

## REVIEW

## Assessment and management of pain in infants

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Infants, including newborn babies, experience pain similarly and probably more intensely than older children and adults. They are also at risk of adverse long term effects on behaviour and development, through inadequate attention towards pain relief in early life. However, the issue of analgesia in young babies has been largely neglected in most clinical settings, despite subjecting them to painful diagnostic and therapeutic procedures. Several therapeutic and preventive strategies, including systemic and local pharmacological and non-pharmacological interventions, are reported to be effective in relieving pain in infants. A judicious application of these interventions, backed by awareness and sensitivity to pain perception, on the part of the caregivers is likely to yield the best results. This article is a review of the mechanisms of pain perception, objective assessment, and management strategies of pain in infants.

appreciation of the quality of pain and the affective component. The neuronal pathways are modulated by neurotransmitters that amplify or attenuate transmission. Similarly, affective and emotional components of the painful stimulus are modulated through past experience and memory.

The periaqueductal grey and periventricular mesencephalic regions serve as an inherent analgesia system. Signals from these regions are transmitted through nuclei in the pons and medulla, to the dorsal horn of the spinal cord, to block the sensation of pain. The neurotransmitters involved in the suppression of pain are endogenous opiates that include  $\beta$ -endorphin, met and leu enkephalins, and dynorphin. Other neurotransmitters such as serotonin and gamma-aminobutyric acid (GABA) also decrease the sensation of pain. Figure 1 summarises the mechanisms of pain perception and suppression in the human body.

The anatomical, physiological, and biochemical prerequisites for pain perception are present by the early part of intrauterine life. Therefore, even preterm infants can perceive pain comparable to older children.<sup>2,3</sup> In addition, newborn babies have a well developed endocrine system that is able to release cortisol and catecholamines in response to painful stresses,<sup>4</sup> resulting in biochemical and physiological alterations that make it possible to objectively assess response to pain. Nevertheless, there are some basic differences in the neurophysiology of pain perception in infants. Nociceptive impulses in babies travel to the spinal cord through unmyelinated rather than myelinated fibres, and there is also a relative paucity of inhibitory neurotransmitters in them.<sup>5</sup> Babies also have larger receptive fields and possibly a higher concentration of substance P receptors.<sup>6,7</sup> They have a lower threshold for excitation and sensitisation, resulting in more central effects of nociceptive stimuli.<sup>8,9</sup> These factors are believed to make infants feel pain more severely than older persons.

**P**ain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”.<sup>1</sup> Obviously, this definition may not be easily applicable in day to day situations, particularly in infants whose responses to pain are not very different from their response to fear and distress due to non-painful conditions. Therefore, it may be worthwhile to widen the scope of the definition of pain to include pain related distress as well. Owing to a variety of reasons, emphasis on the assessment and management of pain in this age group is lacking. Some of the possible reasons are highlighted in box 1.

**PERCEPTION OF PAIN IN INFANTS**

Infants perceive pain in the same way as adults. The receptors of nociceptive stimuli are free nerve endings that are widely distributed all over the body. They are maximally present in the superficial layers of the skin and internal tissues such as periosteum, arterial walls, and joint surfaces. Mechanical, chemical, or thermal stimuli excite the nociceptors and electrical impulses are transmitted to the dorsal horn of the spinal cord through two sets of nerve fibres—namely, large myelinated A-delta (A- $\delta$ ) fibres and slower conducting, non-myelinated C fibres. The spinothalamic pathway transmits the impulses to the thalamus where pain is perceived. Third order neurons terminating in the sensory cortex and basal areas of the brain probably influence the

**ASSESSMENT OF PAIN**

Although self reporting of pain is the gold standard for assessment of the site, nature, and severity of pain, it is not precisely applicable in children below 3 years of age. Hence in infants, surrogate markers are used. Pain is associated with physiological, biochemical, behavioural, and psychological alterations that can be recorded and to some

**Abbreviations:** GABA, gamma-amino butyric acid; NSAIDs, non-steroidal anti-inflammatory drugs

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**Box 1: Possible reasons for the neglect of pain relief in infant management**

- Lack of awareness of infants' capability to perceive pain.
- Lack of awareness of clinical situations wherein pain is perceived.
- Inability of infants to express pain specifically.
- Medical attention focused towards treatment of primary clinical condition.
- Infants' expression(s) of pain interpreted as expressions of fear.
- Caregivers' temptation to perform quick procedures without analgesia.
- Reluctance to use analgesics due to side effects.
- Fear of inducing dependence on opioid drugs.
- Lack of awareness of painless routes and methods of analgesia.

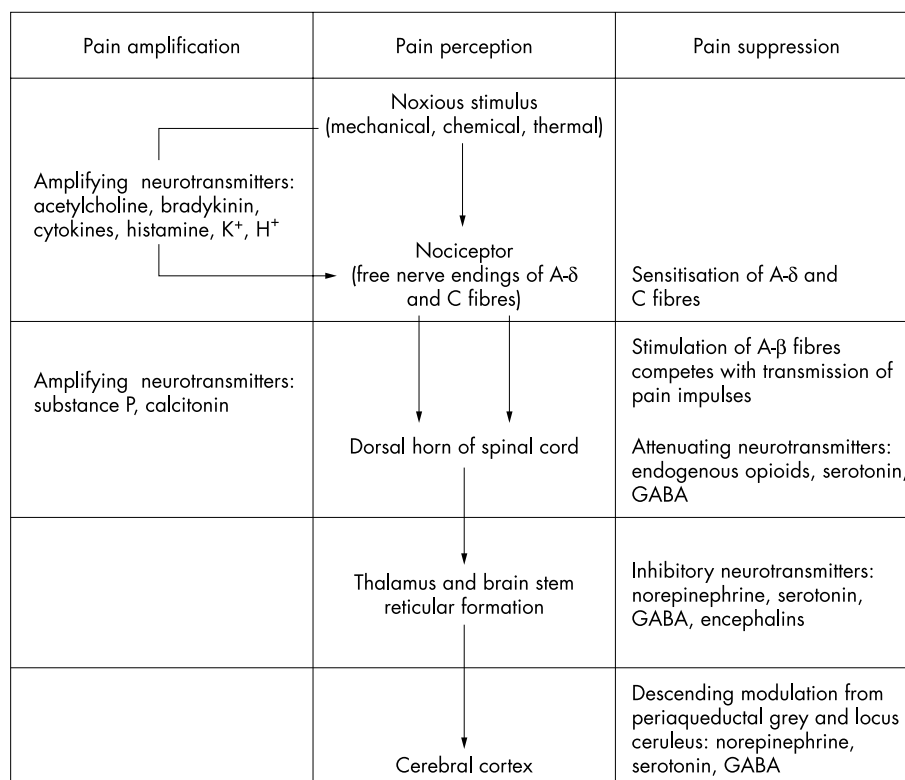
extent, quantified. These changes are summarised in table 1. It is reported that there may be up to 20% increase in the measurable physiological parameters in response to pain. Box 2 highlights a case study reflecting this aspect of pain response. These changes are secondary to increased cortisol and catecholamine secretion, which sets up the classical fight or flight sequence in older children and adults. It is relatively easy to measure alterations in most of the physiological parameters without invasive equipment. These measurements coupled with certain consistent behavioural responses are very sensitive indicators of infant pain. Of the behavioural changes, the facial expression of the baby is considered the most reliable and consistent indicator,<sup>15</sup> with the least interobserver disagreement as well.<sup>16</sup> Although the biochemical changes are perhaps the most sensitive quantifiable parameters, the need to use invasive methods is a major drawback. Hence they are not routinely used for assessment of pain perception. There is some evidence that a combination of physiological and behavioural changes provides a better estimate of infant pain.

In order to introduce objectivity in the assessment of infant pain, various pain scales have been designed and validated. These are based either on physiological variations, behavioural changes, or a combination of both. A detailed description of these scoring systems is beyond the scope of this article. Box 3 lists some of the commonly used systems. While all these methods of pain assessment are exciting for accurate measurement in research settings, it must be emphasised that highly sensitive techniques may not always be necessary for effective management of pain. The mainstays of appropriate management include the physician's awareness of infant pain, appreciation of situations wherein pain occurs, sensitivity to the need for controlling pain, and a generous measure of common sense.

Although the physiological and behavioural responses are very sensitive indicators of pain, they have poor specificity; and can occur with apprehension, stress related to disease, and discomfort. The responses may also be altered by the physiological state of the baby immediately preceding the painful stimulus, such as the stage of wakefulness,<sup>17</sup> duration since last feed, restraint techniques used, etc. Despite these pitfalls, assessment of behavioural and physiological responses remains the most readily available, reliable, and feasible method of assessing pain in infants.

**CLINICAL SETTINGS FOR PAIN IN NEONATES AND INFANTS**

The clinical settings for pain in infants are extremely varied. They include painful disease conditions—both acute and chronic—as well as diagnostic and therapeutic procedures performed for the treatment of these conditions. It must be emphasised that procedures need not always be invasive in order to cause pain. Even simple actions such as removal of sticking tapes, limb compression during restraint, postural changes during ventilation, and physiotherapy manoeuvres can be intensely painful. Table 2 is a partial list of some of the situations wherein infants experience pain.



**Figure 1** Mechanisms of pain perception and pain suppression (GABA, gamma-amino butyric acid).

**Table 1** Responses of infants to pain

Physiological changes	Behavioural changes	Biochemical changes
Increase in: <ul style="list-style-type: none"> <li>Heart rate</li> <li>Blood pressure</li> <li>Respiratory rate</li> <li>Oxygen consumption</li> <li>Mean airway pressure</li> <li>Muscle tone</li> <li>Intracranial pressure</li> </ul>	Change in facial expression <sup>12</sup> : <ul style="list-style-type: none"> <li>Grimacing</li> <li>Screwing up of eyes</li> <li>Nasal flaring</li> <li>Deep nasolabial groove</li> <li>Curving of the tongue</li> <li>Quivering of the chin</li> </ul>	Increased release of: <ul style="list-style-type: none"> <li>Cortisol</li> <li>Catecholamines</li> <li>Glucagon</li> <li>Growth hormone</li> <li>Renin</li> <li>Aldosterone</li> <li>Antidiuretic hormone</li> </ul>
Autonomic changes <sup>10 11</sup> : <ul style="list-style-type: none"> <li>Mydriasis</li> <li>Sweating</li> <li>Flushing</li> <li>Pallor</li> </ul>	Body movements <sup>13</sup> : <ul style="list-style-type: none"> <li>Finger clenching</li> <li>Thrashing of limbs</li> <li>Writhing</li> <li>Arching of back</li> <li>Head banging</li> </ul>	Decreased secretion of: <ul style="list-style-type: none"> <li>Insulin</li> </ul>

## CONSEQUENCES OF PAIN

Pain is a dynamic experience that is often beneficial by warning of impending or actual injury, thereby preventing or restricting tissue damage. However, barring this aspect, pain has only damaging effects in terms of metabolic and behavioural responses induced by it. Box 4 lists some of the adverse effects on infant pain. In the long term, memory of painful experiences has effects on subsequent pain perception and response. The classical studies that demonstrated differences in response to vaccination among infants who underwent circumcision without anaesthesia and those who received anaesthesia, testify to this.<sup>19, 20</sup> It is believed that learning about pain starts with the first painful experience and it may have effects on subsequent pain perception and response. There is also some evidence that neonatal pain experience may have far reaching effects even up to the preschool age<sup>21, 22</sup> and beyond.<sup>23</sup> Multiple influences, including infant factors as well as characteristics of the caregivers, together contribute to such events in development.<sup>24</sup>

From the point of view of those caring for neonates and infants, pain has two important deleterious consequences. The first is the mistrust and fear towards the caregiver, generated

by failure to prevent or relieve pain. Secondly, inadequate analgesia for initial procedures can decrease the effect of adequate analgesic doses in subsequent procedures.

## MANAGEMENT

The management of infant pain rests primarily on the tripod of (a) awareness of infants' capacity to perceive pain, (b) sensitivity towards clinical situations wherein pain may be encountered, and (c) appropriate steps to prevent and treat pain. In this context, it is interesting that even in tertiary care centres, there is a wide variation in strategies for pain management, ranging from the absolute absence of use of pain assessment techniques<sup>25</sup> to protocols wherein doses, regimens and routes of administration are not standardised.<sup>26</sup> Box 5 reflects the basis of infant pain management.

### Pharmacological interventions

#### Systemic administration of drugs

The opioids, including morphine, methadone, oxymorphone, codeine, fentanyl, alfentanil, and sufentanil are the most potent class of analgesic drugs. They have the added advantage of a sedative and anxiolytic effect. Another relative advantage of this group is that in the event of over dosage, the effects are easily reversed. However, these drugs have the potential for tolerance and dependence, the long term effects of which have not been studied in babies.<sup>27</sup> They also have a

### Box 2: Case study

An 18 month male baby with a diagnosis of Guillain-Barré syndrome was mechanically ventilated for neuromuscular paralysis in the intensive care unit of a teaching hospital. Intubation was performed under cover of 0.01 mg/kg intravenous midazolam. He was also being given bolus doses of 0.01 mg/kg morphine intravenously every six hours. Despite respiratory stabilisation and normal arterial blood gas analysis, the baby had persistent tachycardia, borderline hypertension, excessive sweating, and marked restlessness. These findings were interpreted as autonomic instability associated with the primary clinical condition. Propranolol in the dose of 1 mg/kg every eight hours was started; the blood pressure showed a slight decline, but the other features of sympathetic overactivity did not subside. On the advice of one of the authors, morphine bolus doses were replaced by infusion of 0.01 mg/kg/hour, which led to resolution of the symptoms and the omission of propranolol.

The case study highlights the importance of:

- Being sensitive to infants' perception of pain.
- Recognition of infants' responses to pain, which may be misinterpreted.
- Benefit of continuous infusion of morphine over intermittent bolus doses to relieve infant pain.<sup>14</sup>

### Box 3: Pain assessment scales in infants

#### Based on behavioural changes

- Neonatal Facial Coding System (NFCS).
- Infant Body Coding System (IBCS).
- Neonatal Infant Pain Scale (NIPS).
- Pain assessment in Neonates (PAIN).
- Liverpool Infant Distress Scale (LIDS).
- Modified Behavioural Pain Scale.
- Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).
- Neonatal Assessment of Pain Inventory (NAPI).
- Behavioural pain score.
- Clinical scoring system.

#### Combination of physiological and behavioural changes

- CRIES (acronym for crying, change in transcutaneous oxygen saturation, heart rate, blood pressure, facial expression and alteration in sleep pattern).
- Pain Assessment Tool (PAT).
- Premature Infant Pain Profile (PIPP).
- Scale for Use in Newborns (SUN).
- COMFORT Score.

**Table 2** Clinical settings wherein infants experience pain (a partial list)

Disease conditions	Diagnostic procedures	Therapeutic procedures
<ul style="list-style-type: none"> <li>• Otitis media</li> <li>• Pharyngitis and oral infections</li> <li>• Aphthous ulcers</li> <li>• Chest pain associated with coughing</li> <li>• Infantile colic</li> <li>• Headache due a variety of causes</li> <li>• Tissue injury due to trauma</li> <li>• Hydrocephalus</li> <li>• Intracranial bleeding</li> <li>• Necrotising enterocolitis</li> <li>• Intestinal obstruction</li> <li>• Spasticity</li> <li>• Thrombophlebitis</li> </ul>	<ul style="list-style-type: none"> <li>• Heel puncture</li> <li>• Venous and arterial puncture</li> <li>• Suprapubic bladder puncture</li> <li>• Squeezing muscles during blood sampling</li> <li>• Lumbar puncture</li> <li>• Ventricular puncture</li> <li>• Endotracheal suction</li> <li>• Bronchoscopy</li> <li>• Paracentesis thoracis</li> <li>• Ascitic fluid aspiration</li> <li>• Gastrointestinal endoscopy</li> <li>• Cystoscopy</li> </ul>	<ul style="list-style-type: none"> <li>• Intravenous cannulation</li> <li>• Intramuscular injection</li> <li>• Umbilical catheterisation</li> <li>• Insertion or removal of infant feeding tube</li> <li>• Urinary bladder catheterisation</li> <li>• Endotracheal intubation and suction</li> <li>• Circumcision</li> <li>• Wound dressing</li> <li>• Incision and drainage procedures</li> <li>• Postoperative state</li> <li>• Insertion/removal of drainage tubes</li> <li>• Endoscopic sclerotherapy</li> </ul>

variable half life period that often depends on the gestational age; hence dose and frequency of administration must be titrated against clinical effects. Although there is plenty of scientific evidence to support the use of opioid drugs in infants, the risk of adverse effects, particularly of respiratory and central nervous system depression, often hampers the rational use of these agents, especially in young babies. These effects can be reduced by modifying the route and method of administration as well as meticulous monitoring.

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used to treat pain of lesser intensity and as an adjunct to reduce the total dose of opioids.<sup>28</sup> Only some of these drugs have been studied in young infants; however, they may be valuable in situations where pain relief is required for a longer duration, and where the risks of inducing opioid dependence may be a significant problem. One of the popular NSAIDs, nimesulide, has recently been banned for use in children due to potential hepatotoxic effects. Even a brief description of the available analgesics is outside the scope of this article. From practical experience, it would be rational to use a combination of analgesics with differing properties, to achieve the best results with the fewest side effects.

Before any analgesic or anaesthetic drug is systemically administered to infants, the pharmacokinetic and pharmacodynamic properties of the drug must be studied. This is because most of these drugs are handled differently in babies compared with adults. In addition, the clinical status of the baby with special reference to drug metabolising and excreting capacity must be thoroughly understood. Young babies, especially those who are premature and of very low

birth weight, have immature drug handling capabilities that necessitate reduction in dosage or increasing the interval between doses. Another aspect that must be looked into before administration of these agents is the type of medication the baby is already receiving for the clinical condition, so that undesirable interactions do not occur.

#### Local techniques

Local anaesthetic agents block the transmission of impulses from receptors to the spinal cord. Theoretically speaking, they can be administered in any one of three ways—infiltration into the local area, nerve blockade, or intravenous regional block. The latter two methods demand a high degree of technical expertise and may not be feasible during routine diagnostic and therapeutic procedures. The safety and efficacy of infiltration of local anaesthetic drugs have been well documented for short surgical procedures such as circumcision and diagnostic procedures like bone marrow aspiration, biopsies, etc. Nevertheless, they are not widely used, for two major reasons. The first is the real or supposed risk of side effects of local anaesthetic, which includes anaphylaxis, hypotension, and other less serious effects. This is a risk that has to be taken into account. However, the more common reason probably is the temptation on the part of the physician to perform a “quick in, quick out” procedure and “spare” the baby the pain of two needle pricks. Such an attitude must be vigorously discouraged, particularly as the pain of local anaesthetic infiltration can be substantially minimised or even obviated by using narrowest available needles for infiltration, neutralising the pH of the local anaesthetic,<sup>20</sup> warming the drug to body temperature before use, and injecting as slowly as possible. It is also recommended to infiltrate the subcutaneous space before raising a wheal, as epidermal stretching is very painful.

The various local anaesthetic agents used are lignocaine, available as injectable, spray and gel preparations, bupivacaine, amethocaine gel,<sup>21</sup> and ropivacaine. Mixing the local anaesthetic with adrenaline increases the duration of action; however this must never be used in regions supplied by end arteries such as the penis, fingers, and toes. Local anaesthetic

#### Box 4: Consequences of pain in infants

##### Immediate effects

- Irritability.
- Fear.
- Disturbance of sleep and wakefulness state.
- Increased oxygen consumption.
- Ventilation-perfusion mismatch.
- Diminished nutrient intake.
- Increased gastric acidity.

##### Short term effects

- Enhanced catabolism.
- Altered immunological function.
- Delayed healing.
- Impaired emotional bonding.<sup>18</sup>

##### Long term effects

- Memory of pain.
- Developmental retardation.
- Alteration in response to subsequent painful experience.

#### Box 5: Basis of management strategies for infant pain

- Awareness of infants' capacity to perceive pain.
- Sensitivity to situations where infants may experience pain.
- Prevention of pain.
- Assessment of cause and severity of pain.
- Pharmacological interventions.
- Non-pharmacological interventions.
- Modification of techniques used for diagnostic and therapeutic procedures.

### Box 6: Non-pharmacological interventions to relieve infant pain

- Positioning and restraining the infant in a relatively flexed posture.<sup>29</sup>
- Stimulation of nerve fibres transmitting tactile and thermal sensations.
- Combining these methods with soothing vocal stimulation.<sup>13</sup>
- Breast feeding.<sup>30 31</sup>
- Feeding of sweet compounds such as sucrose,<sup>32 33</sup> glucose,<sup>34 35</sup> and saccharine.
- Non-nutritive sucking on pacifiers.<sup>36 37</sup>

agents are regarded as having a relatively poor safety margin, and hence resuscitation equipment should be available before use.

A eutectic mixture of 2.5% lignocaine and 2.5% prilocaine, designated EMLA (eutectic mixture of local anaesthetics) is becoming increasingly popular. The eutectic combination is a mixture of the two local anaesthetic drugs in a 1:1 weight ratio, whereby the crystalline powders melt at a lower temperature than they do separately, hence they constitute a liquid at room temperature. This combination increases the concentration of the drugs in the emulsion droplets and is more effective than using both drugs together.<sup>22</sup> Applied about 60 minutes before the intended procedure, it penetrates up to a depth of 5–10 mm, providing good anaesthesia for several minutes. The penetration can be increased by applying occlusive dressings onto the smeared surface. However, EMLA must not be used on abraded skin surfaces or mucus membranes. The major drawbacks of EMLA are vasoconstriction and risk of methaemoglobinaemia. A mixture of tetracaine, amethocaine, and cocaine abbreviated as TAC, is another popular local anaesthetic in some parts of the world.

#### Adjunctive drugs

These are drugs with little analgesic or anaesthetic effect, but useful as adjuncts with analgesics, by virtue of their sedative and/or hypnotic properties. However, they are not replacements for analgesics. In fact, they can suppress some of the behavioural responses associated with pain, thereby interfering with assessment and appropriate management. With appropriate monitoring of heart rate, respiratory rate and transcutaneous oxygen saturation, these agents can be safely and efficaciously used to advantage.

#### Non-pharmacological interventions

These are interventions that enhance activity in descending inhibitory systems and thereby decrease pain perception. Attenuation of transmission of impulses to the spinal cord can be achieved by stimulation of large sensory nerve fibres mediating sensations of touch and heat/cold. The non-pharmacological interventions may also modulate pain sensation and response to pain through changes in attention and decreasing apprehension. Some of the strategies are listed in box 6. It must be re-emphasised that non-pharmacological interventions practised in isolation are unlikely to relieve pain. They are more useful as complementary strategies to pharmacological methods of relieving acute pain.

The non-pharmacological interventions have the allure of being easy to administer and require no intensive monitoring. Although there are no adverse effects reported with their use, a recently published double blind, randomised, controlled trial has noted that the repeated use of sucrose analgesia in infants less than 31 weeks' gestation may put them at risk for poorer neurobehavioural development and physiological outcomes in later weeks of life.<sup>38</sup>

#### Modification of techniques

The basic principle behind modifying operational techniques is to reduce the incidence and frequency of stimuli that may be perceived as noxious. This encompasses minimal handling of sick babies, avoiding sampling and painful procedures during sleep cycles, not sticking adhesive tapes onto hair, moistening tapes before removal, reducing harsh noise and light in treatment areas,<sup>13</sup> and controlling thermal stress.

Often, a change in procedural practice may help in reducing pain of neonates and infants. For example, infants show significantly fewer signs of pain during heel puncture with the use of mechanical lancets as opposed to manual lancets.<sup>39 40</sup> Similarly, venous puncture for blood sampling is reportedly less painful than heel puncture.<sup>41</sup> One may also consider insertion of central venous catheters in babies requiring frequent blood sampling or intravenous medications, as against repeated venous and heel punctures. Naturally, such an option must be weighed in the light of expected duration of cannulation and risks of infection and thrombosis. However, there are data showing that infection rate in centrally cannulated babies is not higher than in those undergoing multiple punctures. In neonatal circumcisions, use of the Mogen clamp is preferred to the Gomco clamp because it is associated with less pain.<sup>42</sup>

#### CHRONIC PAIN

There are certain conditions that result in pain over prolonged periods, either as repeated short episodes or as a continuous phenomenon. A frequently encountered situation is the infant with a malignant condition. In such situations, the goals of pain relief are to provide maximum comfort for prolonged periods of time. Hence analgesics and anaesthetic agents with a long duration of action but few systemic side effects are desired. Butamben is a local anaesthetic agent that can produce sensory blockade for several months when injected epidurally. Its added advantage is the sparing of motor neurones, though this aspect is controversial at present. An alternate method of increasing the duration of anaesthetic activity may be to use slow release preparations of local anaesthetic. There is some progress towards preparation of liposomes and sustained release microspheres containing local anaesthetic. Another option may be to consider nerve plexus blockade<sup>43</sup> or even ablation using alcohol or phenol; this is supposed to be effective for up to six months. The instillation of analgesics through indwelling epidural catheters<sup>44</sup> and the intrathecal route<sup>45</sup> is also under consideration.

The World Health Organisation has suggested a protocol of a four step graded approach to pain management in cancer. This involves starting with non-opioid analgesics, then using opioids orally, followed by parenteral use of potent opioids, and lastly more invasive treatment such as intrathecal or epidural administration of drugs, nerve blockade, etc. It is the opinion of some experts that such treatment is likely to be inferior to using a multipronged attack in the management of chronic pain.

#### PRE-EMPTIVE ANALGESIA—PREVENTION IS BETTER THAN CURE

The general tendency among those caring for young babies is to treat pain after it has occurred.<sup>46</sup> However, prevention being better than cure, it is appropriate to administer appropriate dosages of analgesics with or without sedatives whenever pain is anticipated in babies. Such an approach is not only more humane, reducing the distress of infants, their parents and caregivers, but it also has the added benefit of making management of the child's clinical condition as well as diagnostic or therapeutic procedures easier to perform.

#### CONCLUSION—PAIN IN PERSPECTIVE

The physician caring for neonates and infants has to be sensitive to the fact that babies perceive pain as much as adults,

although their expression of this may be subject to misinterpretation. Pain experience in young babies may have far reaching consequences not only in the short term, but in the long term as well. Appropriate assessment and management of pain is not only good clinical practice, but is also necessary to prevent adverse effects in sick babies. There is a wide variety of therapeutic approaches to choose from; and the ideal may be to use a combination strategy.<sup>47</sup> It may also be worthwhile to develop institutional protocols for the specific purpose of pain management in infants.

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