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Review

The efficacy of non-pharmacological interventions in the management of procedural pain in preterm and term neonates A systematic literature review

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Abstract

Background: Neonates in a neonatal intensive care unit are exposed to a high number of painful procedures. Since repeated and sustained pain can have consequences for the neurological and behaviour-oriented development of the newborn, the greatest attention needs to be paid to systematic pain management in neonatology. Non-pharmacological treatment methods are being increasingly discussed with regard to pain prevention and relief either alone or in combination with pharmacological treatment.
Aims: To identify effective non-pharmacological interventions with regard to procedural pain in neonates.
Methods: A literature search was conducted via the MedLine, CINAHL, Cochrane Library databases and complemented by a handsearch. The literature search covered the period from 1984 to 2004. Data were extracted according to pre-defined criteria by two independent reviewers and methodological quality was assessed.
Results: 13 randomised controlled studies and two meta-analyses were taken into consideration with regard to the question of current nursing practice of non-pharmacological pain management methods. The selected interventions were ''non-nutritive sucking'', ''music'', ''swaddling'', ''positioning'', ''olfactory and multisensorial stimulation'', ''kangaroo care'' and ''maternal touch''. There is evidence that the methods of ''non-nutritive sucking'', ''swaddling'' and ''facilitated tucking'' do have a pain-alleviating effect on neonates.
Conclusions: Some of the non-pharmacological interventions have an evident favourable effect on pulse rate, respiration and oxygen saturation, on the reduction of motor activity, and on the excitation states after invasive measures. However, unambiguous evidence of this still remains to be presented. Further research should emphasise the use of validated pain assessment instruments for the evaluation of the pain-alleviating effect of non-pharmacological interventions.

Keywords: Newborn; Non-pharmacological pain management; Neonatal nursing; Procedural pain

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1. Introduction

1.1. Problem statement

Intensive care treatment of preterm and sick term infants in the neonatology unit entails a period of hospitalisation which may last from several weeks to several months. These children are exposed to an environment characterised by highly variable, sometimes excessive stimulation (light, noise and activity related to monitors and respirators as well as medical emergencies), lack of diurnal variation and frequently changing caregivers. Furthermore, neonatal intensive care involves a high number of diagnostic and therapeutic procedures which are associated with pain for the neonates concerned. Stevens et al. (1999), for example, described an average of 134 painful procedures within the first two weeks of life for each of 124 preterm neonates with a gestational age of 27–31 weeks. One preterm infant even underwent 766 invasive procedures in the course of the entire hospitalisation period (Porter et al., 1998). Among 151 neonates, an average of 14 ± 4 painful interventions were recorded during the first 14 days of life within a period of 24 h (Simons et al., 2003). In a study covering 54 neonates, more than 3000 painful interventions were documented during their entire hospitalisation period, of which 74% involved preterm infants under 31 weeks gestation (Barker and Rutter, 1995). Most of the painful interventions included capillary blood sampling by heel stick, followed by endotracheal suctioning. Preliminary intermediate results from a study in Switzerland involving a random sample of the vulnerable group of intubated preterm neonates during their first 14 days of life showed a total number of 4092 interventions among 11 children alone, 64.8% of these interventions being related to intubated preterm infants below 28 weeks gestation. According to this study, every preterm infant experiences an average of 372 interventions within the first 14 days of their life (Cignacco et al., 2005, manuscript in preparation). These studies are restricted to the description of brief acute pain stimuli. The fact that neonates in an intensive care unit are also subjected to chronic pain (e.g., in the case of illnesses and abnormalities) and post-operative pain must not be disregarded.

The number of painful and distressing events (light, noise, manipulations) can influence the metabolic rate by increasing the demand for oxygen (Ambuel et al., 1992) and be the cause for cerebral oxygenation disturbances (Gagnon et al., 1999). As a number of studies show, repeated and sustained pain can have direct and long-term consequences on the neurological and behaviour-oriented development of the neonate (Anand and Carr, 1989; Grunau et al., 1994, 1998, 2001; Gagnon et al., 1999; Oberlander et al., 2000; Anand, 2000; Grunau, 2002; Peters et al., 2005). Data from animal models confirmed that prolonged exposure to pain is harmful to development. It affects the normal development of the nociceptive neural circuits and leads to an altered development of the pain system, characterised by lowered pain thresholds during later infancy (Anand et al., 1999; Ruda et al., 2000; Bhutta et al., 2001) and both hypoalgesia after puberty and hyperalgesia in adulthood (Ren et al., 2004). Therefore, strategies for stress reduction, such as the concept of developmental care (Sizun et al., 2002; Als et al., 1996), and systematic pain management are central issues in neonatal intensive care to promote the wellbeing and unimpeded development of the neonate. In particular, the use of non-pharmacological interventions is of great importance, since they are based on nurses' clinical assessment of pain and can be carried out by nursing staff without instructions by physicians. However, pain management in a neonatal intensive care unit (NICU) remains an interdisciplinary task.

1.2. Pain assessment instruments for neonates

A precondition for an adequate pain treatment procedure is the accurate assessment of the pain. Recently, a growing number of reliable and valid measurement tools for neonates have been developed. In the clinical setting, the validated instruments "Bernese Pain Scale for Neonates" (Cignacco et al., 2004), the "Premature Infant Pain Profile" (Ballantyne et al., 1999) and the "Comfort Scale" (Ambuel et al., 1992; Van Dijk et al., 2000) are widely used. However, in spite of these developments, many conceptual and measurement issues remain. Thus, the influence of contextual factors on the expression of pain, such as the gestational age and the associated immaturity of the central nervous system, as well as the influence of states of illness and of consciousness (for example, in the case of sedation during mechanical ventilation) has not yet been comprehensively explained. No instruments have been definitively validated with regard to these influences. Although the use of multidimensional instruments is recommended for pain assessment in neonates (McGrath et al., 1985; Abu-Saad, 1990, 1998; Cignacco, 2001), there are reports of either no correlation or low correlation ($r = 0.3$) between physiological and behavioural outcomes of pain (Stevens and Johnston, 1994; Barr, 1998). According to these studies, using measures which combine the interpretation of behavioural and physiological responses into a single score for assessing the efficacy of pain-alleviating interventions may not reveal the individual effects on each of the two systems. Such dissociations suggest that physiological systems are only loosely coupled to behavioural responsive systems (Barr, 1998). This renders any evaluation of the effectiveness of interventions difficult, which particularly applies to the evaluation of the efficacy of non-pharmacological interventions. According to some studies, there was only a reduction in behav-

ioural indicators, not in physiological ones (Johnston et al., 2003; Field and Goldson, 1984). The use of multidimensional instruments is therefore under discussion. The validation study of the Bernese Pain Scale for Neonates yielded contrary results. The study proved a good correlation (Cronbach's Alpha $r = 0.80$) between two physiological indicators (heart rate and oxygen saturation) and seven behavioural indicators (Cignacco et al., 2004). Consequently, the Bernese Pain Scale for Neonates also appears to be a valid pain assessment instrument in the evaluation of non-pharmacological interventions with a more marked effect on behavioural indicators. With regard to the dissociation described between physiological and behavioural indicators of individual pain assessment instruments, further validation studies are necessary.

1.3. Interventions in pain management

Up to 80–90% of the medications which are used among sick preterm and term neonates in an intensive care unit are either not approved for the illness concerned (off-label use), or are administered in a form other than that officially approved (unlicensed use) (Conroy et al., 1999; Roth, 2004). As a rule, their use is based on clinical guidelines. The reticence in systematic application for routine short interventions can be justified with a view to their long-term effects and possible side-effects (Anand et al., 2004). By contrast, non-pharmacological methods are suitable to counteract procedural pain because of their short-term efficacy and good tolerance, and are therefore increasingly being recommended for pain prevention and pain management. In order to achieve optimum efficacy, both pharmacological and non-pharmacological interventions additionally require a reduction of external stimuli, such as loud noise and bright light (Franck and Lawhon, 1998; Stevens et al., 2000). The initiation of non-pharmacological treatment is recommended for mild pain (American and Canadian Academy of Pediatrics, 2000; Anand and the International Evidence-Based Group for Neonatal Pain, 2001). Although the immature pain system in preterm infants predisposes them to greater clinical and behavioural sequelae (Anand, 2000), there has been little progress in the provision of effective procedural pain management (Anand, 2001; Anand and Selankio, 1996; Stevens, 1996).

The administration of sucrose has been the most frequently studied non-pharmacological intervention for the relief of procedural pain in neonates (Stevens et al., 1997; Blass and Watt, 1999; Kaufmann et al., 2002; Gibbins et al., 2002). The effects of sucrose are thought to be mediated by endogenous opioid pathways activated by sweet taste, and endure after sucrose is orally administered. There is evidence that the combination of sucrose and "non-nutritive sucking" is the most efficacious intervention for single heel stick (Stevens et al., 2004). However, there was some inconsistency as to the concentration of sucrose at which it was effective, and therefore the optimum concentration to be used in preterm and/or term infants has not yet been identified. There is still little evidence with regard to the long-term effect of sucrose. In a study by Johnston et al. (2002), the analgesic effect of sucrose even after several administrations has been confirmed. In the case of prolonged administration of sucrose, however, the authors describe a possible risk of impaired neurological development at the corrected age of 40 weeks gestation in preterms of less than 31 weeks gestation. Studies regarding the real long term effects, i.e., neurological outcome at one year and beyond are not available.

Although there are other non-pharmacological methods for pain relief currently in use in the neonatal setting, there is a paucity of data about their efficacy. This stresses the need for further research into the efficacy and safety of non-pharmacological management of pain in preterm infants.

1.4. Mechanism of non-pharmacological pain interventions

Non-pharmacological pain intervention is a prophylactic and complementary approach to reduce pain (Franck and Lawhon, 1998). It is assumed that non-pharmacological interventions activate the gate control mechanism (Melzack and Wall, 1965). Some of them lead to an endogenous endorphine dispersal, which contributes to the modulation of the pain pulse at the level of the spinal cord, and have the effect of relieving pain. These interventions can also activate the attention of neonates, distract them from the pain, and thus modify the pain (Bellieni et al., 2001). It is postulated that they reduce the pain by pre-empting hypersensitivity (Stevens et al., 2000). However, it is likely that further multiple parallel physiological analgetic systems are involved. Effective coping strategies, such as "maternal touch", "non-nutritive sucking" and "kangaroo care" (Johnston et al., 2003), may elicit activation of neuropeptides systems, such as cholecystokinin. Cholecystokinin is an opioid-modulating substance that promotes stressor adaptability and can achieve an analgetic effect through the potentiation of opioid activity (Hebb et al., 2005). Furthermore, infants are particularly responsive to olfactory cues emanating from their mothers' nipple regions (Porter and Winberg, 1999). Familiar odours may also stimulate the release of cholecystokinin.

1.5. Objective of the literature overview

The aim of this systematic literature review is to gain insight into the efficacy of non-pharmacological

interventions in pain management for preterm and term neonates in a neonatal intensive care setting. The selected interventions, such as ''non-nutritive sucking'', ''music'', ''swaddling'', ''positioning'', ''olfactory and multisensorial stimulation'', ''kangaroo care'' and ''maternal touch'', are all part of current nursing practice. As the use of sucrose has been reviewed recently (Stevens et al., 2004) in a Cochrane review and judged to have a high level of evidence, we choose not to investigate this intervention again.

2. Methods

In line with the research objective, a systematic search was conducted via the MedLine, CINAHL and Cochrane Library databases, and also via the Medscape provider. The literature search covered the period from 1984 to 2004, focusing on randomised controlled intervention studies and meta-analyses. Since non-pharmacological interventions are a central issue for the nursing profession, two MESH headings were entered (''Infant, Newborn'' and ''Neonatal Nursing''), working in combination with the following search terms: ''pain management'', ''neonatal pain and comfort'', ''neonatal pain and nursing intervention'', ''neonatal pain and non-nutritive sucking'', ''neonatal pain and sensory stimulation'', ''neonatal pain and music'', ''neonatal pain and facilitated tucking'' AND ''positioning'', ''neonatal pain and kangaroo'', ''pain prevention and neonate''. Studies which exclusively examined the administration of sucrose were not included in this review since the effect of sucrose alone has been extensively studied before and there is sufficient evidence available regarding its efficacy. After examining 89 abstracts, 30 studies were analysed in greater detail on the basis of established inclusion criteria (Table 1). Furthermore, a handsearch was carried out in the Bern University Library which also included the reference lists of all located articles. The search attempted to identify all relevant studies in English, German, French and Italian. In total, 13 studies and two meta-analyses were taken into consideration with regard to the question of non-pharmacological pain management methods among neonates.

2.1. Quality examination of the studies selected

The quality examination of randomised controlled trials (RCTs) includes a consensus statement prepared by an expert survey (Verhagen et al., 1998). In this context, criteria are determined which allow for qualitative statements regarding RCTs. Accordingly, important quality features of the randomisation process are the explicit determination of inclusion and exclusion criteria, the comparability of patients, double-blinding (both examiner and patient) and the intention-to-treat analysis. In this present study, with the exception of double-blinding, which is not applicable within the framework of trials involving neonates, all of these features were taken into account for the quality examination. The use of pain assessment instruments was also examined. To appraise the quality, a numeric scale of 1–10 was used, 10 representing the best score. The appraisal was shared between two authors. The independent appraisal achieved a correlation of Kappa $r = 0.613$ (see Table 2). The evidence presented by the studies was assigned on the basis of an existing and generally acknowledged classification (Gray, 1997). The studies selected do exhibit weaknesses with respect to some criteria, which does not allow for authoritative statements with regard to the efficacy of non-pharmacological interventions. These deficiencies are taken into consideration and explained in the results and discussion sections.

3. Results

3.1. Features of the studies

The studies taken into consideration (Table 2) differ with respect to the variables examined (physiological and/or behaviour-oriented parameters), the patients (ventilated and non-ventilated neonates) and the methods of the non-pharmacological interventions. ''Swaddling'' of the neonates and ''positioning'', as well as ''non-nutritive sucking'', are described as the most frequently applied methods for pain relief. Eleven studies examined the routine intervention ''heel stick'' and one study (Ward-Larson et al., 2004) focused on the relief of pain during endotracheal suctioning. The two

Table 1
Inclusion criteria

- Randomised controlled trials or meta-analysis
- German, French, Italian and English articles
- Articles on non-pharmacological interventions, which are part of current nursing practice (music, kangaroo-care, facilitated tucking, swaddling, non-nutritive sucking, olfactorial and multisensorial stimulation, positioning, etc.)
- Articles in which interventions before, during and after a painful stimulus were studied
- Articles which included preterm and term infants hospitalised in a neonatal intensive care unit up to 44 weeks gestational age
- Studies with ventilated and not ventilated preterm and term neonates

Table 2
The efficacy of non-pharmacological interventions on behavioural and physiological indicators

Authors	Design/evidence degree (Gray, 1997)	Type of intervention	Subjects	Procedure	Measures	Results	Quality assessment by 2 investigators on the basis of a numeric scale from 1–10 in accordance with the criteria by Verhagen et al. (1998) Inter-rater reliability for all the studies between two raters: Kappa $r = 0..613$		Efficacy of the interventions based on methodological criteria
Non-nutritive and nutritive sucking									
Field and Goldson (1984) USA	Design: RCT Evidence degree: II	1 Intervention during procedure: • NNS	*144 new-borns* 48 PN with IMC48 PN with IC 48 TN GA between 29 and 40	Heel stick PA unknown	Sleep–wake stateHRRR	Reduction in behaviour indicators (PN and TN with and without postnatal complications). Reduction in HR and RR (PN without postnatal complications). TN: No measures regarding HR and RR.	Author 1 6	Author 2 7	++
Shiao et al. (1997) USA	Design: Meta-analysis Evidence degree: I	1 Intervention during procedure: • NNS	281 PN and TN	Heel stick PA unknown	HR tcpAO2	Reduction in HR ($p = .0001$): The longer the NNS, the greater the effect of NNS on attenuating HR increase during procedure NNS had greater effect on tcpAO2 for PN than for TNNNS with a modified feeding nipple decreased HR and tcpAO2	Author 1 9	Author 2 8	++
Stevens et al. (1999) Canada and USA	Design: Randomised and controlled crossover design Multicentre study Evidence degree: II	3 Interventions during procedure: • Prone position • NNS with Aqua Dest (supine or side position) • NNS with sucrose 24% (supine or side position)	122 PN GA between 27 and 31	Heel stick PA between 1 and 28 days	PIPP Secondary aim of the study: Contextual variables that were controlled included GA, PA, severity of illness, frequency of painful procedures	Prone position did not decrease pain ($p = .137$) NNS with sucrose ($p < .0001$) and NNS with Aqua Dest ($p = .003$) significantly reduced pain Results indicated that GA, PA and frequency of painful procedures influence PIPP score, but only the frequency of painful procedures was significant ($p = .01$)	Author 1 8	Author 2 8	++
Bellieni et al. (2001) Italy	Design: Randomised and controlled crossover design Evidence degree: II	4 Interventions before and during procedure: • Multisensorial stimulation • Oral water 0.2–0.3 ml plus sucking • Oral glucose 10% 0.2–0.3 ml plus sucking • Oral glucose 10% without sucking	17 PN, GA < 35	Heel stick PA between 1 and 10 days	PIPP	Multisensorial stimulation and sucking plus oral glucose have a greater analgesic effect compared with no intervention. The effect of multisensorial stimulation is better than that of oral glucose plus sucking ($p < .01$) The results could be biased by the unblinded intervention (multisensorial stimulation)	Author 1 6	Author 2 6	++
Corbo et al. (2000) Italy	Design: Randomised and controlled crossover design Evidence degree: II	1 intervention during procedure: • NNS	26 PN (23 PN, GA > 25; 3 TN, GA < 39)	Heel stick PA between 1 and 14 days	Brazelton scale HR, RR, tcpAO2 HR, RR and tcpAO2 interobserver agreement at the beginning of the trial was above 90%	NNS had no effect on RR or tcpAO2, but reduced the time of crying ($p = .0001$), and the HR increased during the procedure	Author 1 5	Author 2 5	++

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Table 2 (*continued*)

Authors	Design/evidence degree (Gray, 1997)	Type of intervention	Subjects	Procedure	Measures	Results	Quality assessment by 2 investigators on the basis of a numeric scale from 1–10 in accordance with the criteria by Verhagen et al. (1998)		Efficacy of the interventions based on methodological criteria
							Inter-rater reliability for all the studies between two raters: Kappa $r = 0..613$		
Music									
Bo and Callaghan (2000) China	Design: Randomised and controlled crossover design Evidence degree: II	3 Interventions during procedure: • NNS • Music with intrauterine sounds • Music with intrauterine sounds and NNS	27 PN and TN GA between 30 and 41	Heel stick PA unknown	NIPS HR and tcpAO2h	All interventions had an analgesic effect, especially NNS combined with music ($p < .001$) Music had a greater effect on HR than other interventions ($p < .001$) tcpAO2 levels in TN were highest when the intervention in PN and TN combined music and NNS ($p < .001$)	Author 1 7	Author 2 6	++
Butt and Kisilevsky (2000) Canada	Design: Controlled crossover design Evidence degree: II	1 Intervention immediately after procedure during 10 min: • Vocal or instrumental music	14 PN GA between 28 and 34	Heel stick PA unknown	Brazelton scale, NFCS HR and SaO2	Music is an effective NICU intervention in infants older than 31 GA. The results demonstrate that music modulates physiological (reduction of HR $p < .01$) and behavioural and facial expressions of pain response in PN older than 31 GA	Author 1 6	Author 2 6	+
Facilitated tucking									
Ward-Larson et al. (2004) USA	Design: Randomised and controlled crossover design Evidence degree: II	1 Intervention during procedure: • Facilitated tucking	40 PN GA between 23 and 32	Endotracheal suctioning PA $\leqslant$ 28 days	PIPP	Significant difference between PIPP for tucking and non-tucking positions ($p = .001$) Facilitated tucking reduces the pain independently of GA	Author 1 8	Author 2 8	+++
Huang et al. (2004) Taiwan	Design: Randomised and controlled crossover design Evidence degree: II	2 interventions during procedure: • Facilitated tucking • Swaddling	32 PN GA between 25 and 36	Heel stick PA unknown	PIPP	Both interventions alleviate pain response. Swaddling, however, had a significantly greater effect, the HR returning to the baseline more quickly (after 9 min). There was no significant difference between the interventions regarding SaO2 during the procedure	Author 1 7	Author 2 7	++
Corff et al. (1995) USA	Design: Randomised and controlled crossover design Evidence degree: II	1 intervention during and until 15 min after procedure: • Facilitated tucking	30 PN GA between:(a) 25 and 28(b) 29 and 31(c) 32 and 35 Each group with 10 PN	Heel stick PA between 4 and 21 days	Sleep–wake state HR and SaO2	Time to first quieting and total crying time were reduced significantly ($p < .005$; $p < .001$). Faster return to baseline HR (6–10 min after procedure) with significantly lower mean HR in facilitated tucking group ($p < .04$). SaO2 did not show statistically significant difference between control and experimental groups.	Author 1 5	Author 2 6	++

Swaddling									
Prasopkittikun and Tilokskulchai (2003) Thailand	Meta-analysis Evidence degree: I	3 interventions during procedure: • Swaddling: 2 • Hold and maternal touch: 1 • Prone position: 1	108 PN and TN Mean for average GA: PN: 33.6 TN: 39.2	Heel stick PA unknown	NFCS PIPP	All interventions were effective in attenuating neonates' pain scores. Prone position appears to be the most appropriate non-pharmacological intervention especially for PN	Author 1 9	Author 2 9	+++
Huang et al. (2004) Taiwan	Design: Randomised and controlled crossover design Evidence degree: II	2 Interventions during procedure: • Facilitated tucking • Swaddling	32 PN GA between 25 and 36	Heel stick PA unknown	PIPP	Both interventions alleviate pain response. Swaddling, however, had a significantly greater effect, the HR returning to the baseline more quickly (after 9 min). There was no significant difference between the interventions regarding SaO2 during the procedure	Author 1 7	Author 2 7	++
Fearon et al. (1997) Canada	Design: Randomised and controlled crossover design Evidence degree: II	1 intervention immediately after procedure: • Swaddling	15 PN • 7 PN: GA 27–30 • 8 PN: GA 31–36	Heel stick PA between 13 and 16 days	NFCS Brazelton scale HR and SaO2	During the recovery period, facial activity and HR decreased more rapidly in the swaddling condition than in the control condition. This effect was shown in PN older than 31 GA For all PN swaddling resulted in a faster increase and faster stability in SaO2 not found in the control condition	Author 1 6	Author 2 7	++
Positioning									
Stevens et al. (1999) Canada and USA	Design: Randomised and controlled crossover design Multicentre study Evidence degree: II	3 interventions during procedure: • Prone position • NNS with Aqua Dest (supine or side position) • NNS with sucrose 24% (supine or side position)	122 PN GA between 27 and 31	Heel stick PA between 1 and 28 days	PIPP Secondary aim of the study: Contextual variables that were controlled included GA, PA, severity of illness, frequency of painful procedures	Prone position did not decrease pain ($p = .137$)NNS with sucrose ($p < .0001$) and NNS with Aqua Dest ($p = .003$) significantly reduced pain Results indicated that GA, PA and frequency of painful procedures influence PIPP score, but only the frequency of painful procedures was significant ($p = .01$)	Author 1 8	Author 2 8	+
Prasopkittikun and Tilokskulchai (2003) Thailand	Meta-analysis Evidence degree: I	3 interventions during procedure: • Swaddling: 2 • Hold and maternal touch: 1 • Prone position: 1	108 PN and TN Mean for average GA: PN: 33.6 TN: 39.2	Heel stick PA unknown	NFCS PIPP	All interventions were effective in attenuating neonates' pain scores. Prone position appears to be the most appropriate non-pharmacological intervention especially for PN	Author 1 9	Author 2 9	+++
Grunau et al. (2004) Canada	Design: RCT Evidence degree: II	2 interventions during procedure: • Prone position • Supine position	38 PN GA between 25 and 32	Heel stick PA 32 GA	NFCS Sleep–wake state HR	Prone position promotes deep sleep in PN at 32 GA when they are undisturbed ($p = .0001$) No significant difference between prone and supine positions ($p = .56$) Prone position is not a sufficient intervention for painful procedures	Author 1 8	Author 2 8	+
Olfactory stimulation/multisensorial stimulation									
Bellieni et al. (2001) Italy	Design: Randomised and controlled crossover design Evidence degree: II	4 interventions before and during procedure: • Multisensorial stimulation • Oral water 0.2–0.3 ml plus sucking • Oral glucose 10% 0.2–0.3 ml plus sucking • Oral glucose 10% without sucking	17 PN, GA < 35	Heel stick PA between 1 and 10 days	PIPP	Multisensorial stimulation and sucking plus oral glucose have a greater analgesic effect than no intervention. The effect of multisensorial stimulation is greater than that of glucose plus sucking ($p < .01$) The results could be biased by the unblinded intervention (multisensorial stimulation)	Author 1 6	Author 2 6	++

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Table 2 (*continued*)

Authors	Design/evidence degree (Gray, 1997)	Type of intervention	Subjects	Procedure	Measures	Results	Quality assessment by 2 investigators on the basis of a numeric scale from 1–10 in accordance with the criteria by Verhagen et al. (1998)		Efficacy of the interventions based on methodological criteria
							Inter-rater reliability for all the studies between two raters: Kappa $r = 0..613$		
Goubet et al. (2003) France	Design: RCTRCT: Venipuncture back of the hand or Heel stick Evidence degree: II	Both groups were divided into three subgroups.3 Interventions during procedure: • FAM: PN were familiarised with a vanillin odour prior to testing and during procedure • NFAM: PN were not familiarised with vanillin odour, but odour was presented during procedure • Control group: PN had no familiarisation and no odour during procedure	51 PN GA between 31 and 33	Venipuncture back of the hand or Heel stick PA between 5 and 7 days	Crying scale Grimacing scale Head movements	PN tended to cry less and grimace less when they received a venipuncture than when they received a Heel stick (moderate pain). In the venipuncture condition, PN familiarised with vanilla (FAM) showed no significant increase in crying between baseline and blood collectionSignificant reduction in grimacing in the venipuncture group during blood collection ($p < .05$) The FAM and NFAM groups (Heel stick) and the NFAM and control groups (venipuncture) showed a significant decrease in grimaces during recovery compared to blood collection ($p < .02$) In the venipuncture group, PN showed fewer head movements compared to the Heel stick condition ($p < .03$)	Author 1 7	Author 2 8	++
Kangaroo care/maternal touch									
Johnston et al. (2003) Canada	Design: Randomised and controlled crossover design Evidence degree: II	1 Intervention during procedure: • Kangaroo care (KC)	74 PN GA between 32 and 36	Heel stick PA between 1 and 10 days	PIPP HR and SaO2	Reduction in pain response 30/60/90 s after procedure ($p = .04$; $p = .002$; $p = .02$)HR and SaO2 were similar in both conditions, but the facial actions contributed significantly ($.000 < p < .005$) to the total pain score, with facial actions on average 20% greater in the control condition vs. the KC condition	Author 1 8	Author 2 8	+++
Prasopkittikun and Tilokskulchai (2003) Thailand	Meta-analysis Evidence degree: I	3 Interventions during procedure: • Swaddling: 2 • Hold and maternal touch: 1 • Prone position: 1	108 PN und TN Mean for average GA: PN: 33.6 TN: 39.2	Heel stick PA unknown	NFCS PIPP	All interventions were effective in attenuating neonates' pain scores. Prone position appears to be the most appropriate non-pharmacological intervention especially for PN	Author 1 9	Author 2 9	+++

Preterm newborn (PN); term newborn (TN); postnatal age (PA); gestational age (GA); intermediate care (IMC); intensive care (IC); neonatal intensive care unit (NICU); heart rate (HR); respiratory rate (RR); transcutaneous oxygen tension (tcpAO2); oxygen saturation (SaO2); non-nutritive sucking (NNS); randomised controlled trial (RCT); premature infant pain profile (PIPP); neonatal infant pain scale (NIPS); neonatal facial coding system (NFCS); Echelle de Douleur et d'Incomfort (EDIN).
+, low efficacy; ++, moderate efficacy; +++, high efficacy.

meta-analyses (Prasopkittikun and Tilokskulchai, 2003; Shiao et al., 1997) were likewise restricted to the heel stick. The pain response was determined with different assessment instruments, which were described in the main as valid and reliable.

3.2. Efficacy of non-pharmacological interventions

3.2.1. Non-nutritive and nutritive sucking

"Non-nutritive sucking" refers to the placement of a pacifier in an infant's mouth to promote sucking behaviour without breast or formula milk to provide nutrition. As Table 2 shows, the intervention "non-nutritive sucking" achieves a moderate effect on the behaviour of preterm and term neonates, regardless of neonatal complications (Field and Goldson, 1984; Corbo et al., 2000). As a result of "non-nutritive sucking", they become calmer and more attentive, and a reduction in crying was observed (Field and Goldson, 1984; Corbo et al., 2000). "Non-nutritive sucking" on a pacifier or a cotton wool stick also resulted in a significant reduction in the pulse rate (Field and Goldson, 1984; Shiao et al., 1997; Corbo et al., 2000) and seems to be highly effective. Interestingly, this effect was not demonstrated among neonates with neonatal complications (Field and Goldson, 1984). It was not possible to provide conclusive proof of an effect on transcutaneous partial oxygen saturation or the respiratory rate (Shiao et al., 1997; Corbo et al., 2000). One meta-analysis confirmed that the type of pacifier (shape, material) and the duration of sucking influence the physiological pain indicators (Shiao et al., 1997). Sucking on a pacifier or a cotton wool stick which had been sprinkled with distilled water, glucose 10%, or sucrose 24% resulted in a reduction in pain response. A statistically significant reduction in pain response was achieved by sucking on a pacifier with distilled water (Stevens et al., 1999; Bellieni et al., 2001). However, with regard to pain relief, sucking on a pacifier with glucose 10% was more effective than sucking on a pacifier with distilled water (Bellieni et al., 2001). This difference could not be observed between distilled water and sucrose 24%. Both interventions seem to be highly effective (Stevens et al., 1999).

3.2.2. Music

A number of studies examined the effects of different forms of music: music with intrauterine sounds, instrumental music or a capella singing (Bo and Callaghan, 2000; Butt and Kisilevsky, 2000). Regardless of the type of music, a positive effect on the pain response was invariably recorded, such as the regulation and reduction of the pulse rate, a more rapid reversion of physiological parameters to the initial values, a rise in oxygen saturation and a reduction in the excitation state. "Music" decreased the pain response particularly when combined with non-nutritive sucking in a sample of neonates from 30 to 41 weeks gestation as shown by the "Neonatal Infant Pain Scale" (Bo and Callaghan, 2000).

Butt and Kisilevsky (2000), however, could not identify an effect of instrumental music and a capella singing on the pulse rate of preterm infants below 31 weeks gestation. Facial relaxation, was also delayed in this group. Evidence of a pain-relieving effect achieved by instrumental music and a capella singing was only confirmed in preterm infants older than 31 weeks gestation, which was measured by the "Neonatal Facial Coding System". This study, however, is restricted in its analytical value because of the small randomised sample size (14 neonates). The authors of both studies are in agreement that "music" should not be provided for longer than 15 min per intervention due to the risk of sensory overload.

3.2.3. Facilitated tucking

"Facilitated tucking" (see Picture 1) was tested in three studies with randomised samples of 30–40 preterm infants (Corff et al., 1995; Ward-Larson et al., 2004; Huang et al., 2004). The authors describe facilitated tucking as an effective pain-relieving intervention. "Facilitated tucking" leads to a significant reduction in the pulse rate. Time to first quieting and total crying time were reduced significantly in comparison to the control group (see Table 2) (Corff et al., 1995). With regard to oxygen saturation, however, this intervention showed no effect (Corff et al., 1995; Huang et al., 2004). It is important to mention, that Corff et al., 1995 did not use an objective measurement tool, but based the assessment on heart rate, oxygen saturation and sleep/wake state. The other two studies used the "Premature Infant Pain Profile" as an outcome measure of pain. Among a group of 40 intubated and ventilated preterm neonates between 23 and 32 weeks gestation, "facilitated tucking" during endotracheal suctioning achieved significant pain relief (Ward-Larson et al., 2004).

Picture 1.

3.2.4. Swaddling

"Swaddling" involves wrapping the neonates in a fabric cloth (see Picture 2). Among 15 preterm infants aged above 31 weeks gestation, it was found that "swaddling" after a painful intervention was associated with a clear reduction in the pulse rate (Fearon et al., 1997). Among preterm infants under 31 weeks gestation, by contrast, no effect could be demonstrated with this intervention. A contradictory result was obtained by Huang et al. (2004), who found in their study of 32 preterm infants that swaddling was even effective, as measured by the "Premature Infant Pain Profile", for infants younger than 31 weeks (Ballantyne et al., 1999). Likewise, "swaddling" is described as having an effect on oxygen saturation for all age groups (Fearon et al., 1997). During the recovery phase, the preterm neonates demonstrated a significantly faster increase in oxygen saturation, and in the process attained stability more rapidly than the control group. Again, however, a contrary result was obtained by Huang et al. (2004): neither during nor after the intervention was any significant effect on oxygen saturation recorded. The behaviour-oriented indicators, such as facial mimicry, body language and crying, were attenuated as a result of "swaddling" (Fearon et al., 1997; Huang et al., 2004) although, in the former study, this effect could only be demonstrated in neonates older than 31 weeks gestation. In a meta-analysis with a random sample of 108 term and preterm neonates, a pain-relieving effect was also recorded, the effect being maintained, interestingly, for a longer time among term infants (up to 4 min). Among preterm infants, the effect was also present but lasted for a significantly shorter time (Prasopkittikun and Tilokskulchai, 2003).

3.2.5. Positioning

Laying the neonate in a prone position is a frequent measure in everyday practice as it is expected that the counter-pressure of the mattress will relieve the pain being experienced. Furthermore it promotes better breathing and a decrease of oxygen needed. In a meta-analysis, the non-pharmacological interventions of "swaddling", "maternal skin contact" and "positioning" were found to have a moderate (mean effect size 0.53, 95% CI = 0.27–0.80) to large (mean effect size 0.79, 95% CI = 0.27–0.80) effect as methods of pain relief (Prasopkittikun and Tilokskulchai, 2003). The findings suggest that the moderate to large effect of "positioning" continued throughout the poststick period. In contrast, the effects of "swaddling" (in both full-term and preterm neonates) and of "maternal holding and touching" tended to decrease over time. Grunau et al. (2004) were unable to confirm the effect of the prone position. It was, however, observed that during the measurement of the baseline before the painful intervention, the prone position was an indication of deeper sleep in preterm neonates than in the control group. Likewise in a further study with 122 very preterm infants was concluded that the prone position did not have a pain-relieving effect (Stevens et al., 1999). The evidence for the effect of "positioning" remains inconclusive.

Picture 2.

3.2.6. Olfactory and multisensorial stimulation

In accordance with study results which showed a stress-relieving effect of the smell of breast milk, Goubet et al. (2003) tested the hypothesis that a familiar odour might be effective in relieving distress associated with painful stimuli in preterm infants. They tested the pain-relieving effect of a familiar vanillin aroma among preterm neonates while sampling capillary blood or while taking venous blood. In both groups, three interventions were tested: one group was familiarised with a vanillin odour prior to testing and was presented with it during the procedure; the second group was not familiarised with vanillin but was presented with it during the procedure; the third group was neither familiarised nor presented with an odour at all. In the group familiarised with the vanillin aroma, pain relief was demonstrated by a significant reduction in facial mimicry and crying, but only while taking venous blood. While drawing capillary blood, no effect was observed. This indicates that the olfactory intervention is probably only effective in cases of slight to moderate pain. The authors concluded that presenting a purely "attentional distracter" like an unfamiliar odour did not relieve the pain in newborns. Only when the odour presented was an "experiential distracter" could a pain-relieving effect be achieved. They qualified the familiar odour as "experiential" because its effect rested on a prior memory of the encounter with the odour in the incubator. Similar results were obtained by the testing of "multisensorial stimulation" (Bellieni et al., 2001). "Multisensorial stimulation" addresses the neonate on a number of different sensory levels: tactile, auditory, olfactory and orogustatory. The neonate

is calmed during, and in particular after, a painful stimulus in a tactile manner by massaging his/her back and face. A few drops of a pleasant-smelling oil are spread onto the hand used for this (orogustatory level). During the massage, the child is also spoken to gently (auditory level). Furthermore, the infant is provided with a cotton wool stick which has been sprinkled with glucose 10% so that he/she can suck on it (olfactory level). In a study of 17 preterm neonates, the authors were able to describe this intervention as being significantly more pain-relieving than when using distilled water and standard nursing. In particular, this intervention had a positive effect on crying, with the multisensorially stimulated preterms not expressing any crying reaction. However, Bellieni et al. (2001) specify that the assessment of the intervention of ''multisensorial stimulation'' was not blinded, which is to be criticised as a clear bias and calls into question the efficacy of this non-pharmacological intervention as described.

3.2.7. Kangaroo care and maternal touch

''Kangaroo care'' involves the neonate being taken out of the incubator and laid on the bare skin of the mother or father. The neonate is covered with towels so that there is no loss of body temperature. A study of 74 preterm neonates older than 32 weeks gestation confirmed that ''kangaroo care'' produces a reduction in pain response, using the ''Premature Infant Pain Profile'' as a validated pain assessment tool (Johnston et al., 2003). The ''kangaroo care'' intervention showed a significant reduction in pain response in comparison with the controls at 30, 60 and 90 s after the painful procedure. Heart rate and oxygen saturation were similar in both groups, but the facial activity as an indicator of pain being experienced was on average 20% more marked in the control group. One meta-analysis (Prasopkittikun and Tilokskulchai, 2003) described the greatest pain-relieving effect occurring with ''maternal calming'' rather than with ''swaddling'' and ''positioning'', but the effect dropped off more rapidly in comparison with the other two interventions, where it was sustained over 4–5 min. Pain relief was only described for term neonates; preterm neonates had not been taken into consideration in the studies covered by the meta-analysis. There are no results at all for preterm neonates below the gestational age of 32 weeks.

4. Discussion

The present systematic literature review provides evidence that non-pharmacological interventions do have a pain-relieving effect among preterm and term neonates. The results indicate that non-pharmacological methods mitigate both physiological and behaviour-oriented reactions. In particular, ''non-nutritive sucking'', ''swaddling'' and ''facilitated tucking'' seem to have an evident pain-relieving effect. A considerable limitation concerning the verification of efficacy is the fact that all the non-pharmacological measures discussed were tested exclusively with one-off painful procedural interventions. Neonates in a neonatal intensive care unit are subjected to a large number of painful stimuli, but it remains unclear whether the non-pharmacological methods described also have a beneficial effect on any possible long-term consequences of prolonged exposure to pain. Unfortunately, there are no studies available on this subject.

The influence of contextual factors (gestational age, state of illness, state of consciousness) is still a matter of controversy. Butt and Kisilevsky (2000) and Fearon et al. (1997) were able to determine the pain-relieving effect of music and swaddling exclusively among neonates of more than 31 weeks gestation. For preterm neonates younger than 31 weeks, these interventions for pain relief only had an effect on oxygen saturation but not on the behaviour of the neonates. Both studies are limited in their analytical value because of their small sample sizes (14 and 15 neonates, respectively). Prasopkittikun and Tilokskulchai (2003) found a rapid recovery phase in swaddled preterm and term neonates, the preterm neonates being older than 31 weeks gestation. The pain-relieving effect was, however, observed to last longer among term neonates than among preterm infants. Both ''olfactory and multisensorial stimulation'' achieve pain relief regardless of the infants' gestational age. Bellieni et al. (2001) describe significant pain relief after exposure to pain. These results must be interpreted with caution, however, due to the methodological deficits. In addition, the neonates' state of health is described as an influencing variable; the non-pharmacological intervention of ''non-nutritive sucking'' achieved an effect among healthy preterm neonates only, not among sick neonates (Field and Goldson, 1984). For the latter group, changes were only shown in their behaviour (facial mimicry, body language), but not in pulse rate, respiration or oxygen saturation. Stevens et al. (1999) were unable, however, to demonstrate any difference in pain expression either among extremely preterm neonates or among sick preterm infants in comparison with healthy and older ones. Sucking on a pacifier with distilled water or with glucose 10% attained a pain-relieving effect in all the neonates in this study. By analysing 10 studies ($n = 281$), Shiao et al. (1997) were able to confirm a significant effect of ''non-nutritive sucking'' in all the preterm and term neonates examined.

Among the highly vulnerable group of intubated preterm neonates with a restricted state of consciousness caused by sedatives, ''facilitated tucking'' achieved a perceptible pain-relieving effect with regard to

endotracheal suctioning (Ward-Larson et al., 2004). This is to be emphasised, in particular, since endotracheal suctioning represents the second most frequent painful intervention, following capillary blood sampling. The question also arises in this context, however, as to whether the neonates' behaviour-oriented expression of pain is influenced by sedatives. This is not critically discussed in the study.

4.1. Methodological constraints

There are a number of methodological deficiencies to be taken into account in the interpretation of the results. For example, four of the studies analysed did not use a validated pain assessment instrument for preterm and term neonates (Field and Goldson, 1984; Corff et al., 1995; Corbo et al., 2000; Goubet et al., 2003). In these studies, the calming of the preterm neonates was examined only on the basis of pulse rate and oxygen saturation. These parameters may give an indication of a possible state of pain, but they are regarded in isolation from other pain indicators, such as facial mimicry, body language or crying; the studies are therefore unreliable in their conclusion regarding pain. In addition, precise data are missing as to how the blinding in respect of the pain assessment was carried out. A number of studies indicate that video recordings were made, which were then manipulated in such a way that the intervention could not be identified, while other studies provide no details regarding this. Bellieni et al. (2001) specify that the assessment of the intervention of "multisensorial stimulation" was not blinded, which is to be criticised as a clear bias and calls into question the efficacy of this non-pharmacological intervention as described. In 10 studies the sample size was very small, with less than 50 neonates, which undoubtedly affects the power to detect the effects of the interventions under study. It is expressly to be pointed out, that the vulnerability of preterm neonates is one of the crucial factors which undoubtedly hinders the inclusion in randomised trials. A further critical issue is the lack of standardisation of non-pharmacological interventions. The handling can be subjected to many individual factors of health care providers, which not only hampers comparison but complicates controlling and testing these interventions in RCTs.

The investigation methods follow a randomised controlled procedure and correspond in the majority of cases to an evidence degree II (Gray, 1997). This high quality of the evidence is, however, prejudiced by the criticism already voiced. To support the evidence in favour of non-pharmacological interventions, care would have to be taken in future investigations to ensure the use of validated instruments and consistent blinding.

5. Conclusion

This present study supports the view that the non-pharmacological nursing interventions described are to some degree beneficial to neonates who undergo painful procedures. Contextual factors, such as the gestational age or the neonates' state of health, do not yet allow for any conclusive answers with regard to the efficacy of non-pharmacological interventions. It remains an open question as to which non-pharmacological measures relieve pain in the vulnerable group of sick and ventilated preterms. Further studies need to be conducted in this respect, in order to promote the welfare of these preterm neonates and to allow them to experience normal cognitive and motor development.

It needs to be emphasised, however, that non-pharmacological interventions cannot replace pharmacological treatment in cases of severe and chronic pain. Future research projects should address the question of whether non-pharmacological interventions are an effective measure in pain relief among the vulnerable group of ventilated or severely sick preterm and term neonates suffering from chronic pain.

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