British Journal of Anaesthesia **101 (1):** 101–10 (2008)
doi:10.1093/bja/aen097 Advance Access publication April 21, 2008

BJA

Pain in children: recent advances and ongoing challenges

S. M. Walker*

Portex Department of Anaesthesia, 6th Floor Cardiac Wing, UCL Institute of Child Health and Great Ormond Street Hospital NHS Trust, 30 Guilford Street, London WC1N 1EH, UK

**E-mail: suellen.walker@ich.ucl.ac.uk*

Significant advances in the assessment and management of acute pain in children have been made, and are supported by an increase in the availability and accessibility of evidence-based data. However, methodological and practical issues in the design and performance of clinical paediatric trials limit the quantity, and may influence the quality, of current data, which lags behind that available for adult practice. Collaborations within research networks, which incorporate both preclinical and clinical studies, may increase the feasibility and specificity of future trials. In early life, the developing nervous system responds differently to pain, analgesia, and injury, resulting in effects not seen in later life and which may have long-term consequences. Translational laboratory studies further our understanding of developmental changes in nociceptor pathway structure and function, analgesic pharmacodynamics, and the impact of different forms of injury. Chronic pain in children has a negative impact on quality of life, resulting in social and emotional consequences for both the child and the family. Despite age-related differences in many chronic pain conditions, such as neuropathic pain, management in children is often empirically based on data from studies in adults. There is a major need for further clinical research, training of health-care providers, and increased resources, to improve management and outcomes for children with chronic pain.

Br J Anaesth 2008; **101**: 101–10

Keywords: children; neonates; pain, acute; pain, chronic

Effective management of pain in children is a major priority for patients, parents, and health-care providers, and has been highlighted as a priority in the Children's National Service Framework from the UK Department of Health (www.dh.gov.uk/en/Healthcare/NationalServiceFrameworks/ChildrenServices). 'Children' encompasses an extremely broad group from premature neonates to adolescents. There are marked age-related changes affecting all aspects of pain management including assessment, physiological and pharmacological responses, and in the importance of different clinical outcomes. Recent advances in paediatric pain management have been reliant on multiple factors including: knowledge of the developmental neurobiology of pain processing and developmental pharmacokinetics of analgesic agents; improved age-appropriate tools for pain assessment; and increased availability and accessibility of current best evidence in clinical practice guidelines. Details for clinical management are available in the referenced reviews and guidelines and are not the focus of this review. Rather, recent research and significant ongoing challenges associated with pain management in children will be highlighted. Methodological and practical difficulties can limit the quantity or quality of data from paediatric clinical trials, and there are insufficient data to guide acute pain management in all clinical settings, particularly during the neonatal period. The immature nervous system can respond very differently to pain and analgesia, and injury in early life may produce long-term changes in sensory processing and/or pain sensitivity. Finally, chronic pain in children, which may be more common than previously recognized, has a significant impact on quality of life, and further research and resources are required to improve management and outcomes.

Evidence-based paediatric acute pain management

Guidelines and practice recommendations

The significant advances in the assessment and management of acute pain in children are supported by an increase in the availability of evidence-based data. In the first edition of *Acute Pain Medicine: Scientific Evidence* in 1999 only 8% of paediatric citations were based on Levels I and II evidence (in contrast to 67% of adult citations), increasing to 50% in the second edition in 2005.[17] A recent update of Level I evidence (meta-analyses and systematic reviews) in December 2007 included 13 new citations relevant to paediatric practice (www.anzca.edu.

au/resources/books-and-publications). Recommendations and guidance specifically relating to paediatric acute pain management include Statements on the Management of Procedure-related Pain in Neonates and Management of Procedure-related Pain in Children and Adolescents by The Paediatrics and Child Health Division of the Royal Australasian College of Physicians (www.racp.edu.au/index.cfm?objectId=A4268489-2A57-5487-DEF14F15791C4F22), and more recently Good Practice in Postoperative and Procedural Pain by the Association of Paediatric Anaesthetists of Great Britain and Ireland.[18] The aim of evidence-based acute pain guidelines is not to provide global standards or absolute requirements, but to provide current data in an accessible form to assist decision-making about healthcare. As treatment settings vary markedly in size, resources, complexity, and patient populations, there can be no 'one size fits all' recommendation, and the efficacy of any intervention must be assessed and titrated in individual patients.[136]

Evaluating the evidence

Many paediatric treatments are empirically based on data from adults, gaps in knowledge persist, and there are insufficient data to guide treatment in all practice settings.[24 63] Many practical and methodological factors in the design and performance of clinical paediatric trials can limit the quality or quantity of available research data. This not only has an impact on the grading of recommendations in clinical practice guidelines, but also should be considered by individual practitioners when reading and interpreting published data. Factors affecting trial sensitivity include the following:

(i) *Sample size*: The challenge of recruiting paediatric patients into clinical trials often results in small or heterogeneous groups being compared. Inclusion of children across a wide age range may increase sample size but at the cost of increased variability due to age-related changes in analgesic requirement. Additionally, the validity of combining data from varying age-appropriate observational and self-report assessment tools has not been fully established. Younger children in particular may not fully understand the equal interval properties of scales and be more likely to choose the extremes of self-report scales.

(ii) *Ethical issues*: In addition to parental consent, child assent should be gained if possible,[121] and all efforts should be made to ensure clarity of consent documents.[122] In children, comparison with another active treatment rather than a placebo is usually employed, necessitating a larger sample size to ensure the study is adequately powered. Increasingly, regulatory or legislative requirements, such as directives from the European Union medicines regulatory regime[93] (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm) and the UK Medicines and Healthcare products Regulatory Agency (MHRA; www.mhra.gov.uk), must be incorporated in the design and conduct of clinical trials.

(iii) *Outcome measures*: Outcome measures with limited sensitivity or specificity reduce the power of clinical studies and increase the likelihood of a Type II error (i.e. failure to find a difference when a difference does exist).

Outcomes commonly used in analgesic trials include the following:

(i) *Pain intensity*: Recent systematic reviews have evaluated the validity, utility, and reliability of assessment tools for children aged 3 yr and above. Recommended observer-based behavioural scales include: FLACC and CHEOPS for acute procedural and postoperative pain; the COMFORT scale for children in intensive care; and the Parents Postoperative Pain Measure (PPPM) for postoperative pain managed by parents at home.[126] Recommended self-report tools include: pieces of Hurt tool for children aged 3–4 yr; Faces Pain Scale-Revised for 4–12 yr; and visual analogue scale for children more than 8–10 yr.[118] Uniform adoption of fewer assessment tools would aid comparison across trials and the combination of data in future meta-analyses.[58] In clinical practice, regular and consistent use of an assessment tool within a hospital may be more important than which tool is chosen.

(ii) *Time to first analgesia*: This measure requires the return of pain before analgesia, and the trigger for analgesic administration will influence the results. In a meta-analysis examining addition of clonidine to caudal local anaesthetic, the use of different criteria from a range of scales (e.g. VAS >4/10 or 6/10; CHEOPS >6 or >9) limited the ability to combine the raw data.[16]

(iii) *Analgesic consumption*: If rescue analgesia is being effectively titrated in a clinical study, all subjects should achieve similar pain scores and therefore a difference in analgesic consumption rather than pain score should be seen. However, inter-individual variability in analgesic requirements and in pharmacokinetics will reduce the sensitivity of this measure, particularly if patients from a range of ages are included. Differences in metabolism due to age-related changes in enzyme activity or genetic polymorphism will have an impact with studies using codeine[139] or tramadol.[3] As noted above, criteria or triggers for administration of analgesia must be standardized, and in studies after day case surgery, this will be influenced by parental assessment and administration of analgesia.[45]

Suggestions for improved study design have been outlined with the aim of stimulating further research,[4] and