Systematic Review and Meta-Analysis

PAIN

OPEN

The use and reporting of neonatal pain scales: a systematic review of randomized trials

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Abstract

The burden of pain in newborn infants has been investigated in numerous studies, but little is known about the appropriateness of the use of pain scales according to the specific type of pain or infant condition. This systematic review aimed to evaluate the reporting of neonatal pain scales in randomized trials. A systematic search up to March 2019 was performed in Embase, PubMed, PsycINFO, CINAHL, Cochrane Library, Scopus, and Luxid. Randomized and quasirandomized trials reporting neonatal pain scales were included. Screening of the studies for inclusion, data extraction, and quality assessment was performed independently by 2 researchers. Of 3718 trials found, 352 with 29,137 infants and 22 published pain scales were included. Most studies (92%) concerned procedural pain, where the most frequently used pain scales were the Premature Infant Pain Profile or Premature Infant Pain Profile—Revised (48%), followed by the Neonatal Infant Pain Scale (23%). Although the Neonatal Infant Pain Scale is validated only for acute pain, it was also the second most used scale for ongoing and postoperative pain (21%). Only in a third of the trials, blinding for those performing the pain assessment was described. In 55 studies (16%), pain scales that were used lacked validation for the specific neonatal population or type of pain. Six validated pain scales were used in 90% of all trials, although not always in the correct population or type of pain. Depending on the type of pain and population of infants included in a study, appropriate scales should be selected. The inappropriate use raises serious concerns about research ethics and use of resources.

Keywords: Pain, Assessment, Neonatal

1. Introduction

Newborn infants, especially those born preterm, are highly vulnerable to pain.[67] Preterm birth and illness, in addition to the necessary medical treatment and nursing care, inflict pain and stress on the infants.[72] Infants in neonatal intensive care undergo as many as 10 to 15 painful procedures per day.[18,56] Pain leads to immediate cardiovascular changes, behavioral changes, disrupted feeding, disturbed sleep, and increased energy expenditure that may lead to complications and a need for intensified and prolonged care.[1] The immature nervous system and repeated exposure to pain may lower pain thresholds, which in return can make the infant even more sensitive to subsequent painful events.[13] Changes in pain sensitivity may persist beyond the neonatal period,[15,35] and neonatal pain may also result in poorer brain development.[14,55,71] Pharmacological pain treatment needs to be used selectively because of the infants' immature drug metabolism and well-known drug-specific negative side effects, eg, hypotension and respiratory depression, along with the neuroapoptotic effect of analgesic and sedative drugs shown in animal research[6,57] and studies reporting on their influence on brain development.[28,53] To minimize the pharmacological treatment, nonpharmacological and caring strategies are widely used, eg, breastfeeding and skin-to-skin contact.[16,30]

The fact that stress increases the pain experience is well known in all patients; in the newborn population, this relates to the degree of prematurity, and it is also very difficult to discriminate between stress and pain, especially in the premature population. To effectively treat stress and pain, as well as diminish the negative effects in the neonatal period, the severity of the painful stimuli must be adequately recognized.[73] In the nonverbal newborn patient, traditional self-report is not possible. Instead, there is a need for valid and reliable tools to assess the intensity of the stress and pain. Several observational scales have been constructed and tested for different newborn populations and different types of pain. Around 40 pain assessment instruments have been published, but their validity varies widely.[25,29] Clinical use of measures that are insufficiently validated poses a risk to patient safety, as they may result in both overassessment and underassessment of pain. Using a validated pain scale with appropriate cutoff values is of course desirable, and if not so, overassessment may cause unnecessary use of pain-relieving

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 162 (2021) 353–360

http://dx.doi.org/10.1097/j.pain.0000000000002046

medication with potential side effects, whereas underassessment may cause unnecessary pain and suffering.[51]

Objective and reliable pain assessment is considered the basis for safe and adequate pain management.[29,51] There are unfortunately still no fully objective pain assessment tools for the assessment of pain/stress in the very sick patients in the neonatal intensive care unit (NICU). Different neurohormonal and neurophysiological monitoring measures such as skin conductance/galvanic skin response, heart rate variability and the adaption of it (Newborn Infant Parasympathetic Evaluation), near-infrared spectroscopy, electroencephalography, and functional magnetic resonance imaging have been evaluated and proven reliable in the assessment of pain in newborn infants and are used mainly in the research context and not as much in the clinical setting. These methods of pain assessments are not addressed in this review that focuses on observational scales.

It is essential that the pain assessment instruments used in clinical studies and also in the daily care of newborns are valid and reliable for the particular patient population (preterm vs term infants) and clinical situation (procedural pain, postoperative pain, and continuous pain/stress due to, eg, ventilator support), so the result of the assessment can be trustworthy. Little is known about the reporting of pain scales in clinical trials and whether they are correctly implemented for the specific type of pain or group of infants included in the studies. The aim of this study was therefore to evaluate the characteristics and the reporting of pain scales in randomized trials where newborns are exposed to any type of painful interventions or conditions.

2. Methods

The protocol of this study was registered in PROSPERO (international prospective register of systematic reviews) before the screening of the studies.[2] The Cochrane methodology for systematic reviews of interventions was used for study screening, inclusion, and data extraction with 2 independent investigators.[36]

2.1. Search strategy and data sources

A systematic and broad search up to March 2019 was performed in Embase, PubMed, PsycINFO, CINAHL, Cochrane Library, Scopus, and Luxid using combinations of the terms/keywords: newborn infant, pain assessment, and trials (the full search strategy for each database is shown in Appendix 1, available at http://links.lww.com/PAIN/B154). Randomized and quasir-andomized trials on neonatal pain (including procedural pain, postoperative pain, and pain associated with clinical conditions) reporting at least 1 pain scale were included. We included trials in both term and preterm infants. Observational studies, study protocols, conference abstracts, and reviews were excluded. There were no limits to publication years, and articles published in English, Swedish, or Italian were included.

2.2. Data extraction and management

Screening of titles and abstracts followed by a full-text screening for eligibility was performed by 2 independent researchers using an online tool for the preparation of systematic reviews.[21] Disagreements were resolved by a third researcher (one of the other coauthors) or in discussion within the group, as recommended in the Cochrane Handbook.[36]

A web-based extraction form for data collection was designed (see Appendix 2, available at http://links.lww.com/PAIN/B154). Data extraction and quality assessment for performance and detection bias were performed by 2 researchers independently, and when disagreements arose, a third researcher appraised the trial and solved the conflict. As the aim of this systematic review was to map the reporting of pain scales rather than assessing the effects of an intervention, pooling data and creating meta-analysis were not planned.

The extracted data were entered into SPSS version 26 (IBM Corp, Armonk, NY: IBM Corp). Analyzed data are presented with frequency in absolute numbers and percentage.

3. Results

The literature search retrieved 3715 scientific articles. In addition, 3 articles were found by expert knowledge of the field. After removing duplicates, 3580 studies were screened for title and abstract, whereas 557 were subsequently read in full text. We finally included 352 trials in the systematic review (supplementary Table 1, available at http://links.lww.com/PAIN/B154). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is shown in **Figure 1**. Characteristics of the included studies and pain scales are presented in the text and in detail in **Tables 1 and 2** and supplementary Tables 1 to 3 (available at http://links.lww.com/PAIN/B154).

A total of 29,137 infants (ranging from 10 to 898 per trial, mean of 82.8) from 41 different countries were enrolled in the 352 included studies (supplementary Table 1, available at http://links.lww.com/PAIN/B154). Twenty-two previously published pain scales (**Table 2**), along with a number of scales designed locally for specific studies or instruments originally not intended for pain assessment, were adopted. Eight pain scales represented 93.7% of the use of published pain scales, and only 6 of them were used in more than 10 of the included studies each: Premature Infant Pain Profile/Premature Infant Pain Profile—Revised,[61,63] 43.9%; Neonatal Infant Pain Scale (NIPS),[47] 23.9%; Neonatal Facial Coding System (NFCS),[33] 9.4%; Douleur Aiguë Nouveau-né [Newborn Acute Pain] (DAN),[17] 5.7%; COMFORTneo (including COMFORT/COMFORT-B),[4,70] 4.3%; and Neonatal Pain, Agitation, and Sedation Scale (N-PASS),[41] 2.8%. The type of pain, intervention, study setting, age group, and study design for those 6 most frequently used scales are summarized in **Table 2**.

Nonvalidated, locally developed pain scales were used in 19 of the studies, eg, "revised NFCS," "pain score developed from CHEOPS and NIPS," or "5-item behavior scale." In many of these studies, the description of the pain scale was vague. Another 19 studies used scales originally not intended or validated for pain assessment, such as Brazelton behavioral states or Prechtl score. Finally, 17 studies used a Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) for pain assessment. In 6 of these studies, the VAS/NRS was combined with one of the COMFORT scales, which is part of that method, and in 8 studies, the VAS/NRS was combined with another pain scale. Seven studies on ongoing pain used scales that were developed and validated for procedural pain, and vice versa, 10 studies on procedural pain used scales intended for ongoing pain. Five studies used scales not validated for the studied age group, eg, CHEOPS to assess postoperative pain in preterm infants. To summarize, of the included trials, 15.6% used a pain scale that was not appropriate for the type of pain investigated in the trial or an inappropriate scale with regard to the age of the included infants.

In most studies (93%), only one pain scale was used. In 26 trials, more than 1 pain scale were used in the same infants, whereas in only 16 of these studies the scales were compared (supplementary Table 2, available at http://links.lww.com/PAIN/B154). In 111 trials, the presence and intensity of pain were

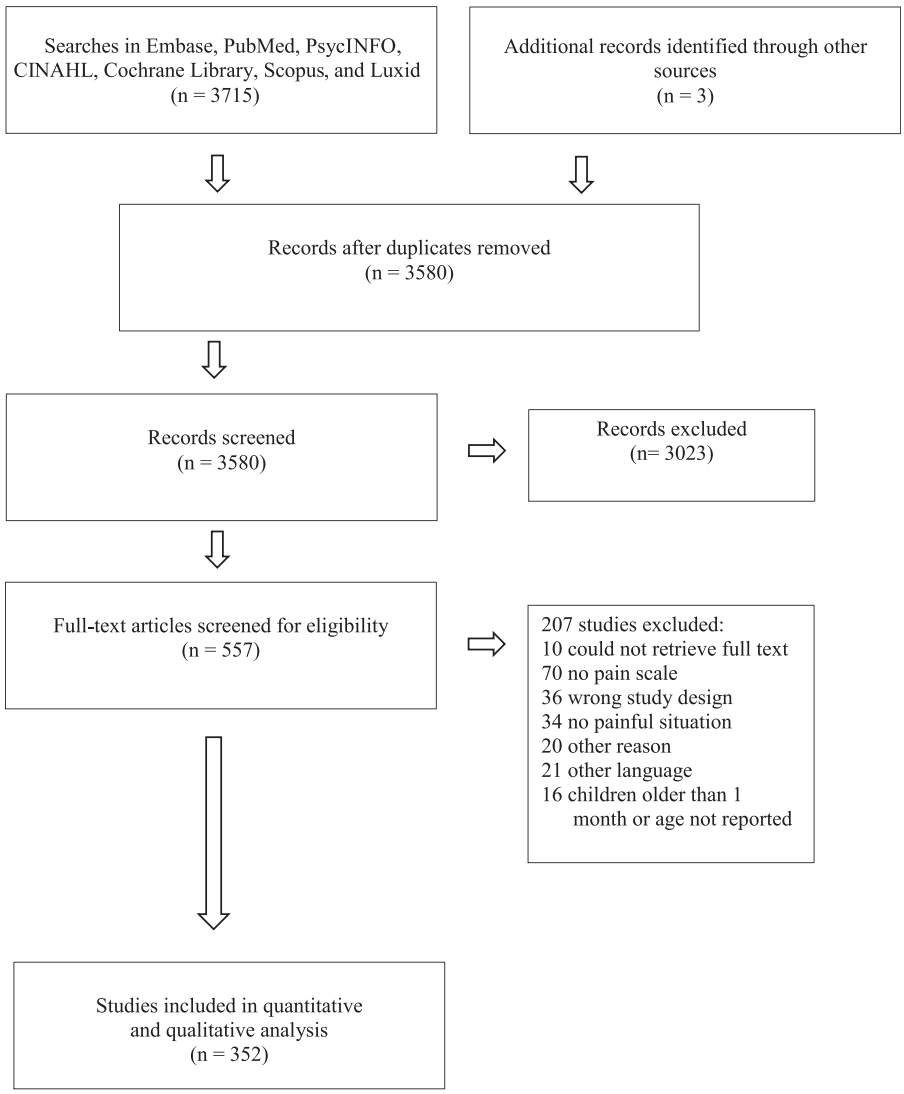

Figure 1. A PRISMA flowchart showing the search, screening, and inclusion procedure. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

assessed independently by 2 or more observers (supplementary Table 3, available at http://links.lww.com/PAIN/B154). However, in only 61 of these trials (54.5%), agreement between the assessors was reported.

Most of the studies were performed in a NICU setting (61.4%, n = 216), followed by maternity units (18.5%, n = 65) and other hospital settings such as pediatric intensive care units and postoperative care units. Most included studies used a design with 2 or more randomized parallel groups (79.2%, n = 279), whereas 18.7% (n = 66) used a cross-over design; 2.0% (n = 7) did not clearly describe a study design.

Only 4.3% (n = 15) and 3.7% (n = 12) of the trials reported on ongoing pain and postoperative pain, respectively. In those trials, any of the COMFORT scales were most frequently used (31.0%), followed by the NIPS (20.7%) and Échelle Douleur Inconfort Nouveau-Né (EDIN) (17.2%). Procedural pain was the most common type of pain being studied (91.8%, n = 323), with heel lance reported as the most common painful procedure (37%, n = 152), followed by venipuncture (15%, n = 63) and intramuscular injection (8%, n = 33). There was an equal amount of studies investigating pharmacological interventions (n = 140) and nonpharmacological interventions (n = 140), whereas 72 of the studies used a combination of both. The pharmacological interventions most frequently reported were sweet solutions such as sucrose or glucose (133 studies), followed by local anesthetics (n = 41) and morphine (n = 20). Nonpharmacological interventions included a range of different strategies where non-nutritive sucking was most frequently reported (n = 24).

Our quality assessment of the included trials focused on performance and detection bias, ie, blinding of those administering the painful procedure and of those assessing the pain scale, respectively (supplementary Table 1, available at http://links.lww.com/PAIN/B154). Only in 119 trials (33.8%), blinding was described for those performing the pain assessment; in 30 (8.5%), blinding was described for those performing the painful procedure and those performing the pain assessment; in 7 (2.0%), blinding was described for those administering the pain-relieving intervention and those performing the pain assessment, and in 78 (22.1%), blinding was described for those administering the pain-relieving intervention, those performing the painful procedure, and those performing the pain assessment. Overall, only 108 trials (30.7%) had a low risk of bias for both performance

Table 1

The 22 published pain scales used in the included trials.

Acronym or abbreviation (number of studies)	Full name	Age validation		Pain-type validation			Development studies	Validation studies
		Preterm	Term	Acute procedural	Ongoing	Postoperative		
PIPP/PIPP-R (154)	Premature Infant Pain Profile/ Premature Infant Pain Profile—Revised	x	x	x			61, 63	26, 31, 62
NIPS (84)	Neonatal Infant Pain Scale	x	x	x			47	11, 40
NFCS (33)	Neonatal Facial Coding System			x		x	34, 33	48, 66
DAN (20)	Douleur Aiguë Nouveau-né [Newborn Acute Pain]	x	x	x			17	10, 66
COMFORTneo/COMFORT/ COMFORT-B (15)	COMFORT-B stands for Comfort Behavioral Scale	x	x		x		69	5, 12, 68
N-PASS (10)	Neonatal Pain, Agitation, and Sedation Scale	x	x	x	x	x	41	42
CRIES (7)	Crying, Requires oxygen, Increased vital signs, Expression, and Sleep	x	x		x		46	60
EDIN (6)	Échelle Douleur Inconfort Nouveau-Né [Neonatal Pain and Discomfort Scale]	x	x	x			27	
ABC (3)	Acuteness of the first cry, Burst rhythmicity, and Constancy in time of cry intensity	x	x	x			10	9
BIIP (3)	Behavioral Indicators of Infant Scale Pain	x	x	x			38	39
BPSN (3)	Bernese Pain Scale for Neonates	x	x	x			19	20
ALPS-Neo/ALPS/ALPS 0 (2)	Astrid Lindgren and Lund Children's Hospital's Pain and Stress Assessment Scale for Preterm and Sick Newborn Infants	x	x		x		49	
CHEOPS (1)	Children's Hospital of Eastern Ontario Pain Scale		x		x	x	52	65
FLACC (1)	Face, Legs, Activity, Cry, and Consolability		x	x			54	23, 50
IBCS (1)	Infant Body Coding System	x	x	x			22	
LNPS (1)	Leuven Neonatal Pain Score	x	x		x		3	
MAX (1)	Maximally discriminative facial movement coding system		x				44	43
MBPS (1)	Modified Behavioral Pain Scale		2-6 m	x			64	24
NPAS (1)	Neonatal Pain Assessment Scale		x	x				59
PAT (1)	Pain Assessment Tool					x	37	60
PCS (1)	The Postoperative Comfort Score		x			x	7	
RIPS (1)	Riley Infant Pain Score		x			x		45, 58

The pain scales are presented in descending order, showing the frequency of their use in the included studies.

and detection bias. Complete lack of blinding and unclear description of blinding were detected in 51 (14.5%) and 61 (17.3%) trials, respectively.

4. Discussion

This is the first systematic review reporting how pain scales are used in randomized trials in the newborn. Although 22 different published pain scales and a number of nonvalidated instruments were used in the 352 included trials, most of the studies used the same pain scales.

Optimally, pain should be monitored in a completely objective way, but unfortunately such strategies are not available in the neonatal setting. Therefore, assessment of pain with the help of validated pain scales is the best available method, which underlines the necessity of the validation process. In numerous

Table 2

The 6 most frequent pain scales, types of pain, studied intervention, study setting, age group at the time of the study, and study design.

	PIPP/ PIPP-R	NIPS	NFCS	DAN	Comfort-neo/Comfort / Comfort-B	N-PASS
No. of studies	154	84	33	20	15	10
Type of pain, n (%)						
Acute/procedural	151 (98.1)	78 (92.8)	31 (93.9)	20 (100.0)	5 (33.3)	9 (90.0)
On-going	2 (1.3)	3 (3.6)	1 (3.0)		2 (13.3)	1 (10.0)
Post-operative		2 (2.4)	1 (3.0)		8 (53.3)	
Other/more than one type	1 (0.6)	1 (1.2)				
Type of intervention, n (%)						
Pharmacological	53 (34.4)	25 (29.8)	15 (45.5)	6 (30.0)	14 (93.3)	4 (40.0)
Non-pharmacological	68 (44.2)	41 (48.8)	12 (36.3)	6 (30.0)	1 (6.7)	5 (50.0)
Both	33 (21.4)	18 (21.4)	6 (18.2)	8 (40.0)		1 (10.0)
Study setting, n (%)						
NICU/Neonatal unit	132 (85,8)	39 (46.4)	18 (54.5)	13 (65.0)	6 (60.0)	8 (80.0)
Nursery/Maternity unit	11 (7.1)	24 (28.6)	10 (30.3)	7 (35.0)	3 (30.0)	1 (10.0)
Other	11 (7.1)	21 (25.0)	5 (15.2)		1 (10.0)	1 (10.0)
Age group at time of the study, n (%)						
<28 w	1 (0.6)					
<28 w-32 w	10 (6.5)	3 (4.9)	1 (6.1)	1(5.0)	2 (14.3)	
<28 w-36 w	18 (11.7)	3 (8.5)	2 (9.1)	1(5.0)	2 (14.3)	
<28 w- >37 w	8 (5.2)		1 (6.1)			
28 w-32 w	3 (1.9)	1 (1.2)				1 (10.0)
28 w-36 w	31 (20.1)	5 (6.1)	3 (9.1)	1 (5.0)	1 (7.1)	2 (20.0)
28 w- >37 w	28 (18.2)	6 (12.2)	4 (18.2)	3 (15.0)	2 (14.3)	
33 w-36 w	5 (3.2)	2 (3.7)				
33 w- >37 w	14 (9.1)	7 (15.9)	4 (6.1)		1 (7.1)	2 (20.0)
>37 w	15 (9.7)	45 (31.7)	20 (27.3)	11 (55.0)	2 (14.3)	5 (50.0)
Unclear	21 (13.6)	11 (11.0)		3 (15.0)	4 (28.6	
Study design, n (%)						
Randomized	112 (72.7)	73 (86.9)	27 (81.8)	16 (80.0)	14 (93.3)	7 (70.0)
Cross-over	39 (25.3)	10 (11.9)	4 (12.1)	4 (20.0)		3 (30.0)
Other	3 (2.0)	1 (1.2)	2 (6.1)		1 (6.7)	

DAN, Douleur Aiguë Nouveau-né; NFCS, Neonatal Facial Coding System; NICU, neonatal intensive care unit; NIPS, Neonatal Infant Pain Scale; N-PASS, Neonatal Pain, Agitation, and Sedation Scale; PIPP, Premature Infant Pain Profile; PIPP-R, Premature Infant Pain Profile—Revised.

trials, the pain scales that were used were lacking validation for the studied population or the types of pain that were assessed. In our review, we report that 15.6% of the included studies used a pain scale that was validated for neither the type of pain studied nor the infant population. For example, the NIPS is validated only for acute pain; however, it was the second most used scale for ongoing and postoperative pain. It is also worth to notice that many of the validation studies are quite old and conducted before the implementation of protocols such as COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). The type and accuracy of the validation is also important when choosing an instrument for a clinical trial.[32] It could be argued that many of the scales are similar and comprise the same items in different combinations, and that using any scale is better than not trying to assess pain. Even if the argument for doing something being better than doing nothing is true, it is not a level of acceptance to stop at. There is probably no need for more scales, but that the scales that are used are valid and responsive, ie, can detect pain but also a reduction in pain after a pain-relieving intervention. More efforts should be put on examining this in existing scales, for infants with different age groups and medical conditions, and on implementing them properly in neonatal care.

Moreover, we found that most trials were conducted in newborns exposed to procedural pain, whereas there is a paucity of studies on postoperative pain and continuous pain/stress. The explanation to this is most probably that the era of pain research started with studies on procedural pain in the 1990s[8] and that these studies are easier to conduct. Research focusing on procedural pain has taught us on pain physiology in preterm and term infants in a very structured way, whereas studies on the complexity of postoperative pain, painful conditions, or continuous pain/stress, eg, during ventilator support in the very sick NICU infants with a variety of different conditions and different clinical states, are more difficult to conduct in an optimal way. Continuous pain for instance due to necrotizing enterocolitis is more difficult to assess, especially in preterm infants who may react with a "shut-down," hypotonia, and immobility, in response to strong pain and stress. It might therefore be possible that in some centers, procedural pain assessment is still used to "assess" continuous pain the way it was before the adequate pain scales for continuous pain were developed, ie, translate a high score at a procedure to indicate that the infant is also inadequately treated for its continuous pain.

In the review, we found very few studies on endotracheal intubation, which is considered a painful procedure. The explanation might be that some of the pharmacological strategies

used include muscle relaxants, and as a result, pain assessment might therefore be inconclusive as the infants lose the ability to breath and move, 2 major items included in most pain assessment scales.

Recently, Giordano and colleagues conducted a systematic review on the validation of pain and sedation scales in newborns and infants.[32] Their work importantly differs from our review by using broader inclusion criteria with regard to the type of studies (not only trials as in this review) and study population (not only newborns). Furthermore, their evidence synthesis included 89 studies, as they focused on the validation rate rather than on how trials report the use of pain scales. Giordano and colleagues[32] also showed that only 28 of 65 scales for infant and toddlers had been tested for construct validity, internal consistency, and interrater reliability. Furthermore, they highlighted the importance of defined and tested cutoff values for pain/no pain for the clinical utility of any scale.

The strengths of our systematic review include the originality of study design and the broad search strategy. We also registered the protocol a priori to avoid intellectual bias.

The limitations include the language restriction to 3 languages and the choice to assess only 2 of the 6 items of the Cochrane risk of bias tool, ie, performance and detection bias.[36] However, this is a minor issue because we did not aim to assess the benefits and harms of different interventions, but instead on how the use of neonatal pain scales is reported in trials. Of note, blinding of both those administering the painful condition and of those using the pain scale was reported in less than one-third of the trials. Whereas the lack of performance bias might be due to the nature of the interventions in some studies, researchers might easily design trials with a low risk of detection bias by ensuring blinding of outcome assessors.

In this review, we can show that there are a few validated pain assessment scales used in most clinical studies, which is positive news. In the clinical setting, it is crucial to choose an appropriate pain assessment scale, validated for the type of pain and population of infants to be able to support the infants in the best way. In research, it is crucial to get reliable results and thereby provide the best evidence-based clinical strategies. The inappropriate use of pain scales in research raises serious concerns on the ethical conduct of research and use of resources.

Furthermore, we reiterate the need for fewer but larger trials, with appropriate sample size to assess clinically relevant outcomes, in addition to the reporting of measurement properties.

Although it was not the scope of our review, the findings raise concerns whether we face a situation of excess of research in the area where studies on procedural pain can be conducted more easily and of lack of research in the more challenging clinical NICU situation with ongoing and postoperative pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgements

The authors thank Matthias Bank (Library and ICT services, Lund University) for defining and running the search strategy and Thomas Evertsson (Library and ICT services, Lund University) for retrieving the full-text articles.
M. Bruschettini has received research funding from the ALF grant (nonprofit—Lund University) and the Crafoord Foundation (nonprofit) for research projects not related to Cochrane.
E. Olsson and M. Eriksson performed the work as part of their university employment.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B154.

Article history:
Received 24 May 2020
Received in revised form 1 August 2020
Accepted 6 August 2020
Available online 17 August 2020

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