IAPA Perioperative Pain Management Advisory for Neonates and Preverbal Children

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Background

Advances in obstetrics and neonatology have greatly improved the survival rate of neonates, including preterm and very preterm infants. As a consequence, an increasing number of neonates especially premature babies and young children with congenital defects undergo painful diagnostic and therapeutic interventions. In the past, management of pain in neonates was regarded as unnecessary, with the belief that neonates have an immature nervous system and do not perceive pain.[1] Till the end of the 1970s, there was no systematic research into pain management in children. Later studies confirmed that neonates certainly do feel pain though they lack the inhibitory mechanisms that modulate excruciating stimuli, unlike in older children.[2] By 20-weeks post conceptual age (PCA) a functional pain system has developed and a fetus is able to mount a stress response to pain N-methyl-D-aspartate (NMDA) receptor mediated windup and central sensitization is in fact more pronounced in neonates.[3]

Exposure to recurring pain-related stress in early life is known to have short and long-term unfavorable sequelae.[3,4] These include physiologic instability, altered neurodevelopment, learning deficits, poor adaptive behavior, and diminished pain threshold. All these can modify a child's subsequent physiologic response to painful or non-painful stimuli. Repeated painful encounters experienced in the newborn period are associated with poor cognitive and motor development by one year of age.[5,6] Pain in preverbal infants and children is also poorly recognized and often undertreated. A large observational study from the Netherlands reported only 34% of neonates received some analgesia before painful procedures.[7] A landmark study by Mather and Mackie highlighted the pathetic state of pain management in older children. The authors observed that 75% children studied had significant pain on the day of surgery and 13% reported severe pain.[8]

Neonates and preverbal children cannot verbally communicate their pain and discomfort but express them through specific behavioral, physiological and biochemical responses. Several pain-measurement tools have been developed for young children as surrogate measures of pain.[9] Consequences of acute pain include acute increases in blood pressure, heart rate, intracranial pressure and fall in arterial oxygen saturation. These changes in cerebral perfusion and blood flow may be associated with an increased risk especially in preterm infants of intraventricular hemorrhage and periventricular leukomalacia. It is therefore, essential to assess, detect and document the presence of pain and to implement appropriate and timely therapeutic interventions.[10]

Applicability

The aim of this advisory is to outline key concepts of pain assessment and suggest a rational approach to its management in neonates and preverbal children. The methods of assessment described can be used by anaesthesiologists, paediatricians, nursing staff and other medical personnel caring for these children.

Definition of pain

In 2020, the International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with or similar to that connected with actual or potential tissue damage." This definition needs to be broadened for neonates and preverbal children, to include behavioral and physiologic indicators.

Pain relief issues in neonates and preverbal children

General principles

Formulation and implementation of a uniform pain management program for small children has several advantages. It can improve understanding, help recognize the presence of pain, the remedies available and the importance of initiating adequate pain control measures. Assessment of pain at regular intervals should be included as a fifth vital sign, after a painful procedure.[9-11] To achieve optimum postoperative pain relief, easily understandable tools and a multimodal treatment module should be tailor-made for each healthcare facility that cares for neonates and young infants. Important components of the program should include:

- Specifying the frequency of pain evaluation and measurement depending on the clinical context.
- Active involvement of parents and health care providers. Cooperation can be achieved by being receptive to their views about their child's behavioural cues of pain and stress. This will help parents be proactive and enhance their coping skills.
- A baseline pain evaluation of all children with painful conditions during the pre-anaesthetic evaluation. Pre-operative discussions should include what to expect in the postoperative period, the basis for pain evaluation and therapeutic interventions available.
- Post-operatively, pain parameters should be documented at 15-minute intervals until optimal analgesia is achieved

- Reassessment of pain should be done 30 minutes after administration of rescue analgesic to establish its effectiveness.

- After discharge from the post anaesthesia care unit (PACU) to the ward, a minimum of 4th hourly assessments can be continued for 48 hours post-operatively for major surgical procedures.

- For children on mechanical ventilation, pain assessment can be documented by nursing staff. They should also document the child's state of consciousness (*e.g.,* fully awake / sleeping comfortably, sedated / paralyzed). The attending intensivist should perform an independent assessment and plan further management.

- All analgesic interventions and their efficacy should be documented.

- Any special concerns should also be documented at the time of scoring and the team should ensure that the hand-over to the person in the next shift includes pain assessment and management to provide continuity of care.

Causes of inadequate perioperative pain management in preverbal children

- Pain assessment in preverbal children is subjective with considerable interobserver variability. On the other hand, using multi-dimensional observational tools can also be time-consuming and difficult, as is pinpointing the exact location of the noxious stimulus.

- There are a diverse range of confounding factors responsible for the physiological changes in the perioperative period.

- Undertreatment may also be due to a fear of side effects of potent opioid analgesics, *e.g.,* depressed levels of consciousness, respiratory depression, cardiovascular collapse and drug dependence.

- Pain management is often left to the discretion of surgical and medical residents, and factors such as lack of time or interest as well as lack of knowledge of pediatric analgesic pharmacology may lead to under- or over-medication.

Pain assessment tools

Several pain assessment tools are available for neonates and preverbal children; and the choice should be based on the pediatric subgroup and the type of pain (acute, postoperative or chronic persistent).[9-12] Ethnic and cultural background and language related factors may influence the

expression and assessment of pain. Pain assessment tools are either unidimensional (based on a single parameter) or multidimensional (dependent on a combination of physiologic, behavioural and other accessory parameters *e.g.,* gestational age and present age).[13,14]

Types of physiologic and behavioural responses indicating pain

Physiologic parameters include heart rate, heart rate variability, blood pressure, breathing pattern, respiratory rate, oxygen saturation, vagal tone, intracranial pressure, skin colour, pupillary size, and palmar sweating.[3,4]

Behavioural responses include crying pattern, facial expression, sleep patterns, hand and body movement, behavioural state changes, muscle tone and consolability.[4,13,14] In neonates and infants, specific facial features such as eye squeeze, brow bulge, nasolabial furrows and open squared mouth are associated with acute pain (*Figure 1*) and commonly utilized pain assessment tools for acute pain in preverbal children are listed in *Table 1*.

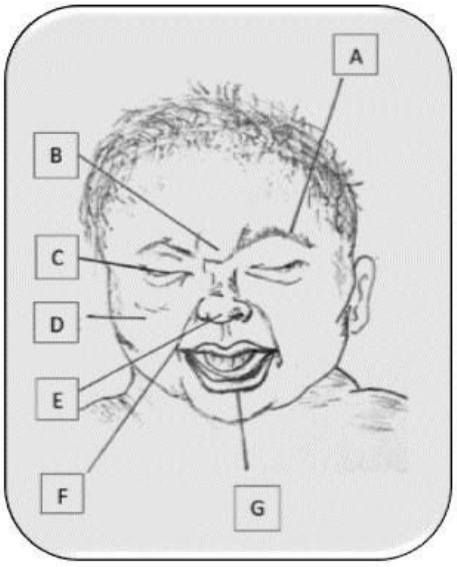

Figure 1: Facial features showing acute pain and distress in infants

A: lowered, drawn together brows

B: bulge between brows, vertical furrows on the forehead

C: tightly closed eyes

D: raised cheeks

E: broadened bulging nose

F: deepened nasolabial fold

G: open, squarish mouth.

The modified pain assessment tool (mPAT)

The mPAT is an observational multidimensional, multicomponent pain assessment scale that was designed specifically for postoperative pain in neonates and has been validated for neonates of 24 weeks PCA to full term neonates.[19] The mPAT is a revision of the previous pain assessment tool score (PAT) devised by Hodgkinson *et al*. in 1994[20] and later modified by O'Sullivan *et al.* in 2016.[21]

The maximum score is 20, a higher score representing greater level of pain. A score of >10 signifies severe pain and the need for opioids in combination with non-opioids and other non-pharmacological measures. For an intubated child on muscle-relaxants, the total score is out of

10, since only the physiological indicators of pain can be recorded. Special considerations should be noted in the mPAT score *e.g.,* altered physiological response in children on inotropes or altered color in neonates with anemia or congenital heart disease which may be considered noncontributory to pain assessment.[15,16] In these cases, deviations from the child's baseline status should be recorded in the mPAT score.

The specific parameters of the mPAT scale are shown in *Table 2*.

***Table 1*: Pain assessment tools for measuring acute pain in neonates and preverbal children[3,9-18]**

Assessment Tool	Variables	Remarks	Age group
Premature Infant Pain Profile (PIPP)	Facial expressions, Heart rate, SpO_2	Studied for acute and postoperative pain- Consistent, valid, well established clinical utility	28 - 40 weeks GA to infants
CRIES Scale	Crying, requires oxygen (< 95% SpO_2), facial expression, sleeplessness, change in vital signs	Validated for postoperative pain, reliable	32 - 36 weeks GA to infants
COMFORT Scale	Movement, calmness, facial stress, attentiveness, muscle tone, respiration rate, heart rate, blood pressure	For the mechanically ventilated patient Reliable, validated against numeric rating scale by trained observers, clinical utility well established	28 - 37 weeks GA to infants
NIPS (Neonatal Infant Pain Score)	Facial expression, respiratory patterns, crying, upper limb and leg activities, arousal level	Consistent, valid for procedural pain	28–38 weeks GA
N-PASS (Neonatal Pain, Agitation and Sedation Score)	Crying, facial expression, irritability, limb tone, changes in vital signs	High consistency. Validated against PIPP and mPAT. Useful for pain assessment in neonatal ICUs and postoperative pain. Better discrimination than mPAT for painful and stressful situations	23 weeks GA to 0-100 days of age
FLACC Scale	Facial appearance, body and limb movement, cry, ability to console	Reliable, valid for postsurgical pain	2 months to 7 years
CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)	Six categories of pain behaviour: cry, facial, verbal, torso, touch and leg position	Reliable, valid observation scale for postoperative pain	1 to 7 years

Note. SpO_2-arterial oxygen saturation; mPAT-modified pain assessment tool; GA-gestational age

Table 2: **The modified pain assessment tool (mPAT)**

Parameter	Score 0	Score 1	Score 2
Posture / Tone	Relaxed	Flexed and / or tense	Extended
Cry	No	Yes, consolable	Yes, loud, can't be consoled
Colour	Pink	Occasionally mottled/pale	Pale/Dusky/Flushed
Expression	Relaxed	Frown Eyes lightly closed, Superficial furrows	Grimace Eyes firmly closed, Deep furrows Pupils dilated
Sleep Pattern	Tranquil	Easily woken	Withdrawn / agitated
Respiration	Normal	Tachypnoea	Apnoea
Heart Rate	Normal	Tachycardia	Fluctuating
Blood Pressure	Normal	Fluctuating	Hypotensive / hypertensive
Oxygen Saturation	Normal	Transitory desaturation	Desaturating
Nurses Perception	Pain not present	Pain with handling	Pain present

Future perspectives of pain assessment

Ongoing research aims to add objectivity to pain assessment tools by using measurable end points to assess pain. These include serum or salivary cortisol levels, neuroimaging (near-infrared spectroscopy or functional magnetic resonance imaging, neurophysiologic (heart rate variability, amplitude-integrated electroencephalography, and changes in skin conductance).[9,13,14] These parameters may potentially reflect pain and stress and are being investigated in both acute or persistent pain. However, as of now, none of these have been shown to have sufficient reliability or universal clinical applicability to be considered as "the gold standard" (as the results are not real-time and may be affected by other confounding factors).

Pain management plan

Pain relief should generally be accomplished with a combination of nonpharmacologic approaches and pharmacologic techniques in a stepwise tiered manner by escalating type and dose of analgesia with anticipated increases in procedural pain. An individualized multimodal pain management approach should be chalked out before the conduct of anaesthesia. Pre-emptive analgesia with systemic analgesics and central neuraxial and peripheral nerve blocks instituted before surgical incision and continued perioperatively greatly reduce postoperative analgesic requirements. Treatment plans can be modified depending on the surgical procedure performed and on perioperative hemodynamic fluctuations. The following pain management approach can be used as a guide to individual clinical judgment. If facilities are available, it is preferable to collaborate with the multidisciplinary pain management team.

General principles recommended for pain management in the neonates and young children include:

I. Non pharmacologic comfort measures should be offered as a first step and to complement systemic pain relief.[11,12]

II. Analgesics should be titrated based upon comprehensive pain assessment including perioperative documentation of trends.

III. For mild to moderate pain, nonopioid analgesics *i.e.,* acetaminophen and ibuprofen are recommended by the WHO for children who are > 3 months old. For infants aged < 3 months, acetaminophen is generally recommended.[5]

IV. For moderate to severe pain, opioid drugs along with non-opioid analgesics is generally prescribed.[5,13,15]

V. For the first 48 hours after surgery, analgesics should preferably be administered by continuous infusion or at regular time intervals rather than by a need-based approach.[12,13]

Non-pharmacologic interventions which may alleviate pain and stress: Step I

There are several non-pharmacological or nursing control measures that are beneficial in reducing pain scores in the neonatal population.[22-24] These include:

- Limiting environmental stressors by lowering light and noise intensity.
- Limiting handling of the baby to facilitate undisturbed sleep by encouraging cluster nursing care
- Kangaroo care
- Facilitated touch and gentle massage
- Encourage breastfeeding when appropriate
- Use pacifiers to encouraging non-nutritive sucking
- Swaddling, positioning with facilitated tucking to minimize movement.
- Psychological interventions [distraction techniques (music and videogames or cartoons for nonverbal infants), cognitive behavior therapy and hypnosis] relaxation and physical therapies
- Oral sucrose and glucose feeds

Skin-to-skin care (with or without sucrose or glucose supplementation) decreases pain scores in preterm and term infants.[25] A meta-analysis of nonpharmacologic nursing control measures used during minor invasive procedure (heel lance, intravenous catheter insertion etc.) found that

swaddling, facilitated-tucking and sucking-related interventions were advantageous for preterm neonates.[26] Rocking, holding and sucking related interventions were found to be beneficial for term neonates.

Psychological strategies

An increasing appreciation for the need to adequately manage distress and pain during needle procedures is being realized. Strategies of distraction and hypnosis in collaboration with parents can help reduce procedural pain, distress, and fear of needles in children aged 2 years and older undergoing vaccination and venipuncture.[26,27] Distraction aims to shift attention away from the noxious source using cognitive measures *e.g.,* blowing bubbles, counting, conversation, music) or behavioural (*e.g.,* videos, toys, games). The age appropriateness and level of engagement of these interventions are important factors contributing to their efficacy. Though the evidence for these strategies remains low at present, their potential benefits and lack of harm support their clinical use.

Oral glucose and sucrose

Providing oral sucrose while performing mild to moderate painful procedures is commonly used in neonates and infants. However, the correct dose, analgesic effects versus soothing benefits, exact mechanism of action, and long-term outcomes are not known. Glucose has similarly been found effective in reducing response to short-term painful procedures. Meta-analysis of studies on glucose and sucrose have determined that sucrose and glucose is safe and useful for procedural pain management.[28] Literature is lacking on its role in postoperative analgesia.

Pharmacologic management: Steps II - V

Step II: Oral or intravenous (IV) paracetamol and / or non-steroidal anti-inflammatory drugs (NSAIDs).

Step III: Topical or subcutaneous infiltration of local anaesthetic or particular peripheral nerve blocks / neuraxial blocks.

Step IV: Use of opioids

Step V: Combination of opioids and other adjuvant analgesic drugs

Pharmacologic treatment strategies

Systemic pharmacologic agents that reduce neonatal pain and stress include; nonopioid analgesics like acetaminophen, non-steroidal anti-inflammatory agents (NSAIDs) like ibuprofen, ketorolac, diclofenac.[16-18] In addition, ketamine, local anaesthetic and opioid analgesics (*e.g.,* fentanyl, alfentanil, morphine etc.) are effective when pain is of greater severity.

Acetaminophen (paracetamol) is effective for treating to moderate procedural or postoperative pain, but ineffective for acute pain when administered alone.[5] Based on the available evidence, it is recommended to be used as an adjunctive analgesic combined with topical anaesthetics or opioid therapy.[25] Intravenous (IV) acetaminophen has a useful opioid sparing action and may reduce the risk of adverse opioid effects. In an opioid-sparing randomized trial design in children undergoing thoraco-abdominal surgery, IV acetaminophen decreased the total morphine consumption by 66 % without any adverse effects.[29] Opioid-sparing effects were also observed in a retrospective cohort study on postoperative morphine consumption in preterm infants (GA < 32 weeks). Minimal opioid-sparing effects have been reported with rectal acetaminophen administered to neonates and infants, possibly due to inadequate rectal absorption.[30]

Route and dose of acetaminophen:

Oral dose: 10 mg/kg 6 hourly or 15 mg/kg 8 hourly.

Intravenous acetaminophen doses in preterm neonates are as shown in Table 3

Post Conceptual Age	Drug Dose	Dosing Interval	Maximum Daily Dose
24 – 30 weeks	7.5-10 mg/kg	12th hourly	20-30 mg/kg/day
31 - 36 weeks	7.5-10 mg/kg	12th hourly	35-50 mg/kg/day
37 - 42 weeks	7.5-10 mg/kg	12th hourly	50-60 mg/kg/day

The IV dosing schedule for infants and children < 2 years of age is 7.5-15 mg/kg/dose every 6 hours up to an upper limit of 60 mg/kg/day.

Side effects: In contrast to its use in older children and adults, neonates rarely manifest hepato-renal toxicity with acetaminophen though vigilance is required in infants with malnutrition or hypoalbuminemia.[31]

Nonsteroidal anti-inflammatory drugs (NSAIDs): The combination of NSAIDs with opioids has beneficial opioid sparing effect, decreasing opioid requirement to about < 30%.[32] NSAIDs are avoided in neonates because of the concerns of renal insufficiency, gastrointestinal bleeding, platelet disfunction and pulmonary hypertension. Though WHO proposes the use of ibuprofen in children >3 months of age, these drugs are commonly used only in infants > 6 months of age due to the apprehensions about gastrointestinal and renal adverse effects.[5,13] NSAIDs are be used with caution in children with decreased renal function and hypovolemia.

Acetaminophen and ibuprofen are the standard first-choice analgesics for treating mild pain. Oral dosage of ibuprofen for infants and children is 10 mg/kg every 4-6 hr. IV dose is 4-10 mg/kg every 6-8 hr. Ketorolac has been used intravenously in the dose of 0.5 mg/kg every 6-8 hr in neonates in the postoperative setting, and in infants after adenotonsillectomy.[13] Unlike adults, postoperative ketorolac has not been associated with increased bleeding in pediatric patients. Diclofenac is an

efficient analgesic in an IV dose of 0.25-0.5 mg/kg for acute postoperative pain in children.[31] The recommended oral/rectal dose is 1mg/kg thrice a day. Rectal diclofenac has a peak action in 30-60 minutes Diclofenac has been found to be twice as effective as acetaminophen for post-surgical pain.[32] Adverse effects though rare in children, include reports of anaphylactoid reactions.

Local anaesthetic (LA) drugs: Neonates and infants < 3 months of age are at much higher risk of local anaesthetic toxicity.[33] Elimination half-lives of local anaesthetic drugs are prolonged 2-3 times and their metabolism by hepatic microsomal enzymes is significantly impaired. Using these agents in limited doses well below their toxic dose for peripheral or central blocks, can form an effective component of multimodal analgesia.[25] Topical agents like eutectic mixture of local anesthetic (EMLA cream, 4% liposomal lidocaine) have a role in postoperative analgesia for superficial procedures like circumcision, alone or in combination with penile nerve blocks.[25,26]

Peripheral nerve blocks or regional anesthesia techniques are an important component of multimodal analgesia for postoperative pain management of majority of the surgical procedures in children.[25,33,34] Adjuvants like clonidine, fentanyl and morphine are generally avoided in infants < 6 months of age, because of possible side effects which should be balanced with its action of prolonging analgesia. Continuous regional analgesic techniques are beneficial when the analgesic requirement is expected to exceed the duration of effect of a single injection. Ultrasound guided blocks are preferred whenever the equipment, skills and expertise are available to reduce complications and local anaesthetic dose. Epidural or spinal (opioids with or without LA) anaesthesia should be routinely considered for postoperative pain management in children undergoing major thoraco-abdominal or lower extremity surgeries, particularly for patients at risk of cardiopulmonary complications or prolonged ileus. The caudal route is generally preferred for access to epidural space in infants. Catheters can be threaded up to thoracic levels for cardiac, mediastinal and pulmonary procedures, preferably under ultrasound guidance. Safe LA doses are lower for young infants and should be carefully maintained well within the recommended doses for single injection or continuous infusions. Duration of infusions should be limited to less than 36 hours for neonates.[33] Vigilant monitoring is strongly recommended for all the children receiving neuraxial analgesic modalities for perioperative analgesia.

Opioids: The most effective treatment for moderate to severe pain relief in newborns is with opioids. They provide analgesia as well as sedation, have a relatively broad therapeutic window and effectively diminish the physiologic stress response. Morphine and fentanyl are the most used opioids for neonates in India, though more potent and shorter-acting drugs like sufentanil, alfentanil and remifentanil can be used depending on availability. Prescriptions of mixed opioids (viz., codeine, tramadol) are gradually declining from pediatric practice after reports on pharmacogenetic changes associated with their use were published.[5,13]

Morphine is used as a continuous infusion or as intermittent IV boluses (0.05 - 0.1 mg/kg/dose) in infants during major surgery. Observational studies and trials suggest that both intermittent boluses and continuous morphine administration are safe and effective in reducing postoperative pain in infants.[35]

Fentanyl is used for postoperative analgesia following major surgeries like cardiac surgery, or children with pulmonary hypertension or congenital heart disease. Recommended bolus dose is 0.5 - 1 μg/kg IV. Slow administration over 3-5 minutes minimizes the incidence of chest wall or skeletal muscle rigidity. The advantage of fentanyl lies in its ability to provide rapid pain relief with minimal blood pressure fluctuations and reduced gastrointestinal motility and urinary retention compared to morphine. However, continuous infusions of fentanyl are not advocated in preterm neonates as per the American Association of Pediatrics and Canadian Paediatric Society guidelines, because of lack of evidence for significant benefit over morphine and potential for adverse effects.[15,17] Bradycardia and chest wall rigidity remain the chief side effects. Naloxone should always be available to reverse respiratory depression associated with use of opioids. Alternate routes of dispensation like transmucosal and inhalational have also been found to be equally effective.[35]

Remifentanil, an ultra-short acting opioid, is a good alternative for short procedures and surgeries because it is not eliminated by liver metabolism.[35] There is limited data available on its use in small children.[13,15]

Worrisome side effects of opioids are respiratory depression, hypotension, delayed feeding and urinary retention. Hence, doses need to be cautiously tailored. Parent or nurse-controlled analgesia is a useful modality to reduce consumption of opioids compared to continuous drug infusions especially in smaller children.[13,36]

Alternative or adjuvant medications: Methadone, ketamine and dexmedetomidine have been used for pain management in infants and young children, but limited due to lack of evidence of effectiveness and concerns about adverse effects and potential for neurotoxicity.[35,37,38] Ketamine is a dissociative anesthetic widely used for procedural, operative or postoperative analgesia and sedation in children. It provides good analgesia, amnesia and sedation, while maintaining the respiratory drive and preserving hemodynamic status in lower doses (IM or IV 0.5 - 2 mg/kg/dose). Ketamine can be an effective analgesic option for hemodynamically unstable children where opioids would not be suitable.

Dexmedetomidine: It has been used in preterm and term infants and demonstrated effective analgesic effect with no respiratory depressant in usual doses.[35] It is increasingly being used for sedation in mechanically ventilated infants and children in the ICU setting and for short term sedation in the non-operating room setting.[38] However, because of the limited data on its safety and efficacy, the routine use of this drug is not recommended in neonates until larger randomized trials demonstrate that it is both advantageous and safe in newborns. Case reports of seizures or bradycardia in neonates have raised further concern on use of dexmedetomidine in this population.[39]

***Table 4*. Commonly used medications for managing pain in preverbal children**

Drug Name	Dose	Frequency (hr)	Max Daily Dose (mg/kg/day)	Precautions
Acetaminophen (Paracetamol) (mg/kg)	Oral: 10-15 IV: 7.5 -15	Preterm:12 Others: 6-8	24-30 weeks: 20-30 31-36weeks: 35-50 > 36 weeks: 50-60	Neonates, 80% metabolism by sulfuration due to immature glucuronidation Side effects: rash, blood dyscrasia, hepatotoxicity
Ibuprofen (mg/kg)	Oral: 10 IV: 4-10	6 - 8	30 – 40	Children > 6 months old Contraindications: asthma, on nephrotoxic drugs. Side effects: gastrointestinal and renal dysfunction, bleeding, rarely anaphylactoid reactions
Diclofenac (mg/kg)	Oral: 1.0 IV: 0.25-0.5	8	3 mg/kg/day	
Morphine (mg/kg)	0.025-0.1	4-6	1-2 mg/kg/day	Caution in < 3 months age (immature blood brain barrier, metabolites have analgesic properties) Side effects: histamine release, respiratory depression, nausea, constipation, rash
Fentanyl	0.5-2 µg/kg	2-4	5 µg/kg/day	100 X more potent than morphine, o histamine release, Side effect: chest wall rigidity

Summary and recommendations

Pain management in preverbal children is often inadequate and neglected due to challenges in its assessment and management. Untreated pain in young children has been correlated with adverse long-term behavioral, neurodevelopmental and cognitive effects. Age-appropriate pain assessment tools should be used and sound understanding of the mechanisms of action and roles of various nonopioid and opioid therapies can help optimize pain management. The IAPA recommendations for managing perioperative or peri-procedural pain in small children are listed in *Table 5*.

***Table 5*: Key recommendations for managing pain in preverbal children**

No.	Recommendations
1.	Paediatric anesthesiologists and other health care workers involved in perioperative and periprocedural pain management should continuously strive to prevent, assess and manage pain effectively *Each facility caring for neonates and preverbal children should formulate protocols for pain management.*
2.	Age-appropriate, easily understandable pain assessment tools should be used consistently before, during and after painful procedures to monitor and achieve optimum postoperative pain relief. *Discussion with parent / caregiver is helpful to tailor optimal pain management for the child.*
3.	Family centered care should be encouraged to help parents feel involved in care of their baby. *After discharge from PACU, pain relief / comfort scores should be recorded 3-4 hourly. Continue pain assessment for 48 hours post-operatively after major surgery.*
4.	Multimodal approach combining pharmacologic, locoregional and nonpharmacologic therapies for postoperative pain are the key to successful pain management. *An interdisciplinary approach involving pharmacologic, cognitive-behavioral, psychologic and physical treatments should be employed whenever feasible.*
5.	Non-pharmacological distraction measures may be sufficient for minor needle procedures like vaccination and venipuncture. *These may be offered as a first step and to complement other pain management remedies.*
6.	Regional anaesthesia (central and peripheral blocks) is an important component of multimodal analgesia in neonates and preverbal infants. *Vigilant monitoring of the baby is important. Meticulous preparation of infusions as well as documentation is important to avoid exceeding the maximum allowed dose. Duration of infusions in neonates should be limited to 36 hours post operatively in neonates.*

7.	Opioid and nonopioid drugs can be used safely and effectively in neonates and young infants either alone or in combination using appropriate dose timings. *Non-opioid adjuvant agents like ketamine, clonidine and dexmedetomidine can be used as a component of multimodal analgesia in younger children. Reduce doses when drug combinations are used.*
8.	Appropriate monitoring must be in place when administering pain medications. Inform care providers of the risks associated with the prescribed analgesic drugs to anticipate and deal with adverse effects (*e.g.,* opioid related respiratory depression, sedation, pruritus and worsening of asthma with NSAIDs *Precise documentation of pain assessment criteria, interventions done and specific concerns are of vital importance in pain management. This has to be in the language best understood by the care providers.*
9.	Exert caution when considering novel medications or techniques that are not yet approved for this age group *The treating physician must weigh the risk and benefit of the technique or drug used. Appropriate facilities to deal with side effects should be immediately available.*
10.	Physicians should maintain communication with the care providers even after discharge from hospital. *This is expected to improve satisfaction and can help in detecting any long-term effects of drugs/technique on child's behavior, mental performance etc.*

References:

1. Merskey, H. On the development of pain. *Headache,* 10 (1970); 116-123.
2. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med.* 1987;317:1321.
3. Craig KD, Whitfield MF, Grunau RV, et al. Pain in the preterm neonate: behavioral and physiological indices. *Pain*. 1993;52:287.
4. Guinsburg R, Kopelman BI, Anand KJ, et al. Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. *J Pediatr*. 1998;132:954.
5. World Health Organization. Persisting pain in children package: WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012). http://apps. who.int/iris/bitstream/handle/1066 5/44540/9789241548120 Guidelines. pdf?sequence=1.

6. Shomaker K, Dutton S, Mark M. Pain prevalence and treatment patterns in a US children's hospital. *Hosp Pediatr*. 2015; 5(7):363-70.

7. Simons SHP, van Dijk M, Anand KS et al. Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Arch Pediatr Adolesc Med.* 2003;157:1058–1064.

8. Mather L, Mackie J. The incidence of postoperative pain in children. *Pain*. 1983;15(3):271-282. doi:10.1016/0304-3959(83)90062-3

9. Giordano V, Edobor J, Deindl P, et al. Pain and sedation scales for neonatal and pediatric patients in a preverbal stage of development: A systematic review. *JAMA Pediatr.* 2019;173(12):1186–1197. doi:10.1001/jamapediatrics.2019.3351

10. Anand KJ, Barton BA, McIntosh N, Lagercrantz H, Pelausa E, Young TE, Vasa R. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial. Neonatal outcome and prolonged analgesia in neonates. *Arch Pediatr Adolesc Med* 1999;153:331–8.

11. Anand KJS, Stevens BJ, McGrath (2007) Pain research and clinical management-pain in neonates and infants, Third Edition, Elsevier, pp 19 and 87-90.

12. American Academy of Pediatrics, American Pain Society. The assessment and management of acute pain in infants, children and adolescents. *Pediatrics.* 2001;108:793-797.

13. Shah P, Siu A. Considerations for neonatal and pediatric pain management. *ASHP* 2019; 1-10. DOI 10.1093/ajhp/zxz166.

14. Burton J, MacKinnon R. Selection of a tool to assess postoperative pain on a neonatal surgical unit. *Infant. 2007*;3: 188-196.

15. Cong X, McGrath JM, Cusson RM. Pain assessment and measurement in neonates-an updated review. *Adv Neonat Care.* 2013;13: 379-395.

16. Australia and New Zealand Collage of Anaesthetics and Faculty of Pain Medicine (ANZCA). (2015) Acute pain management: Scientific Evidence, fourth edition, pp 413-414.

17. AAP committee on fetus and newborn and section on anesthesiology and pain medicine, policy statement- prevention and management of procedural pain in the neonate: An update. *Pediatrics.* 2016; 137: e20154271

18. Canadian Paeditric Society Statement. Prevention and management of pain and stress in the neonate. *J Paediatr Child H*. 2000; 5(1): 31-38.

19. Elessi K, Abed S, Afifi T et al. N-PASS versus mPAT in assessment and management of neonatal pain at neonatal ICUs in Palestine. *Int. J. Inn. Res. Med. Sci* 2019;4:395-404.

20. Hodgkinson K, Bear M, Thorn. J, Blaricum SV. Measuring pain in neonates: evaluating an instrument and developing a common language. *The Aust J Adv Nurs.* 1994; 12:17-22.

21. O'Sullivan AT, Rowley S, Ellis S, Faasse K, Petrie KJ. The validity and clinical utility of the COVERS scale and pain assessment tool for assessing pain in neonates admitted to an intensive care unit. *Clin J Pain.* 2016; 32: 51-57.

22. Gray L, Garza E, Zageris D et al. Sucrose and warmth for analgesia in healthy newborns. *Pediatrics* 2015;135: 3.

23. Gibbins S, Stevens B. State of the art: pain assessment and management in high-risk infants. *Newborn Infant Nurs Rev. 2001*;1: 85-96.

24. Lopez O, Subramanian P, Rahmat N, Theam LC, Chinna K, Rosli R. The effect of facilitated tucking on procedural pain control among premature babies. *J. Clin. Nurs*. 2014; 24:183-191.

25. Witt N, Coynor S, Edwards C, Bradshaw H. A guide to pain assessment and management in the neonate. *Curr Emerg Hosp Med Rep.* 2016; 4:1-10.

26. Lago P, Garetti E, Pirelli A, et al. Non-pharmacological intervention for neonatal pain control. *Ital J Pediatr*. 2014;40(Suppl 2):A52.

27. Landier WN, Tse A. Use of complementary and alternative medical interventions for the management of procedure-related pain, anxiety, and distress in pediatric oncology: an integrative review. *J Pediatr Nurs.* 2010; 25:566-579.

28. Bueno M, Yamada J, Harrison D, et al. A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. *Pain Res Manag*. 2013;18(3):153-161.

29. Ceelie I, de Wildt SN, van Dijk M, et al. Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery: A Randomized Controlled Trial. *JAMA*. 2013;309(2):149–154.

30. Van der Marel CD, Peters JW, Bouwmeester NJ, Jacqz-Aigrain E, van den Anker JN, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. *Br J Anaesth*. 2007;98(3):372-37917284514

31. Palmer GM, Atkins M, Anderson BJ et al. I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth*. 2008;101(4):523-53018628265.

32. Standing JF, Savage I, Pritchard D, Waddington M. WITHDRAWN: Diclofenac for acute pain in children. *Cochrane Database Syst Rev*. 2015;2015(7):CD005538. Published 2015 Jul 2. doi:10.1002/14651858.CD005538.pub3

33. Jöhr M. Regional anaesthesia in neonates, infants and children: an educational review. *Eur J Anaesthesiol*. 2015;32(5):289-297.

34. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012; 116:248-273.

35. Hall RW, Anand KJ. Pain management in newborns. *Clin Perinatol*. 2014;41(4):895-924.

36. Association of Paediatric Anaesthetists of Great Britain and Ireland. Good practice in postoperative and procedural pain management. 2nd ed. 2012. *Pediatr Anesth*. 2012; 22(Suppl 1):1-79.

37. Ranger M, Johnston C, Anand KJS. Current controversies regarding pain assessment in neonates. *Semin Perinatol.* 2007; 3:283-288.

38. Piastra M, Pizza A, Gaddi S, et al. Dexmedetomidine is effective and safe during NIV in infants and young children with acute respiratory failure. *BMC Pediatr*. 2018;18(1):282.

39. Kubota T, Fukasawa T, Kitamura E, et al. Epileptic seizures induced by dexmedetomidine in a neonate. Brain Dev. 2013;35:360–2.