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Paediatric Pain: physiology, assessment and pharmacology

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Introduction

Pain is a common reason for paediatric patients to present to hospital. Pain can have a direct impact on health outcomes and, if uncontrolled, may have a diverse effect on all areas of life. This is because pain is not only a sensory perception but has emotional, cognitive, and behavioural components, which also need to be recognised. The impact and perception of pain is also influenced by a patients' individual developmental, environmental, and sociocultural background. If pain is not adequately managed acutely there is good evidence suggesting that untreated pain may have long-term negative effects on pain sensitivity, immune functioning, neurophysiology, attitudes, and health care behaviour[1]. It is therefore essential that health care professionals looking after children of all ages are trained to recognise and treat pain whether it be acute or chronic.

Good quality, effective management of pain in paediatric patients is therefore an essential component of paediatric anaesthesia. However, achieving this can be difficult for a variety of reasons not least of which is the enormous variations that occur physiologically and psychologically throughout the range of ages encountered in the paediatric population. Firstly, some of the developmental neurobiological issues will be considered.

Development of pain pathways

All neural pathways required for nociception are present from birth and are also functional in premature neonates. However, many molecules, neurotransmitters and receptor-mediated systems are variably expressed depending upon developmental age. As a result, a noxious stimulus may provoke different patterns of activity dependent on the stage of maturity of the paediatric central nervous system.

In the peripheral nervous system, C-fibres are mature in neonates although their cortical connections at the level of the dorsal horn are immature. However, interestingly, at the same stage A-Beta fibres show extended connections within the spinal cord that can produce nociceptive signalling from lower intensity stimuli. These A-Beta fibres only recede once C-fibres have matured. The result of this observation is that there is far less discrimination between the perception of noxious and non-noxious stimuli in the paediatric patient. Furthermore, and of added clinical importance, is that inhibitory pathways are not fully developed in the spinal cord during early life. The combination of widened receptive fields, lower sensory discrimination and reduced inhibitory pathways results in the immature nervous system in paediatric patients experiencing *more* pain in response to noxious stimuli and not less as was previously believed.

Aetiology of paediatric pain

The main causes of acute pain in children are from procedures, surgery, trauma and acute medical illness. Each of these has its own particular considerations but nonetheless, regardless of the cause of pain, a number of general factors are important and should be considered in all circumstances to aide successful pain management. These include education of staff involved in caring for the patient, pain assessment, anticipation of pain, provision of a calm environment and the inclusion of parents.

Procedure related pain

The pain associated with planned medical procedures can be distressing for the patient, parents and medical staff. Unlike acute pain of other causes, procedure related pain often involves a strong element of anticipation. Multiple procedures are frequently required and uncontrolled pain at the time of the first procedure can adversely affect the level of pain and distress experienced on subsequent occasions. Therefore, the aim of procedure related pain management is to minimise pain, physical discomfort and psychological distress.

With regards to procedure related pain, both pharmacological and non-pharmacological methods need to be utilised. Firstly, a number of simple non-pharmacological strategies should be employed to successfully manage paediatric patients in this situation. Prior to any planned procedure both child and parent should be adequately prepared as to what procedure is planned and how this will be conducted. The child should be provided with age and developmentally appropriate information about the procedure and what sensations to expect. Engaging with parents and gaining their confidence is essential in the preparation of children for a procedure as they can provide additional information and reassurance to the child. This can be further aided by giving older children a chance to ask any questions and younger children the opportunity to act out the procedure with a toy medical kit[2,3].

It is preferable that any planned procedure should take place in a dedicated treatment room in a comfortable, calm and friendly environment. Ideally all staff should have knowledge of simple, effective coping strategies to use with children of any age. Staffs experienced and trained in psychological techniques such as Play Therapists have an important role in this regard. Equipment for

distraction should be available. This includes toys, interactive books, puppets, bubbles and electronic games that will quickly distract the child and hold their attention.

A variety of pharmacological methods and techniques are available and include the use of analgesia with or without sedation. The exact method chosen depends on a multitude of factors such as the nature of the planned procedure, age (physiological and developmental) of the child and experience of the responsible Anaesthetist. Some commonly used analgesic techniques utilise topical anaesthesia, local infiltration, peripheral nerve blockade, Bier's block, nitrous oxide, ketamine or intra-nasal fentanyl. Regardless of the technique chosen monitoring is mandatory and emergency equipment should be readily available.

Post-operative pain

Post-operative pain should be discussed pre-operatively with the carers and, where appropriate, with the child. The aim of pain management in this setting is to control pain as early as possible and therefore the initial choice of drug and dose should be appropriate and titrated to response. Early and preventative treatment is more effective resulting in better pain control and less distress. Regional anaesthetic techniques are commonly utilised in this setting and will be discussed in a separate article.

As with post-operative pain management in adults, paediatric pain management includes the principles of multi-modal analgesia whereby different classes of drug are utilised to gain maximum effect. Analgesic treatment should include proper dosing according to body weight, physiologic development, and the clinical situation. Dosages and the interval between doses should be adjusted based on the assessment of the patient's response.

Trauma

Trauma related pain should be addressed in the emergency department as part of initial assessment and treatment. The complex clinical issues present at the time of admission will determine pain management, including choice of drug, dosage, route and mode (continuous vs intermittent). These must be tailored to the requirements of the individual patient and the nature of the injury involved. Morphine is still the most commonly used first line analgesic for severe pain and can be administered incrementally up to a dose of 0.1mg/kg. However, it should be realised that a higher dose than this may be required to achieve adequate pain control. Other important therapies in the emergency setting include the use of topical anaesthesia, inhaled 50% N_20/ 50% 0_2, IV regional anaesthesia and inhalational or transmucosal opioids have all been used to good effect.

Paediatric pain assessment tools

Systematic, routine pain assessment using standardized, validated measures is accepted as the foundation of effective pain management for patients, regardless of age, condition or setting[4]. The assessment tools are based on either self-report or observation of behaviour. Self-report is the only truly direct measure of pain and hence it is considered the 'gold standard' of measurement. However, no single tool can be used for pain assessment across all children or all cases. Therefore, healthcare professionals need to be not only trained in the use of pain assessment tools but also need to be aware of their limitations. If performed successfully, accurate assessment of pain is associated with improvements not only in pain management but also in patient, parent and staff satisfaction. However, despite these benefits pain in paediatric patient is often infrequently assessed.

Recommendations made by the Royal College of Nursing[5] are to anticipate pain wherever possible and be vigilant for any indications of pain in the paediatric patient. Children's self-report of pain is the

preferred method but when this is not possible an appropriate behavioural or composite tool should be used. Indicators that point to the presence of uncontrolled pain include changes in physiological signs such as heart rate, respiratory rate, blood pressure, intracranial pressure and sweating while other important observations include changes in a child's behaviour, appearance or activity level. However, no individual tool can be broadly recommended for pain assessment in all children and across all contexts. It is important to assess, record, and re-evaluate pain at regular intervals; the frequency of which should be determined according to the individual needs of the child and setting. Be aware that language, ethnicity and cultural factors may influence the expression and assessment of pain.

A number of formal means of assessment of paediatric pain are available. Some of these are summarised below and can be divided into self-report and observational.

Self-report

Visual analogue scale (VAS) -Self-report visual analogue scales for pain intensity. It is a horizontal line with "no pain" at one end to "worst possible pain" at the other. Patient draws a line that intersects to indicate intensity. For ages 3- adult.

Wong-Baker Faces Pain Rating Scale[6] - Self-report faces scale for acute pain. Six line-drawn faces range from no pain to worst pain. It assigns a numerical value to each face. The Wong-Baker Scale also adds word descriptors to each face (no hurt, hurts a little, hurts a whole lot, etc.) Age group 3-18 years

Faces Pain Scale-Revised[7] *(FPS-R)* - Self-report faces scale for acute pain. Six cartoon faces range from neutral to high pain expression. These faces can be numbered 0, 2, 4, 6, 8, and 10. Age group 4-16 years.

Poker chip tool[8] - Self-report poker chips are used to represent pain intensity. Child chooses which chips represent the pain they experience with one chip indicating a little hurt and all four chips indicating the most hurt a child could have. Age group 4-7 years

Observational

FLACC Pain Assessment Tool [9] which incorporates five categories of pain behaviours: facial expression; leg movement; activity; cry; and consolability. Each of these five operationally defined categories is given a score from 0 to 2; yielding a total possible range of 0 to 10.The FLACC provides a simple framework for quantifying pain behaviours in children who may not be able to verbalize the presence or severity of pain.

Procedure Behavior Checklist[10] *(PBCL).* Observational measure of pain and anxiety during invasive medical procedures. The behaviours assessed in the PBCL include muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling and physical resistance. Eight operationally defined behaviours rated on occurrence and intensity (scale 1–5).Age group 3-18 years

Children's Hospital of Eastern Ontario Pain Scale[11] *(CHEOPS).* Observational measure of postoperative pain in children. The CHEOPS assesses six behaviours that include cry, facial, child verbal, torso, touch and legs. Each behaviour is coded on a scale of 0 to 3 based on intensity. Age group 1–12 years

COMFORT Scale [12.] Observer rated measure for use in intensive care environments. The COMFORT scale assesses eight domains thought to be indicative of pain and distress including alertness, calmness/agitation, respiratory response, physical movement, mean arterial blood pressure, heart

rate, muscle tone and facial tension. Each dimension is scored between 1 and 5, and the scores are added to yield a measure of sedation. Age group 0–18 years.

Premature Infant Pain Profile[13] *(PIPP).* Seven indicators of pain. Each item is scored on a 4-point scale. The items include physiological (heart rate, oxygen saturation) and behavioural dimensions (facial expression, eye squeeze, brow bulge, nasolabial furrow, and crying)

Pharmacological therapies

The range of pharmacological therapies available for use in paediatric practice is the same as that used in adult populations. However, the pharmacokinetic profile of many analgesics is altered by the rapid changes that occur in body fat, water and plasma protein binding that occurs in the first few weeks and months of life. The changing picture of nociceptive processing can also affect the pharmacodynamics response of drugs. Some of the commonly used analgesics are discussed below.

Paracetamol

Paracetamol should be considered at all stages of pain management. The mechanism of action is not well understood but is thought to involve the inhibition of prostaglandin H2 and cyclo –oxygenase 3 (COX-3), found only in the central nervous system (CNS). Paracetamol has a useful anti-pyretic as well as analgesic action. Paracetamol is commonly administered in the pre and post-operative period with an efficacy equivalent to NSAIDs in pain reduction with an opioid sparing effect. Paracetamol has an excellent safety profile with side effects and adverse reactions being uncommon. Hepatotoxicity is however a recognized complication of overdose and therefore meticulous care needs to be taken in its calculation, administration and documentation.

Paracetamol can be given by a variety of routes depending on the clinical circumstances. The conventional oral dosing regimen is 15 – 20 mg/kg given 4-6 hourly for pain relief and anti-pyresis. The daily maximum dose is 90 mg/kg in children aged > 3 months. It is available in a variety of preparations including oral suspension, tablets, and suppositories and as an intravenous preparation. The loading dose of rectal paracetamol is generally larger due to its unpredictable bioavailability; however, the recommended daily maximum dose by this route remains the same. Intravenous paracetamol has greater dosing accuracy and a rapid and predictable onset of action (within 5 min) because of less pharmacokinetic variability.

Non-steroidal anti-inflammatories (NSAIDs)

NSAIDs act by inhibiting the cyclooxygenase-2 isoenzyme, thereby preventing the conversion of arachidonic acid to prostaglandins and thromboxane. This is important as prostaglandins are proinflammatory mediators that sensitise nociceptors to increase afferent nociceptive signalling. Providing no contra-indications exist, NSAIDS should be considered as part of routine acute analgesic regimen as they are effective analgesics with useful opioid sparing effects.

NSAIDs are commonly used analgesics in mild and moderate pain in all ages of children including infants. There are a number of different NSAIDs in common usage in paediatric practice but the most commonly used agents are diclofenac, ibuprofen and ketoprofen. There is little difference in efficacy between these drugs with use depending on available route of administration and preference. The combination of a NSAID and paracetamol is recommended as there action is synergistic to provide higher quality analgesia and decrease opioid requirements.

Some NSAIDs in common clinical usage include:

Ibuprofen- is available in oral suspension, infant drops, tablet and intravenous formulations. It is used for perioperative pain relief in children weighing > 7 kg and is also used to close patent ductus arteriosus (PDA) in neonates. The dose is 30mg/kg in 3-4 divided doses.

Diclofenac is available as tablets, suppository and parenteral formulations. The dose orally and per rectum is 0.3–1 mg/kg (max. 50 mg) 3 times daily.

Ketorolac can be given intramuscularly, intravenously or orally. It is not licensed for use in children below 16 years of age. It is indicated only for the short term management of acute post-operative pain. When given orally for young adults aged 16–18 years the dose is 10mg every 4–6 hours as required up to 40 mg daily for a maximum of 7 days. For children between 6 months–16 years the intravenous dose is initially 0.5–1 mg/kg (max. 15 mg), then 500 micrograms/kg (max. 15 mg) every 6 hours as required; maximum 60 mg daily and maximum duration of treatment 2 days.

Opioids

Opioids are a cornerstone of acute pain management in both paediatric and adult populations. Opioids act through dedicated receptors, designated Mu, Kappa, Delta and ORL-1 (orphanin like receptor). These receptors are widely distributed throughout the CNS and at sites of peripheral inflammation. The most clinically important of these is the Mu opioid receptor through which all opioid drugs in clinical practice exert their effect.

The pharmacokinetic handling and pharmacodynamics response to opioids varies considerably in paediatric patients and must be adjusted in accordance to age, clinical response and presence of sideeffects. Appropriate education, guidelines and documentation are all important in safe and effective management of opioid therapy. Some of the commonly used opioids are discussed below.

Codeine

Codeine is activated by O-demethylation by the cytochrome CYP2D6 to morphine. The activity of this enzyme is however highly variable. For example, the activity of the enzyme may be at only 25% of adult values at the age of 5 resulting in highly variable conversion of codeine to its active metabolite and thus giving variable analgesic efficacy. This cytochrome also displays considerable inter-individual variation with some alleles of the cytochrome yielding slow or incomplete metabolisation of codeine. Approximately 9% of the Caucasian population are estimated to carry this variant. However, a variant of this allele exists that increases the conversion of codeine to morphine, so called 'supermetabolisers'. These patients may exhibit an exaggerated response to even low dose codeine and put them at risk of excess sedation and respiratory depression even from low doses.

Codeine is most effective when combined with paracetamol and can be given as an oral dose of 0.5 – 1 mg/kg every 4 – 6 hours. Codeine has, however, been found to be not as effective as NSAIDs for musculoskeletal pain.

Morphine

Morphine is a naturally occurring phenanthrene derivative. It remains the most valuable opioid analgesic for severe pain and is the standard against which other opioid analgesics are compared. It can be given by a variety of routes including oral, intravenous, intramuscular, subcutaneous, rectal, intrathecal, epidural and intranasal. Considerable variation in pharmacokinetics exist between age groups with neonates and infants displaying prolonged half-lives and up to a 2-3 fold difference in

plasma concentrations of morphine even when given by constant infusion. No definite correlation between plasma levels of opioid and analgesic effect have been identified.

Intravenous administration of morphine is guided by the age, weight and clinical response of the child. For neonates the initial guidance is for titration of morphine up to 0.5 mg/kg initially.

Morphine is commonly given via the oral and rectal route. For children between 1–6 months of age this can be given initially at a dose of 50–150 micrograms/kg every 4 hours. For a child between 6months– 12 years 100-300 micrograms/kg every 4 hours and child between 12–18 years initially 5–20 mg every 4 hours. The oral route should be preferred due to more reliable absorption.

Fentanyl

Fentanyl is a synthetic phenylpyperidine derivative which is 100 times more potent than morphine and is metabolised to inactive metabolites. The rapid onset and offset suits fentanyl in the management of procedure related pain. It can be given by the intravenous, transmucosal, transdermal, inhalational or intra-nasal route.

Remifentanil

Remifentanil is a synthetic phenylpyperidine derivative given as an intravenous infusion intraoperatively. It is rapidly broken down by non-specific plasma and tissue esterases resulting in a short elimination half-life (3-10 minutes). Intra-operative use of remifentanil has been associated with increase post-operative pain scores possibly indicating an acute opioid induced hyperalgesic effect. Loading dose of 0.1 – 1 mcg/kg over 30 sec if required and continuous infusion between 3 – 80 mcg/kg/h. For older children (12-18 years) infusion can run from 3-120mcg/kg/h.

Tramadol

Tramadol is a centrally acting analgesic that is structurally related to morphine. It is a racemic mixture of two enantiomers that exert synergestic antinociceptive actions. Biotransformation in the liver by cytochrome P450 (CYP2D6) leads to the formation of O-desmethyl-tramadol which has a mu-opioid receptor affinity 200 times greater than tramadol[14]. The wide variation in the pharmacokinetic properties of tramadol are similar in codeine in this respect[15].It is not licensed for use in children under 12 years. It can be given orally to children between 12–18 years at a dose of 50–100 mg every 4 hours to a maximum of 400mg per day. It can also be given by intravenous injection (over 2–3 minutes), intravenous infusion or by intramuscular injection for children between 12–18 years at the same dosage.

Few studies have been carried out on paediatric patients and reports of tramadol's efficacy vary with results indicating that it may simply be better than paracetamol with others reporting equivalency to morphine. Side-effects are the same as those for strong opioids but with a lower incidence of constipation, pruritis and respiratory depression.

Patient Controlled Analgesia (PCA)

PCA can be used in children as young as 5 years of age depending on the ability of the child and carers to understand the concepts of the device. PCA provides considerable flexibility and similar efficacy to opioid infusions. Morphine is most commonly used in PCA's and is given as a bolus dose of 20mcg/kg. Background infusions are more commonly used in paediatric PCAs' at a dose of 4 mcg/kg/hr to maximise analgesia and minimise side-effects. Nurse controlled analgesia is also an accepted and effective variation in practice.

Other Analgesics

Ketamine

Ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist, which blocks peripheral nociception and prevents central sensitization. It is being increasingly used in paediatrics for analgesia in the emergency department and for procedural sedation. It can be used to provide anaesthesia, sedation or analgesia depending on the dose administered. It may be given by intravenous bolus, intravenous infusion, intramuscular injection, epidural, oral, and rectal routes. There are theoretical concerns regarding the possible neurodegenerative effect of ketamine and other anaesthetic agents on the developing brain from animal models that have demonstrated neuroapoptosis, although the clinical significance of this is uncertain[14]. The analgesic dose is 1-2mg/kg intravenously and 4-13mg/kg intramuscularly depending on procedure and is adjusted according to response. Adverse effects include laryngospasm, vomiting, salivation, increased muscle tone, emergence hallucinations, drowsiness, rashes and injection-site reactions.

Nitrous oxide

Nitrous oxide can be given as 50 % with oxygen for sedation and analgesia (Entonox). Self-administration using a demand valve may be used in children who are able to self-regulate their intake (usually over 5 years of age) for painful dressing changes, for wound debridement and in the emergency department. Side effects include nausea, vomiting and dizziness. Exposure of children to nitrous oxide for prolonged periods may result in megaloblastic anaemia owing to interference with the action of vitamin B12.

Conclusion

Paediatric pain management is a challenging area of anaesthesia and pain medicine. There are a multitude of reasons for this including the diverse range of developmental and physiological changes that occur throughout childhood, a lack of education and awareness of the importance of pain management and regular pain assessment. Multiple pharmacological therapies are available but as for adult practice, multi-modal analgesia should be used whenever possible. Local guidelines and protocols significantly aid the delivery of quality pain management and should be developed, implemented and audited to ensure optimum analgesia.

Summary

- The paediatric nervous system is fully developed and able to respond to nociceptive stimuli even in pre-term neonates
- Pain can have lasting physiological and developmental consequences if not appropriately managed
- Regular pain assessment is fundamental to good pain management but is often poorly performed
- A variety of pain assessment tools are available and should be utilised according to a patient's age and developmental stage
- Multi-modal therapy is appropriate for managing all forms of paediatric pain and should utilise cominations of local anaesthetic, paracetamol, NSAIDs and opioids.as appropriate
- Adequate monitoring, safety equipment and resuscitation skills are needed to safely manage patients requiring combinations of sedation and analgesia for painful procedures
- The pharmacokinetic and pharmacodynamic profile of commonly used analgesics can be variable depending on the age and development of the patient.

References

1.Young KD. Pediatric procedural pain Ann Emerg Med. 2005 Feb;45(2):160-71

2. Good Practice in Postoperative and Procedural Pain 2nd Edition, 2012

3.Guideline statement: management of procedure-related pain in children and adolescents.J Paediatr Child Health. 2006 Feb;42 Suppl 1:S1-29.

4. Franck LS, Bruce E et al. Putting pain assessment into practice: Why is it so painful? Pain Res Manag. 2009 Jan–Feb; 14(1): 13–20.

5. Royal College of Nursing (UK). Clinical Guidelines for the Recognition and Assessment of Acute Pain in Children. London: Royal College of Nursing 2009

6. Wong D, Baker C. Pain in children: comparison of assessment scales. Pediatr Nurs 1988; 14: 9–17.

7. Hicks C, Von Baeyer C, Spafford P et al. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain 2001; 93: 173–183.

8. Hester N. The preoperational child's reaction to immunizations. Nurs Res 1979; 28: 250–255.

9. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs. 1997;23:293–7

10. Katz ER, Kellerman J, Siegel SE. Behavioral distress in children with cancer undergoing medical procedures: Developmental considerations. J Consult Clin Psychol. 1980;48:356–65

11. McGrath P, Johnson G, Goodman J et al. CHEOPS: a behavioral scale for rating postoperative pain in children. In: FieldsH, DubnerR, CerveroF, eds Advances in Pain Research and Therapy. New York: Raven Press, 1985; 9: 395–402.

12. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: The COMFORT scale. J Pediatr Psychol. 1992;17:95–109.

13. Stevens B, Johnston C, Petryshen P, Taddio A. Premature infant pain profile: Development and initial validation. Clinical Journal of Pain. 1996;12:13–22.

14 Green SM, Cote CJ. Ketamine and neurotoxicity: clinical perspectives and implications for emergency medicine. Ann Emerg Med 2009;54(2):181-90