Endpoints in pediatric pain studies

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Abstract Assessing pain intensity in (preverbal) children is more difficult than in adults. Tools to measure pain are being used as primary endpoints [e.g., pain intensity, time to first (rescue) analgesia, total analgesic consumption, adverse effects, and long-term effects] in studies on the effects of analgesic drugs. Here, we review current and promising new endpoints used in pediatric pain assessment studies.

Keywords Pain · Assessment · Pharmacokinetics · Pharmacodynamics · Long-term outcome

Introduction

Neurobiology of pediatric pain: essentials for drugs-related studies

The neonatal stage of life is characterized by a high sensitivity to pain and a great vulnerability to neuronal cell death [1]. Anecdotal reports have shown prolonged allodynia and hyperalgesia after pain and tissue damage within the first weeks of life that extend beyond the period associated with tissue healing [2–7]. For example, 4- to 6-month-old term infants who had undergone circumcision responded more intensely to immunization than did their uncircumcised peers [5]. In another study, however, in comparison to age-matched controls, children who had undergone major surgery in combination with preemptive analgesia within the first months of life did not show different behavioral pain responses and saliva cortisol concentrations at 14 and 45 months of age when exposed to vaccinations [8]. Thus, the question is, therefore, whether the preemptive administration of analgesics indeed prevents possible long-term consequences of neonatal pain. Animal experiments have provided a number of clues. In a rodent model, neonatal nerve ligation led to long-term hyper-algesia that was not attenuated when local anesthetics were administered [9]. Also in the rat, neonatal exposure to carrageen or Complete Freud adjuvant (CFA) led to either hyposensitivity or no alterations; however, when the adult animals were re-exposed to inflammatory pain, there was a hypersensitivity reaction [10–14]. In contrast, formalin injections or laparotomy in newborn rats were found to lead to thermal hyposensitivity at an adult age [13–15], which was attenuated by morphine administration [15].

Tissue damage and neonatal pain disturb the normal development of the nociceptive neural circuits, as expressed by structural and functional neuroanatomical changes at both the peripheral [9, 16, 17] and spinal cord level [11, 18]. Moreover, changes in spinal gene expression involved in the transmission of nociception have been documented [13]. These animal experiments may provide an explanation for the long-term effects found in human children.

In summary, at present, we do not know whether adequate analgesia prevents the development of long-term alterations in pain sensitivity and if such alterations do occur, whether they will be restricted to the dermatome of tissue injury (spinal changes) or be generalized all over the body (supraspinal changes) [4].

Exposing neonates to pain or tissue damage is developmentally inappropriate, and analgesics may not prevent them from developing subsequent pain hypersensitivity. The next logical question is whether this pain hypersensi-
tivity will still exist 15 years after tissue injury or whether it has recovered or reverted to hyposensitivity. The few studies on this aspect of pain management provide no or little information on the total analgesic dosages during hospital stay [19, 20]. It would seem, therefore, that more randomized controlled trials (RCTs) on analgesics are needed in children as well as follow-up studies in these same patients through childhood and adolescence in order to gain insight into the long-term effects of neonatal pain and neonatal analgesia.

Endpoints in clinical trials

A clinical trial endpoint is a measure that allows researchers to decide whether the null hypothesis of a clinical trial should be accepted or rejected [21]. Possible endpoints in pediatric analgesic trials are: pain intensity, time to first (rescue) analgesia, total analgesic consumption, adverse effects, and long-term effects [22, 23]. RCTs may have more than one endpoint, in which case it is customary to differentiate between primary and secondary outcomes.

Assessing pain intensity in (preverbal) children is more difficult than in adults. Adults’ self report of pain is generally accepted as the gold standard [International Association for the Study of Pain (IASP)] of pain assessment. However, the discussion merely limits itself to the question of which of the available self report scales is most appropriate in a given situation. Pain intensity in young children can be assessed with validated observational pain assessment instruments or multidimensional pain assessment instruments that include both behavioral and physiological parameters. Self report is feasible from the age of 4–5 years. Because observational pain instruments provide subjective outcomes, it is crucial that observers are well trained and that interrater reliability has been tested and proven to be good. Establishing cutoff points that differentiate between different levels of pain intensity is an important requirement because rescue medication is given when scores exceed specific values.

An important reference article is the one from the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT), in which core domains and measures for clinical pain trials have been defined [22].

The type of outcome measure also depends on the type of pain under study. Physiological parameters, for example, are more promising for acute painful procedures, such as heel lances or venipunctures, than for chronic pain. The different types of endpoints will be presented with a focus on postoperative pain in the following section.

Behavioral assessments

The IASP emphasizes that the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment [24]. Based on this standpoint, behavioral-based pain observation instruments have been developed. The Children’s Hospital Eastern Ontario Pain Scale (CHEOPS) [22, 25] and the Faces, Legs, Arms, Cry and Consolability (FLACC) pain scale [26, 27] have been validated for assessing postoperative pain in 1- to 7-year-old children. To this end, the COMFORT-behavior scale has been validated in 0- to 3-year-old children in the intensive care setting [28]. These scales have several items in common, namely, facial expression, crying, and body movements.

Children with severe intellectual disabilities may show idiosyncratic behavior when they are in pain. Thus, the application of pain scales developed for children without intellectual disabilities to those children with such disabilities has been advised against [29, 30]. At least four validated postoperative pain instruments for children with intellectual disabilities have been developed. One of these is the revised FLACC, which allows for individualized behavior added to each of the five items of the scale. This pain scale has been validated for postoperative pain [31] and proved to have a high degree of clinical utility [32]. The second scale is the Paediatric Pain Profile (PPP), a 20-item scale that has been validated for postoperative pain [33, 34]. The PPP consists of three sets of recordings: two retrospective parent ratings of the child’s behavior—i.e., when the child was at his or her best and during painful episodes, respectively—and a prospective rating by the nurse, for example, postoperatively. Although it may take more time to complete the PPP than the FLACC, use of the PPP may be well worthwhile for research purposes. The third scale is the non-communicating children’s pain checklist (NCCPC) [35] of which the postoperative version (NCCPC-PV) [36] includes 27 items and requires a 10-min observation. A fourth scale is the Checklist Pain Behaviour (CPB), which has been validated for postoperative pain and been reduced without any loss of information to a ten-item version [37, 38]. In addition, a recent study has described the use of an individualized Numeric Rating Scale based solely on the child’s individual pain indicators as described by the parents and caregivers [39]. The psychometric properties of this scale are promising; nevertheless, the essential involvement of the parents may be a drawback, especially when the scale is to be used for research purposes [40].

Self report

An example of a self-report tool for 2- to 3-year-old toddlers is the Poker Chip Tool [41], while the Faces Pain...
Scale-Revised is recommended for research purposes in children aged over 4 years [42, 43]. The Numeric Rating Scale pain (NRS-11) [44] and Visual Analogue Scale pain (VAS) [45] should preferably not be used in children less than 8 years old because both require a certain cognitive level of development to translate pain intensity into numbers or distances on a 10-cm ruler. The Poker Chip Tool, Faces Pain Scale-revised, and VAS have also been recommended as valid self-report tools by the Pediatric Initiative on Methods, Measurements and Pain Assessment in Clinical Trials (PedIMMPACT) and in two reviews [22, 43, 46].

Physiological parameters

As behavior-based assessment instruments remain subjective, researchers continue to search for neurobiological-based and more ‘objective’ parameters of pain intensity [47]. Several instruments indeed go some way to meeting this aim of increased objectivity by including physiological items as well, such as the PIPP and the COMFORT scale [48, 49]. However, heart rate and blood pressure have proven to be insufficiently sensitive for postoperative pain assessment, probably because treatment, blood loss, fever, and other clinical conditions will influence these parameters [50, 51].

New methods, such as near-infrared spectroscopy (NIRS) and skin conductance, may help to objectify pain or stress in nonverbal humans. NIRS measures regional changes in the concentration of oxygenated and deoxygenated hemoglobin. This technique is based on the assumption that increased tissue oxygenation represents a greater regional cerebral blood flow. This, in turn, is associated with higher neuronal activity, as seen in noxious events (encoded by the frequency of firing and number of activated neurons) [52]. The use of NIRS in pediatrics has been limited to the assessment of acute pain in neonates [53–55]. In one study, researchers compared NIRS measurements with facial expression during 33 heel lance procedures in 12 stable newborns and found that brain activity in most of the newborns was related to facial expression. However, some newborns did not show a change in facial expression even though NIRS readings revealed increased cortical activity during the procedure [54].

The measurement of stress by skin conductance is based on neurophysiological arousal, with increased activity in the sympathetic nervous system leading to sweating in the palms of the hand and the foot soles. As such, the level of increase may serve as a surrogate measure of stress and not of pain per se [56].

Biomarkers

Hormonal stress markers, such as salivary cortisol and (nor) epinephrine, may have additional value in the context of analgesia trials [57]. Nevertheless, because stress and pain are correlated but difficult to distinguish, these hormone levels should not be considered as primary endpoints of pain studies. Age-dependent differences in hormonal levels as well as age-dependent differences in circadian rhythm are important confounders. This is especially true in postoperative patients in whom the extent and duration of the so-called hormonal stress response are highly determined by age [57]. However, salivary cortisol could be a substitute marker for pain or stress in severely cognitively impaired children. Remarkably, RCTs in this vulnerable patient group have not yet been performed despite the fact that co-medication, such as anticonvulsants, could influence opioid use during surgery, as reported in a single study from 1990, which has to date never been replicated [58].

Brain activity-related parameters

Experimental approaches involving the use of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans have been tested in the research setting only [59, 60]. PET scans performed solely for pediatric research reasons may, however, meet with ethical and practical obstacles as they involve the administration of radioactively labeled drugs. As a noninvasive procedure, fMRI is more promising for the (semi)clinical evaluation of children and can be combined with quantitative sensory testing [61]. Neurophysiological measurements, such as the electroencephalogram (EEG) and somatosensory response, have so far not identified a specific pain signal that could be useful in daily clinical practice. There is direct EEG evidence of specific noxious-evoked neural activity in the infant brain [62]. Somato-sensory responses have been demonstrated in young infants, but these cannot yet serve as endpoints; we first need to establish normal values of voltage, frequency, and duration.

Time to first (rescue) analgesia and analgesic consumption

As many postoperative patients will receive preemptive analgesic drugs, time to first rescue analgesia may serve as a clinical endpoint together with the total analgesic consumption over the first 12, 24, or 48 h. Consumption should be expressed in micrograms or milligrams per kilogram per hour (or per 24 h) so as to enable comparison. Ideally, these endpoints should be combined with scores obtained from validated pain assessment instruments.

Safety/adverse effects

Documentation of drug safety is highly important, especially in pediatric drug trials. There is some debate on
whether it is better to have a pre-defined list of possible adverse events to be taken into account or to resort to an unstructured approach in which researchers, parents, and/or other individuals report any suspected adverse event [22]. This latter approach may carry the risk of underreporting of adverse events.

Safe and effective pain treatment in neonates and young infants requires a thorough understanding of various developmental aspects of drug disposition and metabolism. In general, the phenotypic variation in drug disposition and metabolism is based on constitutional, genetic and environmental factors. The clearance rate of most drugs is lower in neonates than in adults and older children as neonates still show immature renal function, i.e., decreased glomerular filtration rate and less effective tubular reabsorption and/or excretion. Moreover, they have a lower capacity of drug metabolizing enzymes [39–44]. Furthermore, as reviewed by both Weinshillboum [45] and Evans and McLeod [46], the disposition and action of many drugs are polygenic determined events, with polymorphisms in drug-metabolizing enzymes, transporters, and receptors determining to a large extent the spectrum of drug response (i.e., ranging from no effect to drug toxicity).

Long-term effects of analgesic treatment

The short- and long-term consequences of prolonged opioid use in newborns and infants are largely unknown. Studies in animals suggest potential adverse long-term effects of morphine. Morphine administration to neonatal rats has been found to produce long-term changes in behavior and brain function [63] and to impair cognitive functioning in the adult rat in general [64] and spatial recognition memory in particular [65]. Basic science has shown that the opioid system modulates neural proliferation in vivo [66]. Thus, it may well be that morphine treatment harms the neurogenesis of newborn babies. At the mechanistic level, morphine induces the apoptosis of human microglial cells [67] and stimulates red neuron degeneration in the rat brain, which may lead to cerebral dysfunction [68]. Boasen et al. recently showed in rodents that separate neonatal stress and morphine treatments could independently of each other produce longstanding behavioral effects to a degree sufficient to alter learning, while the combination of neonatal stress and morphine did not [69].

Endpoints in human studies should therefore include cognition, neuropsychological tests, a chronic pain questionnaire, and pain and detection thresholds. The latter thresholds may be assessed with quantitative sensory testing (QST), for which normal values are available [70].

Finally, we should realize that behavioral assessment instruments reveal other aspects of the phenomenon pain than do neurophysiological evaluation or the use of biomarkers. Moreover, no single parameter covers the whole spectrum from a nociceptive stimulus to behavior. It therefore appears to be essential to also evaluate the fate of drugs in the body (pharmacokinetics) as well as the response of the body (pharmacodynamics).

Pharmacokinetics of the parent drug and (active) metabolites in relation to pharmacodynamics

It has become easier to measure plasma levels of drugs in children. Sophisticated analytical methods (e.g., liquid chromatography/tandem mass spectrometry) and statistical analyses (e.g., population pharmacokinetics/pharmacodynamics, such as NONMEM) require smaller and fewer samples [71]. A possible relationship between therapeutic plasma ranges and pharmacodynamic parameters has not yet been found. Mutation analysis can provide answers to individual aberrant responses, although the tailoring of analgesic dosing has still a long way to go [72].

Efforts to improve pain therapy, for example by means of RCTs, should be developed within the context of regulatory initiatives. American legislation (‘Food and Drug Administration Modernization Act’ in 1997, ‘Best Pharmaceuticals for Children Act’ in 2002, and ‘Pediatric Research Equity Act’ in 2003) has come into force to promote drug development and the authorization of medicines for use in pediatric patients. Similar legislation was introduced in the European Union in January 2007 (‘The Pediatric Regulation’) (full text on www.fda.gov and www.emea.europa.eu). These legislations and clinical trial registers (http://clinicaltrials.gov) provide essential information on ongoing studies in other centers and prevent the duplication of studies in this vulnerable age group.

Summary

Tools to measure pain are currently being used as primary endpoints in studies on the effects of analgesic drugs.

Nevertheless, further research is needed to develop more objective pain measurements, to identify causes of variation in pain intensity and responses to pain treatment (both non-pharmacological and pharmacological PK–PD), and to develop age- and disease-specific pain treatment protocols.

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References

1. Fitzgerald M (2005) The development of nociceptive circuits. Nat Rev Neurosci 6(7):507–520
2. Grunau RVE, Whitfield MF, Petrie JH (1998) Children’s judgements about pain at age 8–10 years: do extremely low birthweight (<1000 g) children differ from full birthweight peers? J Child Psychol Psychiatry 39(4):587–594
3. Oberlander TF, Eckstein Grunau R, Whitfield MF, Fitzgerald C, Pitfield S, Saul JP (2000) Biobehavioral pain responses in former extremely low birth weight infants at four months’ corrected age. Pediatrics 105(1):e6
4. Peters JW, Schouw R, Anand KJ, van Dijk M, Duivenvoorden HJ, Tibboel D (2005) Does neonatal surgery lead to increased pain sensitivity in later childhood? Pain 114(3):444–454
5. Taddio A, Katz J, Ilerisich AL, Koren G (1997) Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 349:599–603
6. Andrews KA, Desai D, Dhillon HK, Wilcox DT, Fitzgerald M (2002) Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydrocephrosis. Pain 100(1–2):35–46
7. Buskila D, Neumann L, Zmora E, Feldman M, Bolotin A, Press J (2000) Modelling the prolonged effects of neonatal pain. In: Sandkühler J, Bromm B, Gebhart G (Eds.) Progress in brain nociceptive systems. Pain 99(3):377–498
8. Peters JW, Koot HM, de Boer JB, Passchier J, Bueno-de-Mesquita HM, Koot HM, de Boer JB, Passchier J, Bueno-de-Mesquita (2000) Anxiety and re-inflammation-associated long-term alteration in pain responsivity following short-lasting neonatal local inflammatory insult. Pain 84(2–3):367–373
9. Ruda MA, Ling QD, Hohmann AG, Peng YB, Tachibana T (2000) Altered nociceptive neuronal circuits after neonatal peripheral inflammation. Science 289(5479):628–631
10. Lidow MS (2002) Long-term effects of neonatal pain on nociceptive systems. Pain 99(3):377–383
11. Tachibana T, Ling QD, Ruda MA (2001) Increased Fos induction on the postnatal maturation of primary sensory neuron phenotype in rats. J Pain 2(1):36–45
12. Beland B, Fitzgerald M (2001) Influence of peripheral inflammation on the postnatal maturation of primary sensory neuron phenotype in rats. J Pain 2(1):36–45
13. Tachibana T, Ling QD, Ruda MA (2001) Increased Fos induction in rats following neonatal skin wounds. J Comp Neurol 358(4):487–498
14. Ren K, Anseloni V, Zou SP, Wade EB, Novikova SI, Wade EB, Novikova SI, Ennis M, Traub RJ, Gold MS, Dubner R, Lidow MS (2004) Characterization of basal and re-inflammation-associated long-term alteration in pain responsivity following short-lasting neonatal local inflammatory insult. Pain 110(3):388–596
15. Sternberg WF, Scorr L, Smith LD, Ridgway CG, Stout M (2005) Long-term effects of neonatal surgery on adulthood pain behavior. Pain 113(3):347–353
16. Reynolds ML, Fitzgerald M (1995) Long-term sensory hyperinnervation following neonatal skin wounds. J Comp Neurol 358(4):487–498
17. Beland B, Fitzgerald M (2001) Influence of peripheral inflammation on the postnatal maturation of primary sensory neuron phenotype in rats. J Pain 2(1):36–45
18. Walker SM, Meredith-Middleton J, Cooke-Yarborough C, Fitzgerald M (2003) Neonatal inflammation and primary afferent terminal plasticity in the rat dorsal horn. Pain 105(1–2):185–195
19. Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C (2009) Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. Eur J Pain 13(1):94–101
20. Hermann C, Hohmeister J, Demirakca S, Zohsel K, Flor H (2006) Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 125(3):278–285
21. Bakhti A, Chabra A, Wang D (2006) Endpoints. In: Wang D, Bakhti A (eds) Clinical trials: a practical guide to design, analysis and reporting. Remedica, Limassol, Cyprus, pp 37–45
22. McGrath PJ, Valeo GA, Turk DC, Dworkin RH, Brown MT, Davidson K, Eccleston C, Finley GA, Goldschneider K, Haverkos L, Hertz SH, Ljungman G, Palermo T, Rappaport BA, Rhodes T, Schechter N, Scott J, Sethna N, Svensson OK, Stinson J, von Baeyer CL, Walker L, Weisman S, White RE, Zajicek A, Zeltzer L (2008) Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain 9(9):771–783
23. Walker SM (2008) Pain in children: recent advances and ongoing challenges. Br J Anaesth 101(1):101–110
24. Merskey H, Bogduk N (1994) Classification of chronic pain: description of chronic pain syndromes and definitions of pain terms. IASP Press, Seattle
25. Suraseranivongse S, Santawat U, Kraiprasit K, Patcharatanasophon P, Prakkanondom S, Muntraphon N (2001) Cross-validation of a composite pain scale for preschool children within 24 hours of surgery. Br J Anaesth 87(3):400–405
26. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S (1997) The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 23(3):293–297
27. Voepel-Lewis T, Merkel S, Tait AR, Trzcińska A, Malviya S (2002) The reliability and validity of the Face, Legs, Activity, Cry, Consolability observational tool as a measure of pain in children with cognitive impairment. Anesthesiology 95(5):1224–1229
28. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ (2000) The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0- to 3-year-old infants. Pain 84(2–3):367–377
29. van Dijk M, Valkenburg A, Boerlage AA, Tibboel D, Veerkamp JS (2009) Children with intellectual disabilities and pain perceptions: A review and suggestions for future assessment protocols. Eur Arch Paediatr Dent 10(2):57–60
30. Valkenburg A, Van Dijk M, Klein A, van Den Anker JN, Tibboel D (2010) Pain management in intellectually disabled children: assessment, treatment and translational research. Dev Disabil Res Rev 16:248–257
31. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR (2006) The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Paediatr Anaesth 16(3):258–265
32. Voepel-Lewis T, Malviya S, Tait AR, Merkel S, Foster R, Krane EJ, Davis PJ (2008) A comparison of the clinical utility of pain assessment tools for children with cognitive impairment. Anesthesiology Analgesia 106(1):72–78
33. Hunt A, Goldman A, Seers K, Crichton N, Mastroyannopoulou K, Hunt A, Goldman A, Seers K, Crichton N, Mastroyannopoulou K, Malviya S, V oepel-Lewis T, Shayevitz JR, Malviya S (1997) The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 23(3):293–297
34. Voepel-Lewis T, Merkel S, Tait AR, Trzcinka A, Malviya S (2002) The reliability and validity of the Face, Legs, Activity, Cry, Consolability observational tool as a measure of pain in children with cognitive impairment. Anesthesiology 95(5):1224–1229
35. van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ (2000) The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0- to 3-year-old infants. Pain 84(2–3):367–377
36. van Dijk M, Valkenburg A, Boerlage AA, Tibboel D, Veerkamp JS (2009) Children with intellectual disabilities and pain perceptions: A review and suggestions for future assessment protocols. Eur Arch Paediatr Dent 10(2):57–60
37. Valkenburg A, Van Dijk M, Klein A, van Den Anker JN, Tibboel D (2010) Pain management in intellectually disabled children: assessment, treatment and translational research. Dev Disabil Res Rev 16:248–257
38. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR (2006) The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Paediatr Anaesth 16(3):258–265
39. Voepel-Lewis T, Malviya S, Tait AR, Merkel S, Foster R, Krane EJ, Davis PJ (2008) A comparison of the clinical utility of pain assessment tools for children with cognitive impairment. Anesthesiology Analgesia 106(1):72–78
40. Hunt A, Goldman A, Seers K, Crichton N, Mastroyannopoulou K, Moffat V, Oulton K, Brady M (2004) Clinical validation of the paediatric pain profile: role of video analysis and saliva cortisol in validating a tool to assess pain in children with severe neurological disability. J Pain Symptom Manage 33(3):276–289
35. Breau LM, McGrath PJ, Camfield CS, Finley GA (2002) Psychometric properties of the non-communicating children's pain checklist-revised. Pain 99(1-2):349–357
36. Breau LM, Finley GA, McGrath PJ, Camfield CS (2002) Validation of the Non-communicating Children's Pain Checklist-Postoperative Version. Anesthesiology 96(3):528–535
37. Duivenvoorden HJ, Tibboel D, Koot HM, van Dijk M, Peters JW (2006) Pain assessment in profound cognitive impaired children using the Checklist Pain Behavior; is item reduction valid? Pain 126(1-3):147–154
38. Terstegen C, Koot HM, de Boer JB, Tibboel D (2003) Measuring pain in children with cognitive impairment: pain response to surgical procedures. Pain 103(1-2):187–198
39. Soloduk J, Scott-Sutherland J, Meyers M, Myette B, Shusterman C, Karan VE, Harris SK, Curley MA (2010) Validation of the Individualized Numeric Rating Scale (INRS): a pain assessment tool for nonverbal children with intellectual disability. Pain 150(2):231–236
40. Breau L (2010) The science of pain measurement and the frustration of clinical pain assessment: does an individualized numerical rating scale bridge the gap for children with intellectual disabilities? Pain 150(2):213–214
41. Hester NO, Foster R, Kristensen K (1990) Measurement of pain in children: Generalizability and validity of the pain ladder and poker chip tool. Adv Pain Res Ther 15:79–84
42. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B (2001) The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain 93(2):173–183
43. Tomlinson DJ, von Baeyer CL, Stinson JN, Sung L (2010) A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics 126:e1168–e1198
44. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA (2009) Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. Pain 143(3):222–227
45. Scott PJ, Ansell BM, Huskisson EC (1977) Measurement of pain in juvenile chronic polyarthritis. Ann Rheum Dis 36(2):186–187
46. Huguet A, Stinson JN, McGrath PJ (2010) Measurement of self-reported pain intensity in children and adolescents. J Psychosom Res 68(4):329–336
47. Berde C, McGrath P (2009) Pain measurement and Beecher's challenge: 50 years later. Anesthesiology 111(3):473–474
48. Stevens BJ, Johnston CC, Petryshen P, Taddio A (1996) Premature Infant Pain Profile: development and initial validation. Clin J Pain 12:13–22
49. Ambuel B, Hamlett KW, Marx CM, Blumer JL (1992) Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 17(1):95–109
50. Carnevale FA, Razack S (2002) An item analysis of the COMFORT scale in a pediatric intensive care unit. Pediatr Crit Care Med 3(2):177–180
51. van Dijk M, de Boer JB, Koot HM, Duivenvoorden HJ, Plasscher J, Bouwmester J, Tibboel D (2001) The association between physiological and behavioral pain measures in 0- to 3-year-old infants after major surgery. J Pain Symptom Manage 22(1):600–609
52. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412(6843):150–157
53. Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJ (2006) Pain activates cortical areas in the preterm newborn brain. Pain 122(1-2):109–117
54. Slater R, Cantarella A, Franck L, Meek J, Fitzgerald M (2008) How well do clinical pain assessment tools reflect pain in infants? PLoS Med 5(6):e129
55. Slater R, Cantarella A, Gallela S, Worley A, Boyd S, Meek J, Fitzgerald M (2006) Cortical pain responses in human infants. J Neurosci 26(14):3662–3666
56. Eriksson M, Storm H, Fremming A, Schollin J (2008) Skin conductance compared to a combined behavioural and physiological pain measure in newborn infants. Acta Paediatr 97(1):27–30
57. Bouwmester NJ, Anand KJ, van Dijk M, Hop WC, Boomsma F, Tibboel D (2001) Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial comparing the effects of continuous versus intermittent morphine. Br J Anaesth 87(3):390–399
58. Tempelhoff R, Modica PA, Spitznagel EL Jr (1990) Anticonvulsant therapy increases fentanyl requirements during anesthesia for craniotomy. Can J Anaesth 37(3):327–332
59. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC (1997) Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277(5328):968–971
60. Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol Clin 30(5):263–288
61. Hohmeister J, Kroll A, Wollgarten-Hadamek I, Zohsel K, Demirakca S, Flor H, Hermann C (2010) Cerebral processing of pain in school-aged children with neonatal noceceptive input: an exploratory fMRI study. Pain 150(2):257–267
62. Slater R, Worley A, Fabrizi L, Roberts S, Meek J, Boyd S, Fitzgerald M (2010) Evoked potentials generated by noxious stimulation in the human infant brain. Eur J Pain 14(3):321–326
63. Handelmann GE, Dow-Edwards D (1985) Modulation of brain development by morphine: effects on central motor systems and behavior. Peptides 6(Suppl 2):29–34
64. McPherson RJ, Gleason C, Mascher-Denen M, Chan M, Kellert B, Juul SE (2007) A new model of neonatal stress which produces lasting neurobehavioral effects in adult rats. Neonatology 92(1):33–41
65. Ma MX, Chen YM, He J, Zeng T, Wang JH (2007) Effects of morphine and its withdrawal on Y-maze spatial recognition memory in mice. Neuroscience 147(4):1059–1065
66. Sargeant TJ, Miller JH, Day DJ (2008) Opioidergic regulation of astroglial/neuronal proliferation: where are we now? J Neurochem 107(4):883–897
67. Hu S, Sheng WS, Lokensgard J, Peterson PK (2002) Morphine induces apoptosis of human microglia and neurons. Neuropharmacology 42(6):829–836
68. Atici S, Cinel L, Cinel I, Doruk N, Aktekin M, Akca A, Camdeviren H, Oral U (2004) Opioid neurotoxicity: comparison of morphine and tramadol in an experimental rat model. Int J Neurosci 114(8):1001–1011
69. Boasen JF, McPherson RJ, Hays SL, Juul SE, Gleason CA (2008) Neonatal Stress or Morphine Treatment Alters Adult Mouse Conditioned Place Preference. Neonatology 95(3):230–239
70. Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scheren A, Magele W, Akus F, Zernikow B (2010) Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. Pain 149(1):76–88
71. Danhof M, de Jongh J, De Lange EC, Della Pasqua O, Ploeger BA, Voskuyl RA (2007) Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. Annu Rev Pharmacol Toxicol 47:357–400
72. Smith MT, Muralidharan A (2010) Pharmacogenetics. In: IASP (ed) Pain: Clinical Updates. IASP Press, Seattle