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Review

Pain management in pediatric age. An update

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Abstract. Differently from the adult patients, in paediatric age it is more difficult to assess and treat efficaciously the pain and often this symptom is undertreated or not treated. In children, a selection of appropriate pain assessment tools should consider the age, the cognitive level, the presence of eventual disability, the type of pain and the situation in which it is occurring. Improved understanding of developmental neurobiology and paediatric analgesic drug pharmacokinetics should facilitate a better management of childhood pain. The objective of this update is to discuss the current practice and the recent advances in pediatric pain management. Using PubMed and the Cochrane Library we conducted an extensive literature analysis on pediatric pain assessment and commonly used analgesic agents in this kind of patients. According to our results, a multimodal analgesic regimen provides a better pain control and a functional outcome in children. Cooperation and communication among the anaesthesiologist, the surgeon and the paediatrician remains essential for successful anaesthesia and pain management in childhood. (www.actabiomedica.it)

Key words: Pain, Pain Assessment, Analgesic Drugs, Patient Controlled Analgesia, Childhood

Introduction

Differently from the adult patients in paediatric age it is more difficult to assess and treat efficaciously the pain and often this symptom is undertreated or not treated. In some areas this practice still exists and is a likely reflection of persistence of myths related to the infant's ability to perceive pain. Such myths include the lack of ability to perceive pain, remember painful experiences and other reasons (1). Recent evidence have documented the deleterious physiologic effects of pain and the beneficial results of efficacious analgesia both in adult patients and in children (2). Due to the increasing prevalence of both acute and chronic pain in the paediatric age new techniques for pain management have been developed, mainly before surgical interventions. In 2001 The American Academy of Paediatrics and the American Pain Society issued a statement to ensure an appropriate treatment of pain and suffering in all children and adolescents in order to focus the attention on an interdisciplinary therapeutic approach, including pharmacologic, cognitive-behavioural, psychologic and physical treatments (3). Pain assessment is essential for effective pain management. Not assessing appropriately children for pain leads to underestimation and undertreatment. In particular patients who are non-verbal or who have mental impairments are more vulnerable. Standardized reliable assessment scores stratified by age are actually available but they are not sufficient if used alone. The child's quality of life in terms of sleep, social relations and school activities should be tested as well in order to assure a holistic pain management (4).

The objective of this scoping review is to discuss the current practice and the recent advances in pediatric pain management, focusing on effective assessment tools and updated stepwise pharmacological approaches.

Material and methods

The search was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (5). To be considered eligible for the review, papers had to include the following components: pain management in pediatric subjects; English language; published in a peer-reviewed journal. We excluded: non-English language papers, conference proceedings or case studies, papers in which the sample population was represented by adults. We examined the following bibliographic electronic databases: PubMed and the Cochrane Library, from inception date until February 2023. The key words used for the search across electronic databases were: "Pain" or "Pain Assessment" and "Children" or "Paediatric", "Analgesic Drugs" or "Patient Controlled Analgesia" and "Children" or "Paediatric". The abstracts of the papers were firstly screened to decide whether a paper was eligible for this update according to inclusion criteria. Subsequently each paper that met the eligibility criteria was reviewed and analyzed in full text. Data extraction was performed based on the following categories: authors, year, type of study, sample size, study purpose and major findings. Due to the heterogeneity of the articles examined, we focused on a qualitative analysis. Ethical approval was not required.

Results

Overall, we identified 177 records through database searching. As first step, we excluded 38 records whose related articles were not available, 6 articles concerning ongoing trials and 55 duplicated papers. As second step, we eliminated 63 records by evaluating only title and abstract because they did not match the inclusive criteria we mentioned before. Of the remaining 15 studies, we excluded 5 through a further discussion among authors upon the reliability of data. Thus, 10 selected articles were included in the review. The detailed selection of literature is showed in Figure 1. The characteristics of all included studies are summarized in Table 1.

Acute pain assessment in pediatric age

The pain experience includes physiological, sensory, affective, behavioural, cognitive and sociocultural components. In adults it is easier to assess the pain symptoms. In children a selection of appropriate pain assessment tools should consider age, cognitive level, the presence of eventual disability, the type of pain and the situation in which pain is occurring. There are some commonly used methods of measurement of pain that have been proved to be reliable (6):

- Biological measures consider some physiologic parameters that may be modified by the presence of pain, such as heart and respiratory rates, blood pressure, etc;
- Observational and behavioural measures consider child's reaction to pain;
- Self-report measures rely on the child's description of his experience of pain.

In infants and non-verbal children, self-report measures are unavailable, but behavioural indices (motor responses, vocalization, facial expressions, crying and complex behavioural responses such as the sleep-wake patterns) can be easily evaluated to assess pain. Different behavioural scales have been validated by several studies that enrolled infants and neonates (7). Behavioural parameters, even if non-specific, may be usefully associated to physiologic parameters such as heart rate, cardiac rate, arterial blood pressure, transcutaneous oxygenation and palmar sweating. The Children's Hospital of Estern Ontario Pain Scale (CHEOPS) is one of the commonest scales used for pain management (Table 2).

Children aged 3 to 7 years are increasingly able to describe pain characteristics. Observational scales as well as self-report scales represent useful tools to assess pain in this period of life. Composite measures of pain have been developed combining behavioural and biological items, such as the Objective Pain Scale and the Comfort Scale (Table 3,4,5). The Objective Pain Scale is used to assess both physiologic parameters and behavioural changes in children that may be modified by the presence of pain or discomfort after procedures

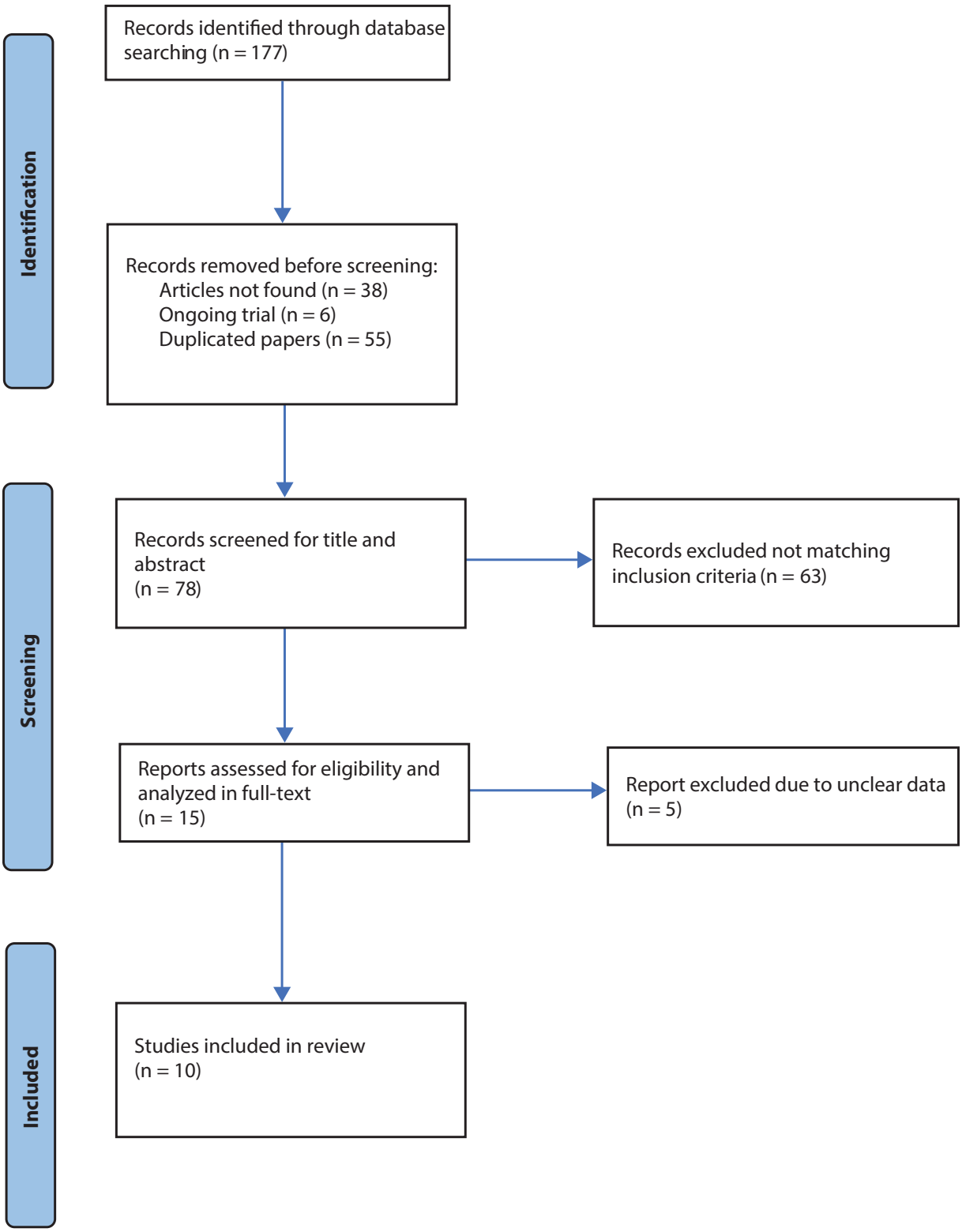

Figure 1. The detailed selection of literature.

Table 1. The characteristics of all included studies.

Author	Year	Type of study	Sample size	Study purpose	Major findings
Baroni et al. (8)	2023	Clinical study	31 patients	To assess the correlation between children's pain levels and patient characteristics (age, sex, history of dental pain), sedation type (level of sedation, sedative regimen), nociception and pain intensity described by the parents in sedated children experiencing minimally invasive dental surgery.	Pain was usually low and more prominent with minimal sedation and higher nociception.
Kamki et al. (9)	2022	Observational study	42 patients	To evaluate the validity of the graphics interchange format (GIF) as a self-reporting pain assessment tool in pediatric patients.	Wong-Baker FACES Pain Rating Scale (WBFPRS) and GIF pain scales showed significant variations when scales were compared to the real pain intensity felt by the patient. The GIF pain scale is a very promising assessment tool for children.
de Jong et al. (10)	2005	Observational study	73 burn care nurses rated pain from 24 fragments of videotaped children during wound care procedures.	To assess if the pain observation scale for young children (POCIS) and the visual analogue scale (VAS) are reliable and valid tools to measure procedural and background pain in burned children aged 0-4 years.	The POCIS has shown poor to moderate inter-rater reliability, moderate to good intra-rater reliability and an acceptable internal consistency. The VAS turned out to have poor inter-rater reliability and poor to moderate intra-rater reliability. Because of poor results of inter-rater reliability in both scales, validation is left undone until more acceptable data are obtained.
Marseglia et al. (11)	2019	Cross-sectional study based on a 17-questions survey accessible online	929 pediatricians presented 6335 cases uniformly distributed across the types examined	To examine the attitude of Italian family pediatricians towards the assessment and treatment of different types of acute pain in children aged 7–12 years.	Several mismatches occur between the current practice of pain assessment and treatment and recommendations. Further attempts are needed to raise awareness and improve education on the possible exposure of children to short- and long-term consequences in case of inappropriate pain management.
Lence et al. (15)	2023	Prospective cohort study	165 patients	To understand: the postoperative pain levels experienced by pediatric urology patients, the factors that correlate with postoperative pain and the number of opioids consumed following pediatric urologic procedures.	The level of pain and opioid use varies by procedure type but that number of narcotics prescribed significantly exceeds number needed.

Kinoshita et al. (24)	2023	Systematic review	331 patients	To assess the benefits and harms of systemic opioid analgesics in neonates who underwent surgery on all-cause mortality, pain, and significant neurodevelopmental disability compared to no intervention, placebo, non-pharmacological interventions, different types of opioids or other drugs.	Limited evidence is available on opioid administration for postoperative pain in newborns compared to either placebo, other opioids or paracetamol.
Ruggiero et al. (26)	2007	Prospective clinical study	18 patients	To evaluate the efficacy and safety of fentanyl administered by Patient-controlled analgesia (PCA) in children with cancer pain.	All children experienced a good degree of analgesia and did not require any other analgesic drug during the treatment. Both subjective and objective parameters improved after starting pain-relieving treatment and no major side effects occurred.
Arafa et al. (27)	2022	Prospective, randomized, controlled clinical trial	105 patients	To evaluate postoperative analgesia of quadratus lomborum block in pediatric patients undergoing renal surgeries by the addition of dexamethasone to bupivacaine compared to intravenous administration.	Dexamethasone may be more efficient when added to bupivacaine than when given systemically in analgesic effects. Dexamethasone as an adjuvant to bupivacaine has a significant effect on prolongation of the postoperative duration of analgesia, less request for rescue analgesia and fewer side effects as compared to bupivacaine if used as a sole agent.
Merry-Sperry et al. (29)	2022	Prospective, single-blinded, randomized-controlled crossover trial	10 patients	To compare lidocaine injection versus EMLA cream for local site analgesia in serial lumbar puncture procedures.	Both lidocaine injection and EMLA cream provide effective pain control post-lumbar puncture in pediatric oncology patients.
Hohl et al. (30)	2013	Retrospective chart review	18 patients	To evaluate the efficacy, dose and safety of methotrimeprazine in palliating end-of-life symptoms in children and infants.	Methotrimeprazine appears to be an effective tool in treating complicated end-of-life symptoms in pediatric patients.

Table 2. The Cheops Score - Minimum score: 4 (minimun pain); Maximum score: 13 (maximum pain).

Cry	No cry	+1
	Moaning	+2
	Crying	+3
	Scream	+4
Facial	Smiling	0
	Composed	+1
	Grimace	+2
Child verbal	Positive	0
	None	+1
	Other complaints	+1
	Pain complaints	+2
	Both	+2
Torso	Neutral	+1
	Shifting	+2
	Tense	+2
	Shivering	+2
	Upright	+2
	Restrained	+2
Touch	Not touching	+1
	Reach	+2
	Touch	+2
	Grab	+2
	Restrained	+2
Legs	Neutral	+1
	Kicking	+2
	Tensed	+2
	Standing	+2
	Restained	+2

Table 3. Objective Pain Scale (OPS) - 4 items for children aged from 1 months to 2 years.

Crying	None	0
	Consolable	+1
	Not consolable	+2
Movement	None	0
	Restless	1
	Trashing	2
Agitation	calm	0
	mild	1
	severe	2
Arterial pressure	+10%	0
	+10-20%	1
	+20%	2

Table 4. Objective Pain Scale (OPS) - 7 items for children aged from 2 to 3 years.

Crying	None	0
	Consolable	+1
	Not consolable	+2
Movement	None	0
	Restless	1
	Trashing	2
Agitation	calm	0
	mild	1
	severe	2
Arterial pressure	+10%	0
	+10-20%	1
	+20%	2
Verbal	asleep	0
	Can't localize	1
	Can localize	2

and/or postoperative interventions (8). The Comfort Scale is used to assess the level of sedation and distress in the paediatric intensive care unit, but recent studies have validated this measurement method also in procedural and postoperative pain.

Self-report measures of pain represent the gold standard in older children who can describe the subjective pain experience (9). These measures require a cognitive and linguistic development related to the capacity to answer to different questions. They are reliable to monitor pain relief in every single patient, while are less specific and effective if utilized to compare different patients. These methods include different strategies such as routine and direct questioning, verbal and non verbal methods (i.e. pictorial scales) and self rating scales. Visual Analogue Scale (VAS), Facial Pain Scale, and FLACC Scale are three of the commonest self rating scales to assess pain intensity in children (Figure 2,3, Table 6). In the VAS children rate the intensity of pain on a 10 cm line anchored at one end by a label such as "no pain" and at the other end "severe pain". The scores are obtained

Table 5. The Comfort Scale - The comfort scale score is ranged between 8 and 40. A total score between 17 and 26 is considered as indicative of good sedation (absence of stress).

Alertness	1. Deeply asleep 2. Lightly asleep 3. Drowsy 4. Fully awake and alert 5. Hyper alert
Calmness	1. Calm 2. Slightly anxious 3. Anxious 4. Very Anxious 5. Panicky
Respiratory distress	1. No coughing and no spontaneous respiration 2. Spontaneous respiration with little or no response to ventilation 3. Occasional cough or resistance to ventilation 4. Actively breathes against ventilator or coughs regularly 5. Fights ventilator; coughing or choking
Crying	1. Quiet breathing, no crying 2. Sobbing or gasping 3. Moaning 4. Crying 5. Screaming
Physical movement	1. No movement 2. Occasional, slight movement 3. Frequent, slight movements 4. Vigorous movement 5. Vigorous movements including torso and head
Muscle tone	1. Muscles totally relaxed; no muscle tone 2. Reduced muscle tone 3. Normal muscle tone 4. Increased muscle tone and flexion of fingers and toes 5. Extreme muscle rigidity and flexion of fingers and toes
Facial tension	1. Facial muscles totally relaxed 2. Facial muscle tone normal; no facial muscle tension evident 3. Tension evident in some facial muscles 4. Tension evident throughout facial muscles 5. Facial muscles contorted and grimacing
Blood pressure (MAP) baseline	1. Blood pressure below baseline 2. Blood pressure consistently at baseline 3. Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation) 4. Frequent elevations of 15% or more above baseline (>3 during 2 minutes observation) 5. Sustained elevations of 15% or more
Heart rate baseline	1. Heart rate below baseline 2. Heart rate consistently at baseline 3. Infrequent elevations of 15% or more above baseline (1-3 during 2 minutes observation) 4. Frequent elevations of 15% or more above baseline (>3 during 2 minutes observation) 5. Sustained elevations of 15% or more

by measuring the distance between the "no pain" and the patient's mark, usually in millimetres. The VAS has many advantages: it is simple and quick to score, avoids imprecise descriptive terms and provides many measuring points. Disadvantages are represented by the need of concentration and coordination, which can be difficult post-operatively or in children with neurological disorders. Faces scales represent another form of self reported measures: faces express different amounts of distress. The Facial Pain Scale is the commonest used in young children who may have difficulty with more cognitively demanding instruments. The original scale was composed by seven faces without an absolute meaning, but related to children's experience. Different versions exist, based anyway on the same measurement principle (10). The FLACC Scale, on the other hand, is utilised to assess pain intensity in children less than 3 year old.

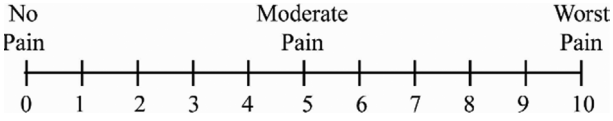

Figure 2. Visual Analogue Scale (VAS) – It consists of a segment of a straight line (generally 10 cm long), the ends of which normally correspond to the indications "no pain" and "the worst possible pain".

Figure 3. Wong-Baker Faces pain rating scale.

Adequate paediatric pain assessment can improve comfort in ill children and avoids pain undertreatment in several cases. Pain should be measured routinely with appropriated tools related to age and disease. Simple pain measurement methods would improve not only pain relief in children, but would also decrease health professionists' workload.

Pain management

Analgesic pharmacotherapy is the mainstay of pain management. Although concurrent use of other interventions is valuable in many patients and essential in some, analgesic drugs are needed in almost every case. The guiding principle of analgesic management is the individualization of therapy. Through a process of repeated evaluations, drug selection and administration is individualised in order to achieve a favourable balance between pain relief and adverse pharmacological effects. An expert committee convened by the World Health Organization (WHO) has proposed a useful approach to drug selection for acute and chronic pain states, which has become known as the 'analgesic ladder' (World Health Organization 1986) (Table 7). Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps:

Table 7. The WHO analgesic ladder.

WHO Analgesic ladder step	**Analgesic of choice**
Mild pain	Non-opioid ± Adjuvant
Moderate pain	Opioid ± Non-opioid ± Adjuvant
Severe pain	Opioid ± Non-opioid ± Adjuvant

Table 6. Flacc scale for pain assessment in children aged less than 3 years.

Category	**0**	**1**	**2**
Face	No expression	Occasional grimace	Frequent quivering chin
Leg	Relaxed	Tense	Kicking
Activity	Lying quietly	Shifting back and forth	Jerking
Cry	No cry	Moans	Screams
Consolability	Relaxed	Reassured by occcasional touching	Difficult to console

Step 1:

Patients with mild to moderate pain should be treated with a non-opioid analgesic, which should be combined with an adjuvant drug if a specific indication exists.

Step 2:

Patients who are relatively opioid naive and present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesic, should be treated with an opioid conventionally used to treat pain of this intensity. This treatment is typically accomplished by using a combination product containing a non-opioid (e.g. aspirin or acetaminophen) and an opioid (such as codeine, oxycodone or tramadol). This drug can also be co-administered with an adjuvant analgesic**.**

Step 3:

Patients who present with severe pain or fail to achieve adequate relief following appropriate administration of drugs on the second rung of the 'analgesic ladder' should receive an opioid agonist conventionally used for pain of this intensity. This drug may also be combined with a non-opioid analgesic or an adjuvant drug.

Analgesic drugs

Based on clinical convention, analgesic drugs can be divided into three groups:

1. the non-opioid analgesics;
2. the opioid analgesics;
3. the adjuvant analgesics

Non-opioids analgesics

The non-opioid analgesics (acetylsalicylic acid, acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs)) constitute a heterogeneous group of compounds that differ in chemical structure but share many pharmacological actions. These drugs are useful alone for mild to moderate pain (step 1 of the analgesic ladder) and provide additive analgesia when combined with opioid drugs in the treatment of more severe pain (11).

Acetylsalicylic acid is a potent inhibitor of cyclooxygenases which is used frequently in medical care, but it should not be used in pregnant women (bleeding, closure of ductus arteriosus) or children before puberty (Reye's syndrome).

Acetaminophen (or paracetamol) is a specific drug with characteristics similar to NSAIDs. Paracetamol has analgesic and antipyretic properties and is devoid of the side effects typical of the NSAIDs. The administration of paracetamol in children and infants is a well established and safe treatment option, if appropriately used. However, if paracetamol is dosed according to traditional recommendations (about 20 mg/kg) frequently a sufficient analgesic effect cannot be achieved immediately after painful interventions (12). Recently, a higher initial dose (40 mg/kg) was suggested for effective postoperative pain control. Current recommendations also involve appropriate timing and route of administration of paracetamol to be more effective under different clinical circumstances. The rectal route of administration is unreliable for eliciting an analgesic effect and the oral route is to be prefer. The risk for liver toxicity appears to be very low if the daily paracetamol dose does not exceed 90 mg/kg body weight in healthy children and if specific risk factors of the individual patient are considered. A structured protocol to treat mild pain using paracetamol as first step is showed in Table 8.

Unlike opioid analgesics, the non-opioid analgesics have a 'ceiling' effect for analgesia and produce neither tolerance nor physical dependence. Some of these agents, like acetylsalicylic acid and the NSAIDs, inhibit the enzyme cyclo-oxygenase and consequently block the biosynthesis of prostaglandins, inflammatory mediators known to sensitize peripheral nociceptors (13). A central mechanism is also likely and appears to predominate in acetaminophen analgesia because of its action on PGE2 synthesis. The safe administration of the non-opioid analgesics requires familiarity with their potential adverse effects. Acetylsalicylic acid and the other NSAIDs have a broad spectrum of potential toxicity. Bleeding diathesis due to inhibition of platelet

Table 8. A structured protocol to treat mild pain.

First step therapy	Locoregional anesthesia	Paracetamol 4 times/day	Intravenous: <1 year 7,5mg/Kg >1 year 15mg/Kg Oral and endorectal administration 15-20 mg/Kg
First step therapy	Without Locoregional anesthesia	Paracetamol + Codeine 3 times /day	< 1 year only Paracetamol 1-10 years child suppository >10 anni adult suppository Oral administration: 15-20 Kg ½ pill 20-40 Kg 1 pill >40 Kg 2 pills
I dose rescue		Tramadol	Slow parenteral 1mg/Kg or orally (1 drop =2,5mg)
II dose rescue		Ketorolac	>1 year 1mg/Kg

aggregation, gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common, while liver failure is rare (14). Less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension.

Of the NSAIDs, the drugs that are relatively selective cyclo-oxygenase-2 inhibitors (e.g. nabumetone, nemuselide and meloxicam) and those that are non-acetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to peptic ulceration or bleeding. These drugs have no effect on bleeding time at the usual clinical doses. The development of NSAIDs that are fully selective cyclo-oxygenase-2 inhibitors may provide additional agents with favourable safety profiles that may be preferred in the treatment of the medically frail. To date, none of the COX 2 inhibitors has been liberated for use in the pediatric age group. Only meloxicam and etoricoxib can be prescribed for adolescents (13 and 16 years, respectively).

The optimal administration of non-opioid analgesics requires an understanding of their clinical pharmacology. There is no certain knowledge of the minimal effective analgesic dose, ceiling dose or toxic dose for any individual patient with post-operative pain. These doses may be higher or lower than the usual dose ranges recommended for the drug involved. These observations support an approach to the administration of NSAIDs that incorporates both low initial doses and dose titration. Through a process of gradual dose escalation, it may be possible to identify the ceiling dose and reduce the risk of significant toxicity. Several days are needed to evaluate the efficacy of a dose when NSAIDs are used in the treatment of grossly inflammatory lesions, such as arthritis. Since failure with one NSAID can be followed by success with another, sequential trials of several NSAIDs may be useful to identify a drug with a favourable balance between analgesia and side effects. Table 9 shows the most commonly NSAIDs used in adults and in children for pain relief.

Opioid analgesics

Pain of moderate or greater intensity should generally be treated with a systemically administered opioid analgesic. Opioids should be used in a multimodal balanced analgesia approach that minimizes opioid requirement and the degree of their side effects. Optimal use of opioid analgesics requires a sound understanding of the general principles of opioid pharmacology, the pharmacological characteristics of each of the commonly used drugs and principles of administration. Fear of potential side effects has limited their use in many countries; this cultural phenomenon seems now to be overcame by the effective opioid titration with the use of incremental doses and a careful monitoring of side effects: this has largely increased their use both in adult patients and especially in children (15).

The mechanism of action of opioid analgesics depends on the interaction of these molecules with specific receptors to which they bind and their intrinsic activity at that receptor. Analgesia involves activation

Table 9. NSAIDs commonly used in pain treatment - O: oral. IV: intravenous. IM: intramuscular. ER: endorectal.

Drug	Pediatric Dosing	Adult dosing	Notes
Paracetamol or Acetaminophen	O. 10-15 mg/kg every 4-5 hours ER: 20-40 mg/kg every 6 hours Or Oral Bolus 20 mg/kg + 15mg/kg every 4 h Bolus 40 mg/kg + 20 mg/kg every 6 hours	O. 325-650 mg every 4-6 hours max 4 gr/day orally	Absence of gastrointestinal and haematological side effects. Antipyretic and analgesic action, not anti-inflammatory. Very low risk of liver toxicity if the daily dose of paracetamol does not exceed 90 mg/kg in healthy children.
Ibuprofen	O. 5-10 mg/kg every 6-8 h	O. 200 mg every 3-4 h	Gastrointestinal and haematological side effects. Anti-inflammatory action.
Naproxen	O. 5 mg/kg every 8-12 h	O. 0.5-1 g/day	Gastrointestinal and haematological side effects. Anti-inflammatory action.
Ketorolac	O. Bolus 1-3 mg/kg every 8 h E.V 0.20 mg/kg/h	O. 10 mg every 4-6 h (max 40 mg/day) EV o IM 10-30 mg every 4-6 hours (max 90 mg/day)	Liver and kidney toxicity.
Acetylsalicylic acid	O. 10-15 mg/kg every 6-8 hours	O. 0.5-1 g every 4-6 hours max 4 g/day	Reye's syndrome (pre-pubertal children). Gastrointestinal and haematological side effects.

Table 10. Opioids commonly used in pediatric age - O: oral. IV: intravenous. SC: subcutaneous.

Drug	Starting dose IV/SC	Starting dose oral	Notes
Codeine	-	0.5-1 mg/kg every 3-4 hours	Nausea, vomit
Hydromorphone	Bolus: 0.015 mg/kg every 2-4 hours Infusion: 0.006 mg/kg/h	0.06 mg/kg every 3-4 hours	Nausea, vomit, urinary retention
Morphine	Bolus: 0.05-0.1 mg/kg every 2-4 hours Infusion: 0.03 mg/kg/h	0.5-1 mg/kg every 3-4 hours	Nausea, vomit, urinary retention
Fentanyl	Bolus: 0.5-1 γ/kg every 1-2 hours Infusion: 0.5-3 γ /kg/h	-	Nausea, vomit, urinary retention, itching, respiratory depression
Remifentanyl	Bolus: 0.1-0.5 γ/kg every hour Infusion: 0.1-0.25 γ /kg/min	-	Nausea, vomit, urinary retention, itching, respiratory depression
Sufentanyl	Bolus: 0.2 γ /kg every hour Infusion: 0.1-0.5 γ /kg/min	-	Respiratoty depressione, hemodynamic alterations

of mu_1 receptors in the brain and kappa receptors in the spinal cord. Humans that have become tolerant to activation of one receptor type are not necessarily tolerant to the others.

Based on their interactions with the various receptor subtypes, opioid compounds can be divided into agonist, partial agonist and mixed agonist-antagonist drugs.

The pure agonist drugs (Table 10) are most commonly used in clinical pain management, both in adult patients and in children. The pure agonist opioid drugs appear to have no ceiling effect for analgesia.

As the dose is raised, analgesic effects increase until either analgesia is achieved or the patient loses consciousness. This increase in effect occurs as a log-linear function: dose increments on a logarithmic scale yield linear increases in analgesia. In practice, it is the appearance of adverse effects, that imposes a limit on the useful dose. The overall efficacy of any drug in a specific patient will be determined by the balance between analgesia and side effects that occurs during dose escalation.

The most frequent side effects of opioid drugs are represented by respiratory depression, nausea, vomiting, urinary retention and physical dependence (16).

When respiratory depression occurs in patients on opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation. An initial dose of naloxone 2-4 μg/kg should be given and repeated to a total of 10 μg/kg. Duration of action of naloxone is shorter than the most opioids and a continuous infusion may be required to maintain reversal.

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. In ambulatory patients, the incidence of nausea and vomiting has been estimated to be 10-40 % and 15-40 %, respectively. The likelihood of these effects is greater at the start of opioid therapy. Routine prophylactic administration of an antiemetic is not necessary, except in patients with a history of severe opioid-induced nausea and vomiting, but patients should have access to an antiemetic at the start of therapy if the need for one arises.

Urinary retention is an infrequent problem that is usually observed in elderly male patients. Physical dependence is a pharmacological property of opioid drugs defined by the development of an abstinence (withdrawal) syndrome following either abrupt dose reduction or administration of an antagonist. Physical dependence rarely becomes a clinical problem if patients are warned to avoid abrupt discontinuation of the drug; a tapering schedule is used if treatment cessation is indicated and opioid antagonist drugs (including agonist-antagonist analgesics) are avoided (17,18).

The division of opioid agonists into 'weak' versus 'strong' opioids was incorporated into the original 'analgesic ladder' proposed by the WHO. This distinction was not based on a fundamental difference in the pharmacology of the pure agonist opioids, but rather reflected the customary manner in which these drugs were used. This explains the observation that some opioids that were customarily used for moderate pain (step 2 of the analgesic ladder), such as oxycodone, are also used for severe pain in selected patients. Indeed, the controlled-release formulation of oxycodone is now widely used in the management of severe pain. Conversely, low-dose formulations of controlled-release morphine are suitable for the management of pain of moderate severity. Weak opioids are indicated in mild to moderate pain, usually associated to other drugs such as paracetamol. A weak opioid should be added to, not substituted for, a non opioid and it's important not to "jump" from weak opioid to weak opioid. If a weak opioid is inadequate when given regularly, the right step is to change to strong opioids.

The factors that influence opioid selection include pain intensity and the presence of co-existing disease.

Pain intensity

Patients with moderate pain are conventionally treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone and propoxyphene. The doses of these combination products can be increased until the customary maximum dose of the non-opioid co-analgesic is attained. Beyond this dose, the opioid contained in the combination product could be increased as a single agent or the patient could be switched to an opioid conventionally used for severe pain. New opioid formulations may improve the convenience of drug administration for patients with moderate pain. These include controlled-release formulations of codeine, dihydrocodeine, oxycodone and tramadol.

Some patients will require sequential trials of several different opioids before a drug effective and well tolerated is identified. The frequency with whom this strategy is needed is unknown, but it is estimated to be in the range of 15-30 % of patients. The existence of different degrees of incomplete cross tolerance to various opioid effects (analgesia and side effects) may explain the utility of these sequential trials. To date, there are no data to suggest a specific order for opioid rotation. It is strongly recommended that clinicians be

familiar with at least three opioid drugs used in the management of severe pain and have the ability to calculate appropriate starting doses using equianalgesic dosing data.

Co-existing disease

Pharmacokinetic studies of meperidine, pentazocine and propoxyphene have revealed that liver disease may decrease the clearance and increase the bioavailability and half-lives of these drugs. These changes may eventuate in plasma concentrations higher than normal. Although mild or moderate hepatic impairment has only minor impact on morphine clearance, advanced disease may be associated with reduced elimination. Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), meperidine (normeperidine) and morphine (morphine-6-glucuronide). In the setting of renal failure or unstable renal function, titration of these drugs requires caution and close monitoring. If adverse effects appear, a switch to an alternative opioid is often recommended (19).

Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia.

Non-invasive routes

The oral route of opioid administration is the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia and those who are unable to manage either the logistics or side effects associated with the oral route. For patients who do not require very high opioid doses, non-invasive alternatives to the oral route of opioid administration include the rectal, transdermal and sublingual routes.

Rectal suppositories containing oxycodone, hydro-morphone, oxymorphone and morphine have been formulated and controlled-release morphine tablets can also be administered per rectum. The potency of opioids administered rectally is believed to approximate oral administration.

Fentanyl and Buprenorphine are actually available as a transdermal preparation (20). Multiple patches may be used simultaneously for patients who require higher doses. At the present time, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain.

Sublingual absorption of any opioid could potentially yield clinical benefit, but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is consequently low. Overall, however, the sublingual route has limited value due to the lack of formulations, poor absorption of most drugs and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl, which incorporates the drug into a candy base, is now available. Studies in cancer patients suggested that it is useful and that it can provide rapid and very effective relief of breakthrough pain.

In the pediatric population results demonstrated some analgesic effect of IN (intranasal) fentanyl following myringotomy, no analgesic effect following voiding cystourethrography, and finally, no significant analgesic difference after long bone fractures, in burns patients and in post-operative pain relief when compared to IV (intravenous) morphine, oral morphine, or IV fentanyl, respectively. Significant analgesic effect of IN fentanyl was demonstrated in the treatment of breakthrough pain in cancer patients. However, the significant deficiencies in trials investigating acute and post-operative pain, and the pediatric population makes firm recommendations impossible (21).

Invasive routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is precluded or there is need for rapid onset of analgesia, or a more convenient regimen. Repeated parenteral bolus injections, which may be administered by the intravenous (IV), intramuscular (IM) or subcutaneous (SC) routes, may be useful in some patients but are often compromised by the occurrence of prominent 'bolus' effects (toxicity at peak concentration or pain breakthrough at the trough).

Repetitive IM injections are a common practice, but they are painful and offer no pharmacokinetic advantage; their use is not recommended. Repeated bolus doses without repeated skin punctures can be accomplished through the use of an indwelling IV or SC infusion device. Intravenous bolus administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid and ranges from 2-5 minutes for methadone to 15-30 minutes for morphine and hydromorphone. This approach is commonly applied in two settings:

1. to provide parenteral opioids to patients who already have venous access and are unable to tolerate oral opioids;
2. to treat very severe pain, for whom IV doses can be repeated at an interval as brief as that determined by the time to peak effect, if necessary, until adequate relief is achieved.

Continuous parenteral infusions are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered IV or SC. In practice, the major indication for continuous infusion occurs among patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical, such as children suffering from acute leukemia (22).

The schedule of opioid administration should be individualized to optimize the balance between patient comfort and convenience. 'Around the clock' dosing and 'as needed' dosing have both a place in clinical practice.

'Around the clock' dosing

Patients with severe pain generally benefit from scheduled 'around the clock' dosing, which can provide the patient with continuous relief by preventing the pain from recurring. Most patients who receive an 'around the clock' opioid regimen should also be provided a so-called 'rescue dose', which is a supplemental dose offered on an 'as needed' basis to treat pain that breaks through the regular schedule. The frequency with whom the rescue dose can be offered depends on the route of administration and the time to peak effect for the particular drug. Oral rescue doses are usually offered up to every 1-2 hours and parenteral doses can be offered as frequently as every 15-30 minutes. The integration of 'around the clock' dosing with 'rescue doses' provides a method for safe and rational stepwise dose escalation, which is applicable to all routes of opioid administration. Patients who require more than 4-6 rescue doses per day should generally undergo escalation of the baseline dose. The quantity of the rescue medication consumed can be used to guide the dose increment, as reported for ketamine infusion (23).

Controlled-release preparations of opioids can lessen the inconvenience associated with the use of 'around the clock' administration of drugs with a short duration of action. Currently, controlled-release formulations are available for administration by the oral, transdermal and rectal routes. Clinical experience suggests that controlled-release formulations should not be used to rapidly titrate the dose in patients with severe pain. The time required to approach steady-state plasma concentration after dosing is initiated or changed (at least 24 hours) may complicate efforts to rapidly identify the appropriate dose. Repeat-dose adjustments for patients with severe pain are performed more efficiently with short-acting preparations, which may be changed to a controlled-release preparation when the effective 'around the clock' dose is identified (23).

'As needed' dosing

In some situations, opioid administration on an 'as needed' basis, without an 'around the clock' dosing regimen, may be beneficial. In the opioid-naive patient, 'as needed' dosing may provide additional safety during the initiation of opioid therapy, particularly when rapid dose escalation is needed or therapy with a long half-life opioid such as methadone or levorphanol is begun. 'As needed' dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pain separated by pain-free intervals (24).

Patient-controlled analgesia

Patient-controlled analgesia (PCA) generally refers to a technique of parenteral drug administration

in which the patient controls an infusion device that delivers a bolus of analgesic drug 'on demand' according to parameters set by the physician. Use of a PCA device allows the patient to overcome variations in both pharmacokinetic and pharmacodynamic factors by carefully titrating the rate of opioid administration to meet individual analgesic needs. Although it should be recognized that the use of oral 'rescue doses' is, in fact, a form of PCA, the term is not commonly applied to this situation. Long-term PCA in postoperative patients is most commonly accomplished via the intravenous route using an ambulatory infusion device. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose. Long-term intravenous PCA can be used for patients who require doses that cannot be comfortably tolerated via the subcutaneous route or in those who develop local reactions to subcutaneous infusion (25).

In pediatric age PCA is recommended for children of 8 years or more, without disabilities, in whom moderate to severe pain is anticipated for 24 hours or more. Most children over the age of 7 years understand the PCA concept, and sometimes even younger children can learn to use PCA, but some may not have the cognitive or emotional resources to use it. In children as young as 5 or 6 years PCA has also been used, however pain relief is not always satisfactory because of poor patient understanding. In these patients Nurse or Parent Controlled Analgesia (NCA/PCA) represent a more suitable modality of drug administration. As continuous infusion, PCA allows a steady analgesic serum concentrations with safety and efficacy in pain control.

Morphine is the most common drug used in PCA, followed by Fentanyl and Hydromorphone (88-91). The selection of opioid used in PCA is perhaps more critical than the appropriate selection of parameters such as bolus dose, lockout and background infusion rate (Table 11). PCA dosage regimens must be individualized on the basis of pain intensity and monitoring pain parameters must be age appropriated. Monitoring involves measurements of respiratory rate, level of sedation and oxygen saturation. Efficacy of PCA therapy is assessed by self-reporting, visual analogue scales, faces pain scales and usage pattern. The effectiveness of analgesic techniques may be limited by the incidence and severity of adverse effects; potential adverse effects of PCA therapy, including respiratory depression, nausea, vomiting and itching, can be prevented or controlled by the use of adjuvant drugs and by careful titration. The patient should be instructed in the use of PCA prior to coming to operating room or even in the anaesthetic room before induction. Clinicians must become aware on age-related and developmental differences in the pharmacokinetic, pharmacodynamic and monitoring parameters for the patients with PCA therapy. To date, safety and efficacy of PCA also in paediatric patients has been established and a role of this procedure has been proposed in postoperative pain management as well as in burns, oncology and palliative care (26).

Adjuvant analgesics

The term 'adjuvant analgesic' describes a drug that has a primary indication other than pain but is analgesic in some conditions. A large group of such drugs, which are derived from different pharmacological classes, is now used to manage non-malignant pain.

Table 11. Patient-controlled analgesia (PCA) protocol with morphine.

PCA protocol	**Aim**	**Recommended starting dose (morphine)**
Loading dose	Get immediate pain control	0.05-0.1 mg/kg (max 10 mg)
Basal dose	Maintain pain control	0.01-0.02 mg/kg/h
Intermittent dose (dose PCA)	Pain control by the patient himself	0.01-0.02 mg/kg
Interval (lockout) 6-15 minutes depending on the device	Prevent overdose	
Limit dose in 4 hours	Prevent overdose	0.25-0.35 mg/kg

These drugs may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. The potential utility of an adjuvant analgesic is usually suggested by the characteristics of the pain or by the existence of another symptom that may be amenable to a non-analgesic effect of the drug. Whenever an adjuvant analgesic is selected, differences between the use of the drug for its primary indication and its use as an analgesic must be appreciated. Because the nature of dose-dependent analgesic effects has not been characterized for most of these drugs, dose titration is reasonable with virtually all. Low initial doses are appropriate given the desire to avoid early side effects. The use of low initial doses and dose titration may delay the onset of analgesia. However, patients must be forewarned of this possibility to improve compliance with the therapy. There is great interindividual variability in the response to all adjuvant analgesics and remarkable intraindividual variability in the response to different drugs, including those within the same class. These observations suggest the potential utility of sequential trials of adjuvant analgesics. The process of sequential drug trials, like the use of low initial doses and dose titration, should be explained to the patient at the start of therapy to enhance compliance and reduce the distress that may occur if treatments fail. The adjuvant drugs more frequently used are corticosteroids, topical and local anaesthetics, neuroleptics and benzodiazepines (Table 12).

Table 12. Adjuvant analgesics.

Cathegory	**Drug**
Antidepressants	Amitriptyline
Anticonvulsants	Gabapentin
	Carbamazepin
Antipsychotic	Chlorpromazine
	Haloperidol
Sedatives	Diazepam
	Midazolam
Antihistamines	Promethazine
Corticosteroids	Dexamethasone
Antiemetics	Ondansetron

Corticosteroids

Corticosteroids are among the most widely used adjuvant analgesics (27). They have been demonstrated to have analgesic effects in different conditions to significantly improve the quality of life and to have beneficial effects on appetite, nausea, mood and malaise. The mechanism of analgesia produced by these drugs may involve anti-oedema effects, anti-inflammatory effects and a direct influence on the electrical activity in damaged nerves. The relative risks and benefits of the various corticosteroids are unknown and dosing is largely empirical. In the United States, the most commonly used drug is dexamethasone, a choice that gains theoretical support from the relatively low mineralocorticoid effect of this agent. Dexamethasone has also been conventionally used in case of raised intracranial pressure and spinal cord compression. Prednisone, methylprednisolone and prednisolone have also been widely used for other indications. Patients who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroid (e.g. dexamethasone 1-2 mg twice daily). In some settings, however, a high-dose regimen may be appropriate. Although high steroid doses are more likely to lead to adverse effects, clinical experience with this approach has been favourable.

Topical and local anaesthetics

Local anaesthetics are amazing drugs now commonly used in prevention and management of postoperative pain. Injected into tissue, around a nerve or for a regional block, they produce a reversible block. The use of local anaesthetics can produce reduced blood loss, faster surgery, reduced morbidity and faster rehabilitation. Local infiltration, blockade of peripheral nerves and plexuses, epidural blockade and regional analgesia represent the most frequent techniques adopted. Lidocaine and Bupivacaine are the most common local anaesthetics used in clinical practice. Particular attention to maximum drug dosing is required; excessive doses can cause seizures, cardiac depression and rhythm anomalies (28).

Topical formulations are useful for needle procedures, including EMLA, a cream containing an

eutecthic mixture of 2 local anaesthetics (lidocaine 2.5% and prilocaine 2.5%).

It is very effective in numbing the skin and the tissues just underneath the skin. Topical local anaesthetics can be used in the management of painful cutaneous and mucosal lesions and as a premedication prior to skin puncture. However, the depth of the skin which becomes numb is dependent upon how long the cream is left on. The maximum depth is about six to seven millimeters, after the cream has been left on the skin for two hours. This medication has been successfully used for a number of painful procedures, such as bone marrow aspiration and lumbar puncture; the cream should be applied from 30 min to 1 hour before the shot or needle procedure (29). Satisfactory numbing of the skin occurs 1 hour after application, reaches a maximum at 2 to 3 hours (1 hour for children less than 3 months), and lasts 1 hours after removal. EMLA has been proved to be safe, with low plasma local anaesthetic concentration. Mild side effects generally disappear spontaneously within 1 or 2 hours (skin paleness, redness, a changed ability to feel hot or cold, swelling, itching and rash). It should not be used in children affected by a rare condition of congenital or idiopathic methaemoglobinemia, or in infants under the age of 12 months who are receiving treatment with methaemoglobin-inducing agents.

Neuroleptics

Methotrimeprazine is a proven analgesic and has been useful in bedridden patients with postoperative pain who experience pain associated with anxiety, restlessness or nausea (30). In this setting the sedative, anxiolytic and antiemetic effects of this drug can be highly favourable and side effects, such as orthostatic hypotension, are less of an issue. Methotrimeprazine may be given by continuous SC administration, SC bolus injection or brief IV infusion (administration over 20-30 minutes). A prudent dosing schedule begins with 5-10 mg every 6 hours or a comparable dose delivered by infusion, which is gradually increased as needed. Most patients will not require more than 20-50 mg every 6 hours to gain the desired effects. Given their potential for serious toxicity and the limited evidence in support of analgesic efficacy, other neuroleptics should be used only for the treatment of delirium and nausea.

Benzodiazepines

There is little evidence that benzodiazepines have meaningful analgesic properties in most clinical circumstances and, indeed, there is some evidence that they may, in some circumstances, antagonize opioid analgesia. These drugs may play a role in the management of anxiety and muscle spasm (31).

Conclusion

Paediatric acute pain has emerged as an important issue because of ethics aspects and associated morbidity and mortality. The diagnosis and treatment of the cause of acute pain must always have high priority. Psychological, behavioural and physical interventions, stratified by age and development, may be added to pharmacological management. As a matter of fact in pediatric patients disorders causing acute pain are usually accompanied by anxiety and distress. A combined stepwise approach to pain and anxiety involves pharmacological and non-pharmacological interventions as integrated treatment. Non-pharmacological approaches can be divided into two general categories: physical comfort measures and distracting activities. Physical comfort measures are specific interventions stratified by age. Neonates and infants have a positive feedback (lowering of painscores, cry duration and heart rate variation) to oral stimulation as well as physical contact or touch during painful procedures. Distracting activities include bubble blowing, sound and music, controlled deep breathing, art, puppets, imitation play, interactive games, books, guided imagery (32). This kind of approach plays a major role especially when a pharmacological treatment is not feasible. Parents are the main support either in assisting the clinician during painful procedures engaging children in other activities either in assisting the child in the hospital context. From this point of view it is essential for the physician to gain their trust and to establish a positive alliance in order to strengthen the doctor-patient relationship (33-35).

Improved understanding of the pharmacology of analgesics and the development of new techniques for analgesic administration have greatly enhanced the ability of medical doctors to successfully manage pain in patients. In some conditions the success of pharmacological strategies is remarkable, especially in adult patients. Even in children and adolescent with the most severe pain early evidence shows that it may be possible to reduce the impact of pain on the lives of patients and their families. However, more action is necessary. Firstly, more paediatric centres are needed in order to develop specific post-operative pain programmes. Secondly, collaboration between centres will be necessary to provide larger samples of patients with the various pain conditions, considering the lack of data on this field. Thirdly, we must consider that the incidence of pain in children is similar to that of adults but that our knowledge on how to help children with acute pain is underdeveloped. The psychological and physiologic uniqueness of children must not be forgotten as well (36). Finally a structured stepwise approach in managing pain should be followed. The first phase is recording a pain history. The second step is assessing the child's pain by using an appropriate tool. The third step is estimating regularly the efficacy of interventions. Caregivers ought to familiarize themselves with the main pain scales and how to use them on a daily basis. In this way, we can improve pain assessment and consequently pain relief (37-39). Cooperation and communication among the anaesthesiologist, the surgeon and the paediatrician remain essential for successful anaesthesia and pain management.

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