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REVIEW ARTICLE

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 hyperalgesia 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-

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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 polygenetic 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 long-lasting 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.europe.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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