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Efficacy of facilitated tucking combined with non-nutritive sucking on very preterm infants' pain during the heel-stick procedure: A randomized controlled trial

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ABSTRACT

Background: Reducing acute pain in premature infants during neonatal care improves their neurophysiological development. The use of pharmacological and non-pharmacological analgesia, such as sucrose, is limited per day, particularly for very preterm infants. Thus, the usual practice of non-nutritive sucking is often used alone. Facilitated tucking could be an additional strategy to non-nutritive sucking for reducing pain. To the best of our knowledge, no randomized trial has compared the combination of facilitated tucking and non-nutritive sucking to non-nutritive sucking alone.

Objectives: To compare the efficacy of facilitated tucking in combination with non-nutritive sucking (intervention group) to non-nutritive sucking alone (control group) in reducing pain during the heel-stick procedure in very preterm infants.

Design: Prospective, randomized controlled trial.

Settings: Level III and II neonatal care units, including the neurosensory care management program.

Methods: Very preterm infants (gestational age between 28 and 32 weeks) were randomly assigned by a computer programme to the intervention or control group during a heel-stick procedure within the first 48 h of life. In both groups, infants were placed in an asymmetric position on a cushion; noise and light were limited following routine care. A heel-stick was performed first in the care sequence. In the intervention group, facilitated tucking was performed by a nurse or nursing assistant. The procedure was video recorded from 15 s (T-15 s) before the procedure until three minutes (T + 3 min) after the end of the procedure. Pain was blindly assessed by two independent specialist nurses. The primary outcome was the pain score evaluated 15 s before the procedure and 30 s immediately after by the premature infant pain profile (PIPP) scale. The secondary outcome was the pain score evaluated between T-15 s and T + 3 min by the DAN scale (a French acronym for the acute pain of a newborn).

Results: Sixty infants were included (30 in each group). The PIPP pain scores did not differ between the intervention group (median: 8.0; interquartile range (IQR): 6.0–12.0) and the control group (median: 9.5; IQR: 7.0–13.0, $p = 0.32$). Pain assessed by the DAN scale at T + 3 min was lower in the intervention group than in the control group (median: 0.3; IQR: 0.0–1.0 and 2.0; IQR: 0.5–3.0, respectively, $p = 0.001$).

Conclusions: The combined use of facilitated tucking and non-nutritive sucking did not significantly alleviate pain during the heel-stick procedure. However, the addition of facilitated tucking facilitated faster pain recovery following the heel-stick procedure.

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What is already known about the topic?

- Infants in intensive care units receive numerous painful procedures daily, including heel-sticks. During care procedures, it has been observed that only half of all newborns receive specific pain relief based on pharmacological and non-pharmacological treatment.
- The use of pharmacological and non-pharmacological analgesia, such as sucrose, is limited per day, particularly for very preterm infants. Thus, non-nutritive sucking is often used alone in this population and is not sufficiently effective in alleviating pain.
- Facilitated tucking can easily be used by health care givers or parents and might help reduce behavioural and physiological manifestations of pain.

What this paper adds

- Relative to non-nutritive sucking, manifestations of very preterm infants' pain evaluated before the heel-stick procedure and 30 s after were not significantly reduced by the addition of facilitated tucking.
- Facilitated tucking combined with non-nutritive sucking may reduce pain at three minutes post-procedure. Whereas non-nutritive sucking is often used when sucrose can no longer be administered, the combination of facilitated tucking and non-nutritive sucking is a notable alternative that merits further exploration.

1. Introduction

Preterm infants are those born alive before 37 weeks of pregnancy are completed. They represent an estimated 15 million infants per year worldwide (World health Organization, 2018). In many countries, an increase in preterm births has been observed in recent years, e.g., France, where preterm births increased from 5.9% in 1995 to 7.5% in 2016 (Enquête Nationale Périnatale, 2016). Among preterm infants in France, 10% are very preterm, born between 28 to 32 weeks of gestational age (Ancel and Rozé, 2015).

The gap between the intrauterine and intensive care unit environments is distressing for preterm infants at a crucial time in their cerebral maturation (Grunau, 2013). Preterm infants are subjected to noise, light, touch and frequent painful procedures. A mean of 16 (range: 0–62) painful procedures per day per infant was observed during a 2-week study in neonatal intensive care units, of which cutaneous procedures, including the heel-stick, were one of the most frequent procedure types (Carbajal et al., 2008). Early nociceptive stimulations are remembered, particularly in very preterm infants, enhancing later sensitivity to pain, with more pronounced painful behavioural manifestations in childhood and consequences on cognitive development (Brummelte et al., 2012; Grunau, 2013; Ranger and Grunau, 2014; Valeri et al., 2016; Vederhus et al., 2012; Vinall et al., 2014; Zwicker et al., 2012).

Despite important improvements in techniques leading to a better survival rate of premature infants, pain management greatly varies among neonatal units. To reduce pain during a heel-stick procedure, intermittent doses of opioid analgesics may be administered but are not efficient (Axelin et al., 2009). The use of topical anaesthetic cream is recommended only once a day because of its toxicity, and it is not often used (Carbajal et al., 2008). A large spectrum of non-pharmacological analgesia is available (Pillai Riddell et al., 2015). A prospective observational study in intensive care units including 562 preterm infants showed that only half of the infants received specific pre-procedural analgesia with pharmacological and non-pharmacological methods, including nutritive sucking with a sweet solution, such as sucrose, and non-nutritive sucking with sterile water (Courtois et al., 2016). Sucrose is an efficient pain reliever for procedural pain, but its administration is limited to four times a day since sucrose can be harmful for muscle tone, motor development, vigilance and orientation (Johnston et al., 2002). The long-term effects of sucrose administration on preterm infants have been extensively studied, showing deleterious impacts on cortical and subcortical grey and white matter (Holsti and Grunau, 2010; Tremblay et al., 2017). Non-nutritive sucking is also used for reducing pain in preterm infants. This strategy reportedly has superior pain-relieving effects compared with those of controls, routine comfort or gentle touch and verbal comfort (Liaw et al., 2012, 2010), but has lower efficacy than sucking with sucrose (Stevens et al., 2016).

Supportive care for sensorimotor development, also called developmental care, aims to improve the environment of the premature infant and adapt care interventions in response to his/her physiological needs (Bullinger, 2015). These developmental care methods are based on environmental and behavioural strategies and the involvement of the parents in the care of their infant. The main objective of developmental care is to reduce sensorimotor adverse stimulations (Bullinger, 2015). Among the different techniques, the facilitated tucking position may improve the self-regulation of stress and may reduce pain in preterm infants (Lopez et al., 2015). This method requires placement of the infant in the foetal position using the hands of health care givers or parents, maintaining an asymmetric position (Bullinger, 2015). This method is straightforward to implement. Infants are contained but not restrained in their movements, which might reassure them and support a fast return to the baseline state after a painful procedure (Axelin et al., 2009).

Several studies have evaluated the efficacy of the facilitated tucking method on preterm infants' pain during the heel-stick procedure with contrasting results (Axelin et al., 2009; Cignacco et al., 2012; Gerull et al., 2013; Gitto et al., 2012; Huang et al., 2004; Liaw et al., 2012; Peng et al., 2018; Yin et al., 2015). Among them, two randomized studies showed no benefits to infants born between 24 and 32 weeks of pregnancy (Gerull et al., 2013; Gitto et al., 2012), whereas four other studies conducted in infants born between 24 and 37 weeks favoured facilitated tucking in conjunction with other methods (Cignacco et al., 2012; Liaw et al., 2012; Peng et al., 2018; Yin et al., 2015).

When sucrose can no longer be administered daily to very preterm infants, non-nutritive sucking is often the only possible procedure to reduce pain during a heel-stick. In that situation, combining facilitated tucking with non-nutritive sucking may have interesting pain-relief effects. However, only one study evaluated the combination of facilitated tucking and non-nutritive sucking in infants born between 27 and 37 weeks, and no benefit was reported relative to gentle touch (Yin et al., 2015). No randomized study has evaluated the combination of facilitated tucking and non-nutritive sucking relative to non-nutritive sucking alone specifically in the very preterm infant population. The Babydoul study [French study name for *'baby'* and *'pain'*] was designed to evaluate the efficacy of adding facilitated tucking to non-nutritive sucking to reduce pain in very preterm infants. This study aimed to address the following research question: do pain scores between very preterm infants receiving non-nutritive sucking alone and infants receiving facilitated tucking combined with non-nutritive sucking differ during the heel-stick procedure?

2. Methods

2.1. Design and settings

This prospective randomized controlled trial was conducted from April 2014 to August 2015 in the level III and level II neonatal intensive care units of a French hospital (Paris), totalling 1670 admissions per year. The very preterm infants included in this study were assigned to either the intervention group (facilitated tucking combined with non-nutritive sucking) or the control group (non-nutritive sucking alone).

2.2. Randomization and allocation

Centralized block balanced randomization in a 1:1 ratio was computer generated by an independent statistician. After obtaining parental

written consent, the nurse investigator electronically randomized the infant and learned the allocation group. The nurses and parents could not be blinded to the allocation because of the nature of the intervention. However, the outcome assessment of the videos was blinded.

2.3. Eligibility criteria

Eligible participants were very preterm infants hospitalized in the participating units born between 28 to 31 weeks + 6 day, with a postnatal age less than 48 h, requiring more than four heel-stick procedures a day and with a validated sucking reflex. The sucking reflex was validated by a nurse who performs oral solicitations, which are performed daily in current practice before starting each nursing care sequence. Gestational age was defined as the time (in weeks) from the first day of the last menstrual period to the date of birth. Infants who had neurological impairment, haemodynamic instability or perinatal asphyxia or who received curare or local anaesthetics were not included. All infants welcomed into the unit during the inclusion period falling in the study age group were verified for eligibility.

2.4. Informed parental consent

After confirming the eligibility criteria of infants, mothers, most of whom were hospitalized, and fathers were contacted by a nurse to make an appointment. At the first meeting with the parents, clear information on the study's objectives and steps in each group (intervention or control) was delivered by the nurse. It was clearly mentioned that participation in the study was voluntary and that refusal would not affect the care received in the unit. If necessary, a second meeting was organized by the nurse within 24 h.

Consent of at least one parent following a reflection period of 8 h or more was required before inclusion and randomization.

The information on the study given by the nurse and the consent was recorded in the medical file. Parents received copies of the signed information sheet and consent form, which were placed in a tamper-proof sealed envelope and archived by the nurse investigator and sponsor.

2.5. Intervention procedures

In both groups, every three hours, the infants received standard care, including that described in the developmental care method according to Bullinger (Bullinger, 2015), respecting environmental precautions such as reducing visual and auditory over-stimulation (decreased brightness, alarm reductions, door closures). Infants were placed in an asymmetric three-quarter position that was maintained using a micro-granular cushion (Bullinger, 2015). The nurse started the care sequence when the infant was calm. The heel-stick, a very quick puncture requiring only a few seconds, was the first procedure performed in the care sequence.

In the control group, while a nurse performed the heel-stick procedure, physiological measurements of the highest value of heart rate and the lowest value of oxygen saturation were recorded by a second nurse before the procedure and immediately after the procedure for 30 s based on continuous and systematic measurements of heart rate and oxygen saturation levels acquired for each infant in the unit with an individual monitor. The functioning of the monitors was checked daily by a nurse and controlled yearly by external biomedical staff. The nurse assistant maintained the Evoprene™ pacifier for 3 min after the heel-stick procedure.

In the intervention group, either a nurse or nurse assistant prepared the infant in the facilitated tucking position at least 15 s before the heel-stick procedure. The infant's arms and legs were held by the nurse in flexed positions close to the midline of the chest, while one nurse's hand was gently placed under the infant's neck and maintained the pacifier with sterile water; the other hand was placed on the buttocks (Bullinger, 2015). A second nurse performed the heel-stick procedure, and a third nurse recorded the physiological measurements, as described above. The facilitated tucking procedure was maintained for 3 min after the heel-stick procedure.

In both groups, video recording was performed by the nurse in charge of the physiological measurements, recording from 15 s (T-15 s) before the procedure until 3 min (T + 3 min) after the end of the procedure. The recorder was placed on a tripod and the nurse assessed the clearness and field of view according to the study procedure. The videos enabled external evaluators to perform remote evaluations.

All nurses participating in the study were previously trained on the facilitated tucking procedure. This procedure was included in a general two-day training on development care offered to the unit by a nurse expert for newly recruited nurses. Before the start of the study, each nurse and nurse assistant received refresher training provided by the principal investigator on the facilitated tucking method and on both group processes (intervention and control), which were detailed in dedicated written procedures distributed to each nurse. The study fidelity was established by monthly distributed letter recommendations and regular meetings between the principal investigator, nurses and research team to review procedures and discuss any problems encountered.

2.6. Outcome measures

The primary outcome was the pain score assessed with the premature infant pain profile (PIPP) scale, a validated and widely used tool to measure periprocedural pain in preterm infants (Ballantyne et al., 1999; Stevens et al., 1996); this technique evaluates seven items of neonatal pain from 15 s before the procedure until 30 s after the procedure (Fig. 1). Each item is scored for pain on a 4-point scale, for a total score ranging from 0 to 21. Two indicators are measured for 15 s before the intervention and are included in the final score: gestational age and sleep state. Five criteria are evaluated immediately after the intervention for 30 s: physiological changes in heart rate, oxygen saturation, and facial expression related to brow bulging, eye squeezing and nasolabial furrowing.

The secondary outcome was the pain score assessed with the "*douleur aiguë du nouveau-né*" (DAN, a French acronym for the acute pain of a newborn) scale, a validated acute pain scale (Carbajal et al., 1997) with a score rated before the procedure (T-15 s), during the procedure (T0) and after the procedure (T + 3 min). The pain scale score ranges from 0 to 10 and evaluates three indicators of neonatal pain. The first indicator, facial expression of physical pain, is rated on a 5-point scale, and the two other indicators, limb movements and vocal expression of pain, are rated on a 4-point scale.

The outcomes were assessed at the end of the study by two external nurses who separately watched the video sequences second-by-second using a timer in a quiet room. All the evaluators had an additional degree in paediatric nurse care and several years of experience in neonatal care in which they were used to observe and graduate pain manifestations. Before the start of the study, the evaluators had a

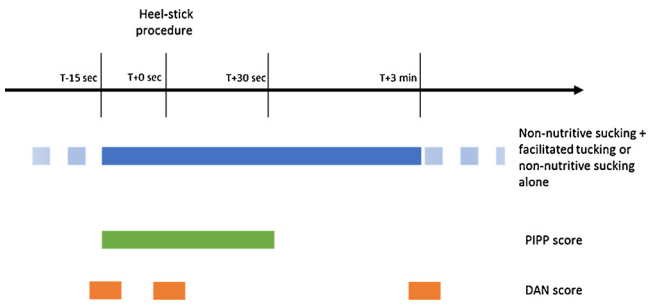

Fig. 1. Study procedures.

refresher training course on the use of tools provided by the research team. Each evaluator was blinded to the study design and goal and to the study group allocation.

In the case of disagreement between the two evaluators for the PIPP score (i.e., a score difference greater than 50%), a third expert's assessment was obtained, and only the score from the third evaluator was considered. The third evaluator was the most experienced.

2.7. Sample size

Based on Gibbins's study, we expected a reduction in the PIPP score of at least 20% (10.19 in the control group versus 8.15 in the intervention group, with a standard deviation of 2.67) (Gibbins et al., 2002). Considering a two-sided α of 5% and an anticipated dropout rate of 10%, 60 infants were needed to achieve 80% power.

2.8. Statistical methods

The statistical analysis was based on the intention-to-treat population. Baseline characteristics of patients in the two study groups were reported using frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables.

Primary and secondary outcomes were analysed using a Wilcoxon-Mann-Whitney test. The mean percent change in the DAN score between T-15 s and T0 was analysed between groups using a Wilcoxon-Mann-Whitney test to establish whether the two groups were the same at baseline. Missing data were accounted for by imputing the maximum score (20 for the PIPP score and 10 for the DAN score) (Pedersen et al., 2017).

Sensitivity analysis was performed using linear regression to assess the impact of the strategy on the PIPP score (log transformed) independently of the weight at inclusion, gestational age and number of previous cutaneous procedures (i.e., venepuncture, arterial puncture, lumbar puncture, intra-muscular injection and heel-stick received from birth to the study procedure were systematically reported by the nurse in charge). Furthermore, PIPP and DAN scores were analysed regarding non-invasive ventilation, which could have altered the evaluation of the scores, using the Wilcoxon-Mann-Whitney test.

Concordance between the two first evaluators for the PIPP and DAN measurements were evaluated using the intraclass correlation coefficient (ICC) and its 95% confidence interval assessed by the bootstrap approach.

All tests were two-sided, and the statistical significance was defined as $p < 0.05$. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA) and R freeware, version 3.1.2 (R Core Team, 2016). The trial was registered (ClinicalTrials.gov Identifier: NCT02096822).

3. Results

3.1. Participants

Sixty very preterm infants were included and randomized: 56 in the level III unit and three in the level II unit (31 females, 28 males), and one infant was excluded because his/her parents withdrew their consent (Fig. 2). One infant did not receive the intervention strategy because of a worsening health condition. The video record was lost for one infant in the control group.

Demographic and clinical baseline data characteristics are described in Table 1. The median gestational age was 30.0 weeks (IQR: 29.0–30.0 weeks) in the control group and 29.0 weeks (IQR: 28.0–31.0 weeks) in the intervention group. The median weight the day of the procedure was 1235.0 g (min, max: 760.0, 1810.0 g) in the control group and 1290.0 g (min, max: 890.0, 2100.0 g) in the intervention group. In both groups, the median number of cutaneous procedures received by the infants from birth to the time of the study procedure (less than 48 h of life) was 12.0 (min, max: 4, 56).

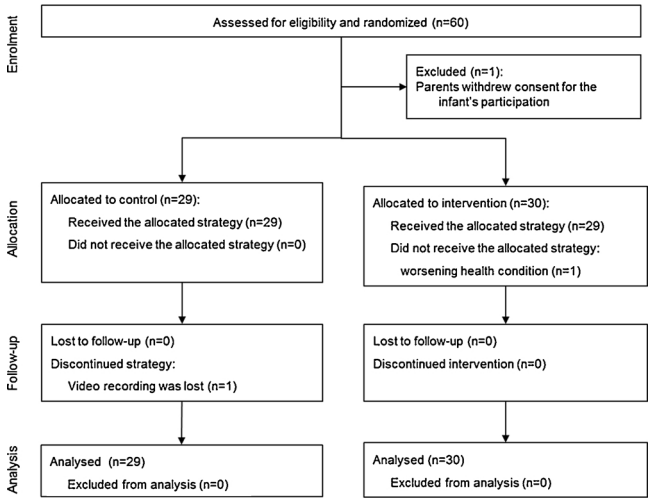

Fig. 2. Flow diagram.

3.2. Primary outcome

The median PIPP scores did not differ between the intervention group (8.0; IQR: 6.0–12.0) and the control group (9.5; IQR: 7.0–13.0, $p = 0.32$) (Table 2). The results remained unchanged after adjustment for weight at inclusion, gestational age, and number of previous cutaneous procedures.

Two infants had a missing value for the primary outcome, and their scores were replaced by the maximum score. For ten infants (17.2%), the PIPP score assessed by the third evaluator was used.

3.3. Secondary outcome

The median DAN scores were lower at T-15 s and at T + 3 min in the intervention group than in the control group. At T-15 s, the median DAN score was 0.0 (IQR: 0.0–1.0) in the intervention group and 1.0 (IQR: 0.5–2.0) in the control group ($p = 0.03$). At T + 3 min, the scores were 0.3 (IQR: 0.0–1.0) and 2.0 (IQR: 0.5–3.0), respectively ($p = 0.001$).

However, the median DAN scores were not different between groups during the procedure at T0. Two infants had a missing value for this outcome, and their scores were replaced by the maximum scores.

The mean percent change in the DAN score between T-15 s and T0 did not differ between the two groups ($p = 0.16$).

Each score, PIPP and DAN, was analysed for infants with or without non-invasive ventilation, and no difference in the median score was found (data not shown).

The ICC was 0.68 (95% confidence interval (CI): 0.52–0.80) for the PIPP score, 0.78 (95% CI: 0.67–0.87) for the DAN score at T0 and 0.69 (95% CI: 0.39–0.86) for the DAN score at T + 3 min.

4. Discussion

In the present randomized study, the addition of the facilitated tucking procedure to non-nutritive sucking in very preterm infants did not significantly improve the PIPP pain score during a heel-stick procedure. However, when assessed with the DAN scale, the pain score was lower at baseline and at 3 min after the procedure with the combined strategy. To the best of our knowledge, this is the first randomized study evaluating the facilitated tucking procedure combined with non-nutritive sucking compared with non-nutritive sucking alone.

Pharmacological relief and non-pharmacological methods may prevent pain during the heel-stick procedure in very preterm infants.

Table 1
Baseline characteristics.

	n[a]	Control, n = 29	n[a]	Intervention, n = 30	n[a]	Total
Gestational age, weeks, median (IQR)	29	30.0 (29.0–30.0)	30	29.0 (28.0–31.0)	59	29.0 (28.0–31.0)
Female sex, n (%)	29	16 (55.2)	30	15 (50.0)	59	31 (52.5)
Birth weight, grams, median (IQR)	29	1280.0 (1150.0–1530.0)	30	1330.0 (1110.0–1525.0)	59	1300.0 (1130.0–1530.0)
Weight at inclusion, grams, median (IQR)	28	1235.0 (1105.0–1490.0)	29	1290.0 (1110.0–1440.0)	57	1280.0 (1110.0–1450.0)
Number of cutaneous procedures from birth to the study procedure, median (IQR)	28	12.5 (8.5–17.5)	26	11.0 (8.0–16.0)	54	12.0 (8.0–17.0)
Delivery mode, n (%)	29		30		59	
Vaginal delivery		9 (31.0)		15 (50.0)		24 (40.7)
Caesarean		20 (69.0)		15 (50.0)		35 (59.3)
Use of forceps, vacuum extractor, spatula, n (%)	29	2 (6.9)	30	1 (3.3)	59	3 (5.1)
Multiple pregnancies for the mother, n (%)	29	12 (41.4)	30	12 (40.0)	59	24 (40.7)
Number of hypnotic sedations, n (%)[b]	29	2 (6.9)	30	0 (0)	59	2 (3.4)
Non-invasive ventilation, n (%)	28	20 (71.4)	29	19 (65.5)	57	39 (68.4)
Oxygen saturation[c], median (IQR)	29	98.0 (94.0–100.0)	29	96.0 (95.0–100.0)	58	98.0 (94.0–100.0)
Heart rate[d], median (IQR)	29	157.0 (149.0–160.0)	29	152.0 (146.0–156.0)	58	153.0 (147.0–160.0)

IQR, interquartile range.
[a] Patients with available data.
[b] n is the number of infants receiving hypnotic sedation, such as midazolam, morphine, fentanyl, sufentanyl and propofol, during the procedure.
[c] Measurement is the lowest oxygen saturation value recorded for the PIPP score before the procedure and immediately after the procedure for 30 s.
[d] Measurement is the highest heart rate value recorded for the PIPP score before the procedure and immediately after the procedure for 30 s.

Table 2
PIPP and DAN median pain scores.

	Control, n = 29	Intervention, n = 30	*p* value
PIPP score, median (IQR)	9.5 (7.0–13.0)	8.0 (6.0–12.0)	0.3239
DAN score at T-15 s, median (IQR)	1.0 (0.5–2.0)	0.0 (0.0–1.0)	0.0278
DAN score at T0, median (IQR)	5.5 (4.0–7.5)	5.0 (1.5–6.0)	0.1962
DAN score at T + 3 min, median (IQR)	2.0 (0.5–3.0)	0.3 (0.0–1.0)	0.0010

PIPP, premature infant pain profile; DAN, *douleur aiguë du nouveau-né* (a French acronym for the acute pain of a newborn).

The most efficient non-pharmacological relief is sucrose associated with non-nutritive sucking, but the number of sucrose administrations per day is limited (Stevens et al., 2016).

In situations where pharmacological analgesia is not indicated and sucrose can no longer be administered to very preterm infants undergoing numerous daily cutaneous procedures, the association between facilitated tucking and non-nutritive sucking is compelling, while non-nutritive sucking has shown a slight improvement for pain and is often used alone in practice.

Previous randomized studies evaluating the facilitated tucking method have had contrasting results (Axelin et al., 2009; Cignacco et al., 2012; Gerull et al., 2013; Gitto et al., 2012; Liaw et al., 2012; Peng et al., 2018; Yin et al., 2015). However, the facilitated tucking method was often used alone and groups of comparison were heterogeneous including pharmacological treatment, sucrose and gentle touch. In infants born between 27 and 32 weeks, the facilitated tucking method alone did not improve pain compared with fentanyl or sensorial saturation based on behavioural and physiological scores (Gitto et al., 2012), neither was it effective compared with sucrose in two other studies (Cignacco et al., 2012; Gerull et al., 2013). Nevertheless, in two trials conducted in infants born between 28 and 37 weeks, the results favoured facilitated tucking alone compared with oral water (Axelin et al., 2009) or gentle touch and verbal comfort (Liaw et al., 2012).

Similarly, the benefits of facilitated tucking combined with sucrose (Cignacco et al., 2012) or with sucking and breastmilk relative to gentle touch (Peng et al., 2018) on pain reduction have been observed.

Only one randomized study evaluated the combination of the facilitated tucking method and non-nutritive sucking and did not show the efficacy of this combination relative to that of gentle touch, the control condition, according to behavioural criteria (Yin et al., 2015).

Our findings suggest that undergoing facilitated tucking with non-nutritive sucking could favour analgesic effects after the heel-stick procedure for a faster recovery in infants. Pain-relieving effects across recovery phases were previously observed in other studies, showing interesting results of facilitated tucking for 3 to 10 minutes after the heel-stick procedure (Cignacco et al., 2012; Liaw et al., 2012; Peng et al., 2018). Similarly, Campbell-Yeo et al. showed that the co-bedding of twins did not lead to lower pain scores but quickened the recovery time after a heel-stick procedure compared with that for twins in separate beds (Campbell-Yeo et al., 2012). A better recovery is important for the vulnerable very preterm infant population, as it could impact their haemodynamic instability (Cignacco et al., 2012; Liaw et al., 2012).

Interestingly, in the group receiving facilitated tucking, we also observed that the median DAN score was lower at baseline, which can be explained by a lower basic state of stress due to the intervention starting before the painful procedure. However, this point was not easy to evaluate in practice.

The facilitated tucking procedure was heterogeneously performed in the studies described above, but the variability of this intervention limits comparisons between studies. In the present study, the staff practices were based on Bullinger's guidelines regarding developmental care. In these guidelines, the facilitated tucking procedure is performed in an asymmetric position, promoting infant autonomy and self-regulation (Bullinger, 2015), whereas other studies adopted a midline position (Peng et al., 2018; Yin et al., 2015), a side-lying, a prone position or a supine position (Axelin et al., 2009; Cignacco et al., 2012; Liaw et al., 2012). In addition, according to Bullinger's guidelines, the positioning of the hands supports and joins the infant in its movements (Bullinger, 2015). Other studies mostly described procedures by flexion and placement of the hand on the head (Gitto et al., 2012; Liaw et al., 2012; Peng et al., 2018; Yin et al., 2015). The position evaluated in the present study favouring greater autonomy for the infant is thus of interest and has been poorly studied.

Among the randomized studies evaluating facilitated tucking during the heel-stick procedure, methods for pain measurements varied and included pain scores and behavioural or biological outcomes (Axelin et al., 2009; Cignacco et al., 2012; Gerull et al., 2013; Gitto et al., 2012; Liaw et al., 2012; Peng et al., 2018; Yin et al., 2015). Three studies used the PIPP scale (Axelin et al., 2009; Liaw et al., 2012; Peng et al., 2018). This internationally recognized scale is used in the very preterm population and was chosen in the present trial because it includes physiological criteria and contextual indicators, while the DAN scale does not. Our study suggested that the recovery to a low state of stress and

pain can be improved by facilitated tucking according to evaluations with the DAN scale, a tool that is straightforward to use. The important benefit of this tool is that it provides evaluations simultaneously with the procedure and during recovery, whereas the PIPP score evaluates the entire procedure without recovery with potential increased variability and therefore an attenuated observed pain-relieving effect. This finding merits further evaluation in future studies.

This trial has several strengths that increase the generalizability of the results. The study utilized a larger sample than other studies evaluating the facilitated tucking procedure (Axelin et al., 2009; Gerull et al., 2013; Liaw et al., 2012). Two experienced evaluators remotely assessed the neonates' pain, whereas in most previous studies, only a single evaluator or the investigator performed pain assessment (Alinejad-Naeini et al., 2014; Lopez et al., 2015; Peng et al., 2018; Yin et al., 2015). This process reduced the risk of evaluation bias, although pain score analysis has shown limited inter-rater reliability. Moreover, reducing care-related pain in the very preterm infant population has been poorly evaluated, and research in this field will help guide clinical practices in neonatal intensive care units.

5. Limitations

Our study has several limitations: (1) The sample size was based on a study with a larger population term of birth, in which the pain reduction can be easier to observe than in very preterm infants, and which probably led to an overestimation of the expected pain score in the intervention group and to a lack of power. (2) Very preterm infants constitute a specific population that is not well documented and in whom hypothetic pain reduction is not straightforward to estimate. (3) The protocol did not preplan measurements of inter-rater and intra-rater agreements before the final analysis, and the reproducibility of the pain assessment using the PIPP score was found to be low. However, in the case of disagreement between the two evaluators, a third reviewer, who was the most experienced, performed the score assessment. Note that during the present study period, the PIPP tool was revised to improve its validity and feasibility (Gibbins et al., 2014). According to the authors of the revision, psychometric data for very preterm infants and exploration of the tool's feasibility were limited prior to the updated version.

Some infants probably need more support than others regarding their physiological development and stress state at the time of the procedure. Including such an individualized approach to the facilitated tucking method based on behavioural observation was not possible in our study; in the future, however, objective behavioural criteria could be considered to offer such an intervention to infants.

Moreover, the study focused on a single pain procedure at the beginning of the care sequence, whereas infants usually receive successive nursing care procedures.

In this study, the PIPP score did not differ during a single heel-stick procedure between infants in the intervention group receiving facilitated tucking and the control group, while the DAN score was lower in the intervention group after the heel-stick procedure. The measurements of pain and recovery after the whole procedure merit supplementary evaluation.

6. Clinical implications

Heel-sticking is a common procedure for very preterm infants in neonatal intensive care units leading to pain and stress which could be prevented by care providers including nurses. When sucrose or pharmacological treatments cannot be administered or are not effective, facilitated tucking in combination with non-nutritive sucking is a non-pharmacological method that is easily applicable by nurses and nurse assistants, requiring only a short training session. The present study, in which very preterm infants underwent a median of 12 cutaneous procedures in less than 48 h, led to an interesting finding of the benefits of facilitated tucking combined with non-nutritive sucking on the infants' recovery after the heel-stick procedure. This strategy probably also decreases the basic state of stress before the painful procedure. These findings may encourage teams in charge of very preterm infants to apply this safe and easy procedure to limit pain and stress during painful procedures.

7. Conclusions

This trial evaluated the impact of a combined strategy of facilitated tucking and non-nutritive sucking as an alternative pain relief method when pharmacological treatments are not efficient, their dose is limited daily, or other non-pharmacological treatments are not available. While infant pain evaluated at the time of the procedure did not differ between strategies, we observed a notable effect of the combination of the facilitated tucking method with non-nutritive sucking on the infants' recovery three minutes after the procedure. This study motivates other mid or long-term explorations of the facilitated tucking method for single or repeated painful procedures. Including this method in developmental and sensorimotor support care could reduce the effect of pain on the neurodevelopment of very preterm infants.

Contributions

Study design: All authors. Data analysis: JL, AR. Manuscript preparation and approval: All authors.

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Conflicts of interest

None.

Ethical approval

The study was approved by the Committee for Patient Protection Ile-de-France XI (no. 14002, January 16, 2014, n° IDRCB: 2013A01715-40) and the French Data Protection Authorities (n°1745377. February 02, 2014).

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