administered the vaccines synchronously according to the actions of the characters in the story. The findings showed that children in the VR group had lower self-reported pain scores than the control group. However, grouping was based on parents' preferences and children's acceptance in the study, which may be biased.

Other Intervention

After 15 minutes of elastic resistance band exercise, the self-reported pain of female adolescents was significantly lower than that of males, suggesting that exercise analgesia can be encouraged in female adolescents before vaccination.[41] WHO recommended that children should be held by a caregiver during vaccination.[42] Further study found that the supine position was more effective in reducing acute pain than the upright position when vaccinating 2-month-old infants.[43] Pre-injection aspiration was originally intended to reduce the risk of intravascular vaccine injection, but there are no large blood vessels at the injection site, so guidelines recommend rapid injection without aspiration before vaccine injection.[44] For infants 4–6 months, rapid injection without aspiration was less painful than slow injection, and the combination of manual compression provided better analgesia.[45,46]

Discussion

The management measures for vaccine-related pain in children mainly involve taste, tactile, olfactory, visual, exercise, and postural interventions and injection technique. The pain outcomes of different studies were generally similar, mainly including a series of physiological parameters such as heart rates, blood oxygen saturation, blood pressure, as well as

pain scales, crying time and behavioral variations. Non-pharmacological interventions are known to be safe and effective, but their application in vaccine-related pain needs further promotion.

Mother's unique odor stimulates the release of cholecystokinin to support pain relief,[47–49] which may explain why both breastfeeding and breast milk odor can relieve pain in children. Breastfeeding is thought to promote mother-infant bonding and provide psychological comfort,[50] which is especially suitable for neonates and infants. The analgesic mechanism of sweeteners is controversial, but its analgesic effects have been confirmed in many studies. It is important to note that the long-term effects of sweeteners on development and neurological function are not yet known,[51] the dose, concentration and duration of taste intervention require further study to clarify.

When referring to analgesic mechanisms of BUZZY, on the one hand, cold can directly affect peripheral nerves and slow down the spread of pain, on the other hand, cold can indirectly reduce pain by relieving edema, swelling and muscle spasm.[52] The analgesic mechanism of Shotblocker, flick, and foot reflexology is similar. In the Gate Control Theory,[53] the pressure exerted by massage, friction and pressure on the skin stimulates smaller diameter, faster-transmitting nerve cells, temporarily blocking the pain signal by closing the door to the central nervous system, thereby reducing the pain experienced.[35] However, the tactile intervention studies included in this scoping review were all compared to standard care, and could not compare the advantages and disadvantages of different tactile interventions.

Exercise is considered an analgesic, and its analgesic mechanisms include activation of the endogenous opioid system,[54] increase of serotonin, influence of descending inhibitory pathways, and decrease of sensory neuron activation.[55] When experiencing vaccine-related pain, 2-month-old infants do not have fully developed neck muscles for effective head control, and do not like being held in upright position. Older children, whose head muscles are fully developed, may prefer upright position.[43] As for the pain-relieving mechanism of rapid injection without aspiration, it can be explained by the shorter residence time of the needle in the skin tissue and less needle shaking.[56]

Limitations

The language of the included literature was restricted to English only, which may lead to bias. Moreover, some of the included studies were compared to standard care, so that the effects of different non-pharmacological interventions could not be compared.

Recommendations for Clinical Practice and Future Research

From existing studies comparing different tactile interventions, we can easily draw the following conclusion: for newborns and infants requiring vaccination, breastfeeding is recommended first, followed by sweeteners and non-nutritive sucking. Although there are few comparative studies of other non-pharmacological interventions, their analgesic effects have been confirmed. Diversified analgesic measures can provide more options for children's analgesia. In addition, analgesic measures should be humanized, and it is suggested that the will and preferences of the children and their parents should be fully considered when choosing an analgesic measure. Moreover, considering that different non-pharmacological interventions may have coordinated analgesic effects, a combination of non-pharmacological interventions is recommended to maximize the analgesic effects.

The study population of the current study focused on neonates and infants, non-pharmacological interventions in older children is lacking. In the future, a multi-center, large-sample, randomized controlled study should be carried out for older children. To enhance the targeting of non-pharmacological interventions, it is recommended that future studies divide children into age groups, and then compare the analgesic effects of different interventions, so as to obtain the best management measures of each age group.

Conclusions

The scoping review clarified the analgesic efficacy of different non-pharmacological interventions, which can provide reference for the relief of vaccine-related pain in children in the healthcare setting. When choosing a non-pharmacological analgesia measure, it is recommended to comprehensively consider the interests of children, the attitude of children's parents, and the effects of non-pharmacological analgesia measures, in order to adopt the best mode of analgesia and effectively reduce vaccine-related pain.

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Disclosure

All authors report no conflicts of interest in this work.

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