health technology assessment

REPORT

RATIONAL USE OF ANALGESICS IN PAEDIATRICS

HEALTH TECHNOLOGY ASSESSMENT UNIT
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
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Head, Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Parcel E,
Government's Office Complex,
62590 Putrajaya,
Malaysia

Tel: 603 – 8883 1228
Fax: 603 – 8883 1230

Available on the following website : http://www.moh.gov.my

MEMBERS OF EXPERT COMMITTEE

Dr Chin Choy Nyok ……. *Chairperson*
Paediatric Consultant
Tengku Ampuan Afzan Hospital
Kuantan, Pahang

Dr Abdul Nasir
Paediatric Consultant
Tuanku Fauziah Hospital
Perlis

Dr Yap Yoke Chin
Paediatric Consultant
Kuala Lumpur Hospital
Kuala Lumpur

Dr Norashidah Wahab
Paediatric Consultant
Selayang Hospital Selayang,
Selangor

Dr Akbar Ali Hitam Ali
Paediatric Consultant
Ipoh Hospital Ipoh,
Perak

Dr Sabeera Begum
Paediatric Specialist
Kuala Lumpur Hospital
Kuala Lumpur

Dr Cheong Soo Tow
Paediatric Specialist
Taiping Hospital
Taiping, Perak

Nur Sufiza Ahmad
Pharmacist
Pharmacy Division
Ministry of Health Malaysia

Puan Norlida Ibrahim
Pharmacist
Kuala Lumpur Hospital
Kuala Lumpur

Project Coordinators

Dr S Sivalal
Deputy Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Dr Rusilawati Jaudin
Principal Assistant Director
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

Ms Jeya Devi Coomarasamy
Senior Nursing Officer
Health Technology Assessment Unit
Medical Development Division
Ministry of Health Malaysia

EXECUTIVE SUMMARY

1. INTRODUCTION

Pain commonly experienced by children is acute pain resulting from injury, illness, and necessary medical procedures, while the other types include chronic pain, recurring pain, and pain associated with terminal illness. It affects children physiologically and emotionally if not managed and treated well. In children it is often inadequately assessed and treated due to the fact that children have difficulty in expressing pain to adult caregivers, while perceptions of their pain also differ widely. There are pharmacological and non-pharmacological approaches in pain management with good efficacy in both acute and chronic pain experienced by the children. A combined approach of non-pharmacological and pharmacological techniques has also been recommended for optimum pain relief and to reduce distress in neonates and children. A validated pain tool is needed for assessing pain in children.

2. POLICY QUESTION

Which are the analgesics and analgesic modalities that are safe, effective and cost effective for use in children?

3. OBJECTIVES

To determine the safety, effectiveness and cost effectiveness of the commonly used pharmacological and non-pharmacological modalities of pain management in paediatric population.

4. METHODOLOGY

The electronic databases, hand-search and search by cited references in some of the papers were carried out. Relevant papers were critically appraised and graded according to the modified CAHTA scale.

5. RESULTS

5.1 Pharmacological agents

Acetaminophen (Paracetamol)

There is sufficient evidence to show that there is minimal risk of developing toxic reactions to acetaminophen when used at therapeutic doses. Acetaminophen is hepatotoxic with inappropriate/excessive dosing, impaired liver function and when ingested with other hepatotoxic drug. Rectal administration of acetaminophen may produce high peak drug levels.

There is good evidence on the effectiveness of paracetamol in providing acute post-operative pain control in various surgical procedures, whether given pre-operatively or in the immediate post-operative period. Rectal acetaminophen has not been to be effective in controlling pain satisfactorily. Evidence also shows that combining paracetamol with other analgesics like codein, diclofenac, ibuprofen or rofecoxib does not provide superior pain control compared to using paracetamol alone.

Non-steroidal anti-inflammatory agents (NSAIDs)

There is sufficient evidence to show that ibuprofen, diclofenac, ketorolac and ketoprofen are reasonably safe. Nausea and vomiting are common side effects. These drugs may also cause mild to severe homeostasis defects peri-operatively. There is also evidence that they are effective in relieving pain in immediate post-operative period and during recovery for various ophthalmic, ear, nose and throat surgical procedures that are administered through various routes i.e. oral, intravascular, intramuscular, rectal or topical.

Opoids

Evidence shows that opoids can cause hypotension and respiratory depression in high doses. Fentanyl has been found to cause fewer side-effects compared to morphine. There is sufficient evidence to show that opiods are potent analgesics for moderate to severe pain. Their sedative and analgesic effects are dose dependent. There is sufficient evidence that morphine and fentanyl are effective for relief of moderate to severe pain post-operatively in various surgical procedures like ophthalmic, ENT, cardiac procedures, and procedures carried out during the neonatal period. Evidence also shows that the synthetic opiod, fentanyl, is 100 times more potent than morphine, and is effective for out-patient procedural care either in the out-patient setting or emergency department, due to its rapid onset and short duration of action. It is also effective for acute pain relief by administration through transmucosal and intra-nasal routes. Patient controlled analgesia has also been found to be effective for the management of moderate to severe pain post-operatively in older children and adolescents.

Local anaesthetic agents

Most evidence indicates that Lidocaine-prolocaine cream, is safe as topical analgesia for pain associated with circumcision and medical procedures such as venepuncture. However, there is a risk of methemoglobinemia particularly in premature infants as well as term infants aged less than 3 months. It is also effective for reducing pain during circumcision but the evidence of its effectiveness for analgesia in medical procedures is inconclusive.

5.2 Non-pharmacological modalities

There is evidence that skin-to-skin contact is a safe intervention against pain in the newborn, but there is insufficient evidence on its effectiveness. As for the other behavioural interventions, there is insufficient evidence on their effectiveness. There is limited evidence on the effectiveness of cognitive behavioural interventions to reduce pain stimuli.

5.3 Other modalities

Evidence shows that sucrose is a safe to be used with minimal side effects. It is an effective intervention against procedural pain in the term newborn. There is some evidence that glucose is a safe intervention against pain associated with minor procedures in neonates, but findings on its effectiveness were inconclusive. There is insufficient evidence of effectiveness of artificial sweetener against pain.

5.4 Assessment tools

There are several pain assessment tools that can be used to measure pain in the different age groups i.e. pre-term infants, neonates, infants and children. Children's families, especially parents, are important in identifying children's behaviour in response to painful stimuli though these may not be as accurate as that of the child.

6. RECOMMENDATIONS

Pharmacological agents like acetaminophen, NSAIDs like ibuprofen, diclofenac, ketorolac and ketoprofen, and opiods like fentanyl are safe and effective analgesics for use in various surgical procedures that produce mild, moderate and severe painful stimuli. However, the side effects of these need to be taken into consideration with constant monitoring carried out.

Pain assessment tools taking into consideration parents' assessment and/or child's self-report can be used to measure pain.

CONTENTS

RATIONAL USE OF ANALGESICS IN PAEDIATRICS

1. INTRODUCTION

Pain is a universal human experience. It is a complex concept, difficult to define or understand (Montes-Sandoval, 1999). Pain, if left unrecognised or neglected, can become established and difficult to control (Wall, 1988; McQuay, 1989). Children suffering from pain, can be affected physiologically and emotionally, if the pain is not managed and treated well (Taddio *et al*, 1997; Van Keuren & Eland, 1997; Stoddard *et al*, 2002). Despite the magnitude of effects that pain can have on children, studies have shown that it is often inadequately assessed and treated by health care professionals (Beyer, 1983; Mather & Mackie, 1983; Rus Anida & Quah, 1998). One of the main reasons for this is that children have difficulty in expressing their pain to adult caregivers, while perceptions of their pain also differ widely (Schecter *et al*, 2002).

The American Academy of Paediatrics and the American Pain Society (2001) state that there are many barriers to the treatment of pain such as:

- the myth that children, especially infants, do not feel pain the way adults do
- lack of assessment and reassessment for the presence of pain
- misunderstanding of how to conceptualize and quantify a subjective experience
- lack of knowledge of pain treatment
- the belief that addressing pain in children takes too much time and effort
- fears of adverse effects of analgesic medications like respiratory depression and addiction

In the past, there was an assumption that infants did not have the cortical maturation to experience pain. As a result some neonates even underwent surgery with minimal anaesthesia (Lippmann *et al*, 1976). Evidence shows, however, that by 29 weeks of gestation, pain pathways and the cortical and sub-cortical centres involved in the perception of pain are well developed (Johnston *et al* 1995; Elander *et al*, 1993; Lindh *et al*, 1997). Exposure of pre-term neonates to repetitive pain has also been shown to lead to clinical instability and complications (Taddio *et al*, 1997).

It has been found that neonates and children can receive analgesia safely if there is careful selection of drugs according to the type and severity of the condition, and proper age-related dosage adjustments. However, no single analgesic can be considered perfect, being able to treat all types of pain Rather, a combination of analgesics has been found to be effective, where the individual agents act through different analgesic mechanisms, but in synergy (Raffa, 2001).

Apart from pharmacologic management of pain, there are several non-pharmacological approaches with good efficacy in children with acute or chronic pain (McGrath *et al*, 1985; Carbajal *et al*, 1999; Blass *et al*, 1999; Ors *et al*, 1999; Polkkei *et al*, 2001; Sparks, 2001; Stevens *et al*, 2001; Johnston *et al*, 2002; Zeltzer *et al*, 2002; Kankkunen *et al*, 2003; Eccleston, 2003). A combined approach of non-pharmacological and pharmacological techniques has also been recommended for optimum pain relief and to reduce distress in neonates and children (AAP Policy Statement, 2001; Tanabe *et al*, 2002). Paediatricians and other health care professionals have the responsibility to recognize, assess and manage all types of pain in children appropriately.

1.1 Types of Pain

The most common type of pain experienced by children is acute pain resulting from injury, illness, and necessary medical procedures. Other types include chronic pain, recurring pain, and pain associated with terminal illness (AAP Policy Statement, 2001).

1.2 Pain Measurement in Paediatric Patients

The type and severity of pain has to be measured. The efficacy of the analgesia administered can only be determined if it has been gauged through continuous assessment. A validated pain tool is needed to measure the level of pain. According to Colwell *et al* (1996) and Manne *et al* (1992), nurses' assessment of children's pain using a validated pain assessment tool, correlates more closely with those of children's self-reported pain. A randomised controlled trial (RCT) by Stevens (1990), where nurses used a pain assessment tool, showed that patients had less severe pain, received more analgesics, and were assessed more frequently, compared to a control group. It has been found that tools to assess children's pain, should be used in conjunction with parents' and health professionals' assessment. Currently, there is no easily administered and widely accepted uniform technique advocated for assessing pain in children. The available methods for measuring pain in children are as follows:

- *Self reported* - routine questions, verbal scales, numeric scales and pictorial scales (Palmero & Drotar, 1996; McGrath *et al*, 1996)
- *Behavioural measures* – motor responses, facial expressions, crying and complex behaviour responses such as sleep-wake patterns (Woodgate & Kristjanson, 1995; Fuller & Conner, 1995; Grunau *et al*, 1990; Taddio *et al*, 1995).
- *Physiological measures* – changes of pulse rate and blood pressure as well as measurement of palmer sweating (Coffman *et al*, 1997; Tyler *et al*, 1993).

1.3 Modalities for Pain Relief in Paediatric Patients

There are various pharmacological and non-pharmacological modalities that can be used in the management of pain in children and neonates.

1.3.1 Pharmacological agents

Numerous drugs are used for pain relief in children and neonates as follows:

- Non-opioid analgesics - commonly used are paracetamol (acetaminophen), non-steroidal anti-inflammatory agents (NSAIDs) and local anaesthetic agents
- Opioid analgesics

1.3.2 Non-pharmacological agents

Among the commonly used modalities are:

- Physical e.g. heat, cold stimulation, electrical nerve stimulation, acupuncture, massage
- Behavioural e.g. relaxation, biofeedback, modelling, desensitisation, art and play therapy
- Cognitive e.g. distraction, imagery, hypnosis, music therapy

2. POLICY QUESTION

Which are the analgesics and analgesic modalities that are safe effective and cost effective for use in children?

3. OBJECTIVES

To determine the safety, effectiveness and cost effectiveness of the commonly used pharmacological and non-pharmacological modalities of pain management in paediatric population.

4. SCOPE OF ASSESSMENT

The scope of this assessment is as follows:

I. Children aged 0 - 18 years (including neonates)
II. Type of pain - acute pain (procedural, post-operative and trauma pain)
III. Pharmacological agents
    a. paracetamol (acetaminophen)
    b. non-steroidal anti-inflammatory drugs (NSAIDs) - ibuprofen, diclofenac, ketorolac and ketoprofen
    c. opioids - morphine and fentanyl
    d. local anaesthetic agent - EMLA cream
IV. Non-pharmacological modalities
    a. Behavioural interventions
        - Multi-sensory stimulation
        - Non-nutritive sucking (pacifiers)
        - Breast feeding
        - Skin-to-skin contact
    b. Cognitive interventions
        - Distraction techniques - music, movies, art, touch, blowing bubbles
V. Other modalities
        - Sucrose
        - Glucose
        - Artificial sweeteners

This assessment does not consider chronic, recurring pain and pain associated with terminal illness. It also does not assess analgesic agents like aspirin, pethidine, tramadol, naproxen, codeine, mefenemic acid and all other drugs that are not included in the list above. Other non-pharmacological modalities such as acupuncture, hypnosis and others are also not considered in this assessment.

5. METHODOLOGY

The electronic databases were searched. Further hand search and search by cited references in some of the papers was carried out (Appendix 1). Papers that were relevant were critically appraised and graded according to the modified CAHTA scale (Appendix 2).

6. RESULTS AND DISCUSSION

6.1 Safety

6.1.1 Pharmacological agents

a. Paracetamol (Acetaminophen)

Paracetamol or acetaminophen or is the most commonly used mild analgesic in children (Kearns, Leeder and Wasserman, 1998). Chemically, it is *N*-acetyl-*para*-aminophenol, a metabolic by-product of phenacitin. The daily cumulative paracetamol dose by the oral or rectal route should not exceed 100 mg/kg/day for children, 75 mg/kg for infants, 60 mg/kg for term and pre-term neonates beyond 32 weeks of post-conception age, and 40 mg/kg for pre-term neonates from 28 to 32 weeks of post-conception age. A pre-term neonate 30 weeks of post-conceptional age should be given 20 mg/kg every 12 hours (Berde & Sethna, 2002).

Rumack (1984), Rodriguez and Jordon (2002) and the American Academy of Paediatrics (2001) state that the risk of developing toxic reactions to acetaminophen when used at therapeutic doses, is minimal or lower in children than adults, and these often occur from intentional overdoses. Adverse effects are unlikely at doses below 150 mg/kg/day (Rumack, 1984). Gee and Ardagh, (1998) and Penna and Buchanan (1991) concluded that death and hepatotoxicity in children were uncommon events, unlike adults. According to Mortensen (2002), serious toxicity or fatalities, have been extremely infrequent following an acetaminophen overdose in young children, possibly because of differences in the way children metabolize acetaminophen. Lesko and Mitchell (1999) found that adverse gastrointestinal or renal events from short-term use of acetaminophen appear to be quite rare in children.

However, Kearn, *et al* (1998) and Heubi *et al* (1998), found that severe toxicity has been observed despite apparently reassuringly low acetaminophen levels. Berde and Sethna (2002) reported that excessive dosing produces hepatic failure in both infants and children. Miles *et al* (2000) reported that accidental paracetamol overdose is associated with fulminating hepatic failure. Rivera-Penera *et al* (1997) state that acetaminophen hepatotoxicity in children is associated with age less than 10 years associated with inappropriate dosing, delays in onset of symptoms after a potentially toxic ingestion, delays in initiation of NAC treatment, unintentional multiple overdosing, and ingestion of acetaminophen along with another hepatotoxic drug. They also found that severe hepatotoxicity in children is due to cumulative toxicity from repeated doses, rather than acute intoxication from a single massive overdose. Heubi *et al* (1998) show that the use of adult rather than paediatric preparation leads to hepatotoxicity in children. The American Academy of Paediatrics (2001) was of the view that the health care providers should consider acetaminophen toxicity in any child who has received acetaminophen, who has signs of acute dysfunction, even if acetaminophen levels are not in the toxic range. Heubi *et al* (1998) advise clinicians to inform parents about the potential hepatotoxicity of acetaminophen when given to ill patients in doses exceeding weight-based recommendations.

Rectal administration of acetaminophen has been found to lead to toxicity because the route of administration produces peak drug levels that may vary as much as nine-fold, and often does not achieve therapeutic levels after the recommended doses are administered (Birmingham *et al* 1997). However, Buck (2001) states that the administration of high doses of acetaminophen in the peri-operative period appears to be safe in children.

b. Non-Steroidal Anti Inflammatory Drugs (NSAIDs)

NSAIDs can produce mild, systemic homeostatic defects by inhibiting normal platelet function, probably through COX-1 inhibition in platelets (Farrar & Lerman, 2002). Studies by Gallagher *et al* (1995), Gunter *et al* (1995) and Rusy *et al* (1995) showed that post-operative bleeding in children taking NSAIDs was significantly greater than those on placebos. In a retrospective review, Robinson and Ahmad (1994) found that the use of NSAIDs before tonsillectomy increased the risk of post-tonsillectomy haemorrhage due to the oral cavity and saliva being rich in fibrinolytic activators. Romsing and Walther-Larsen (1997) cautioned that combining NSAIDs with any type of surgery could lead to peri-operative bleeding, and their use be delayed until surgical bleeding is no longer at risk. Kokki (2003) states that severe adverse effects in children are rare, but NSAIDs should be used with caution in children with liver dysfunction, impaired renal function, hypovolemia or hypotension, coagulation disorders, thrombocytopenia or active bleeding from any cause.

Ibuprofen, diclofenac, ketorolac and ketoprofen are the most extensively evaluated NSAIDs in children.

Ibuprofen

Ibuprofen decreases inflammation by reversibly inhibiting cyclo-oxygenase, as well as inhibiting prostaglandin production (Rodriguez & Jordon, 2002). According to Lesko and Mitchell, (1995) ibuprofen is associated with gastrointestinal bleeding, renal failure, or anaphylaxis, but found to be rare in children less than 12 years old. However, there is no information on the risks of less severe outcomes or the risk of prolonged ibuprofen use. Rodriguez and Jordan (2002) show that ibuprofen causes peptic ulcer disease like all non-steroidals. The adverse effects of ibuprofen are similar to those of other NSAIDs, but clinical experience suggests that ibuprofen is better tolerated by children than adults and it is safer in overdose than paracetamol or aspirin (Autret-Leca, 2003) A study comparing ibuprofen with acetaminophen with codeine for paediatric post tonsillectomy/ adenotonsillectomy patients, reported a mean increase in bleeding time of 2.07 minutes on the third post-operative day in the ibuprofen group (Harley & Dattolo, 1998).

Diclofenac

Patients on diclofenac were found to have a lower rate of nausea and vomiting following tonsillectomy, compared to acetaminophen (Romsing *et al*, 2000). Similarly, rectally administered diclofenac gave less post-operative nausea than IV Morphine after strabismus surgery in children 4 to 16 years of age (Wennstrom & Reinsfelt, 2002). In an RCT on children between 3 and 13 years, Bone and Fell (1988) found rectal diclofenac 2 mg/kg when given for pain relief following tonsillectomy, had significantly less effect upon the respiratory rate compared to IM paperveretum 0.2 mg/kg. Baer *et al* (1992) reported that rectally administered diclofenac to be safe when administered pre-operatively for patients undergoing adenoidectomy with or without myringotomy.

Ketorolac

An RCT comparing IV ketorolac to rectal acetaminophen in children undergoing tonsillectomy, found that hemostasis during tonsillectomy was significantly more difficult in patients receiving ketoralac (Rusy, 1995). However, in another RCT on 50 children 5 to 15 years of age, Romsing *et al* (1998) found that single dose of ketorolac 1 mg/kg intravenously administered either before or immediately after surgery improves post-operative analgesia in children after tonsillectomy, without evidence of increased incidence of bleeding. An RCTl by Shende and Das (1999) comparing ketorolac in a dose of 0.9 mg/kg intravenously at the induction of anesthesia with pethedine 0.5 mg/kg intravenously found less post-operative nausea and vomiting with ketorolac.

Ketoprofen

A prospective RCT by Kokki, Nikanne and Tuovinen (1998) of intra-operative intravenous ketoprofen in 220 children, aged 1 to 7 years, undergoing adenoidectomy, showed no post-operative bleeding which would have required intervention or delayed discharge from hospital. A prospective, longitudinal study in 102 children undergoing tonsillectomy compared ketoprofen capsules at a dose of 3 - 5 mg/kg per 24 hour for post-operative pain control at home, with paracetamol or paracetamol-codeine tablets for rescue analgesia found the former safe for children, but recommend a larger study to show whether or not ketoprofen increases the haemorrhage rate (Salonen, Kokki & Nuutinen, 2002). An RCT on the safety and efficacy of ketoprofen in 109 children, aged 3 to 16 years, during and after tonsillectomy found two patients out of the five in the post-ketoprofen group had post-operative bleeding at 4 and 26 hour, respectively that required electrocautery to stop bleeding. The investigators state that neither the incidence nor the severity of adverse events differed between the study groups (Kokki & Salonen, 2002).

c. Opioids

Opiods are powerful analgesic drugs used for moderate to severe pain. However, they have several adverse effects (Berde, *et al* 1991). The sedative and analgesic effect of opioids are dose dependent and varies with plasma concentration from sub-analgesia, to analgesia and euphoria, to nausea, dysphoria, and somnolence, to respiratory depression, to apnoea and unconsciousness. Other adverse effects include hypotension, nausea and vomiting, constipation, vasodilatation, local urticaria along injected vessel, generalised pruritis, urinary retention and biliary colic (Rodriguez and Jordon, 2002). According to Canadian Paediatric Society (2000) the risk of adverse effects is directly related to rate of drug administration, total dose, and combination with other medications capable of central nervous system depression. The propensity for these adverse effects is reduced by avoiding rapid bolus injection. Administration should be by frequent small aliquots or by infusion over several minutes. The health care professional who administers opioids should be trained in the recognition and treatment of the adverse complications, including the use of bag-mask ventilation, an opioid antagonist to oppose the respiratory depression, or a muscle relaxant to treat glottic and chest wall rigidity.

Morphine

Morphine is found to cause profound hypotension, particularly when the patient is in the hypovolemic state, and can also precipitate bronchospasm secondary to histamine release (Ward and Yealy, 2000). Sabatino, *et al* (1997) studied the haemodynamic effects of intravenous morphine infusion in ventilated pre-term infants and found morphine high-dose regimen (200 ìg/kg/2h followed by 25 ìg/kg/h) resulted in a non-significant reduction of mean arterial blood pressure. Hartley, *et al* (1993) studied the pharmacokinetics of morphine infusion in 17 premature neonates of 26 to 34 weeks gestation and found a non-significant decrease in mean arterial blood pressure only in the high-dose–regimen group (400 ìg/kg/2 h followed by 50 ìg/kg/h). Lynn, *et al* (1993) evaluated the respiratory effects of intravenous morphine infusion in 30 patients (2 to 570 days old) after cardiac surgery and found there was no difference in the susceptibility to respiratory depression in neonates compared with infants and children. According to Hartley, *et al* (1993) and Lynn, *et al* (1993) higher morphine plasma concentrations are often accompanied by more (or more severe) side effects of morphine.

Esmail, *et al* (1999) studied the adverse drug reaction in paediatric patients receiving continuous intravenous morphine infusions for acute post-operative pain and found 42.5% of the patients experienced nausea and vomiting. However, the incidence of respiratory depression was 0%. Other adverse drug reactions included urinary retention (13.5%), prurities (12.7%), dysphoria (7.3%) and hypoxaemia (4.5%). Weinstein (1994) found a single dose of morphine sulphate increases the incidence of vomiting in the first 24 hours after outpatient inguinal surgery in children.

A randomised controlled trial by Quinn (1993) on morphine infusion (100 µg/kg/h for 2 hours followed by continuous infusion of 25 µg/kg/h) for ventilated preterm infant less than or equal to 34 weeks with respiratory distress syndrome showed that morphine is safe. However, in a randomised controlled trial by Anand *et al* (2004) significant adverse effects were found when ventilated preterm neonates were given morphine infusions and they advocate close monitoring of these patients.

Fentanyl

Fentany is a synthetic opioid and 100 times more potent than morphine (Ward and Yealy 2000). It has a rapid onset of action (less than 30 seconds when administered IV) and duration of action of only 30 to 40 minutes. Fentanyl is normally administered intravenously or through the epidural route. The usual dose is between 1-5 µg/kg IV (American Medical Association, Council of Scientific Affairs, 1993). Fentanyl is lipophilic and is readily absorbed across any biological membrane, including the transmucousal (mouth and nose) and transdermal routes.

Ward and Yealy (2000) reported that fentanyl is associated with 50% incidence of emesis. According to Rodrriguez and Jordon, (2002) fentanyl can cause chest wall rigidity and laryngospasm which can make ventilation difficult or impossible. Sachetti, *et al* (1994) stated that chest wall rigidity is more common with rapid administration and high doses (greater than 15 µg/kg). Frush and Bisset (1997) found that fentanyl causes nasal pruritis and stated that steps need to be taken to restrain the patient's hands when doing facial or oral procedures.

However, in a randomised controlled trial on ventilated newborn infants, Saarenmaa, *et al* (1999) found that fentanyl had fewer side effects when compared with morphine. Keidan, *et al* (2004) found the incidence of PONV in children undergoing outpatient adenotonsillectomy was the same for ketrolac and fentanyl.

Using a placebo-controlled, double-blind design Sharar, *et al* (2002) compared oral transmucosal fentanyl citrate (OTFC, approximately 10 µg/kg) and oral oxycodone (0.2 mg/kg) in 22 pediatric outpatient wound care procedures (ages 5 to 14 years) and found it to be a safe analgesia. Ginsberg, *et al* (1998) found that oral transmucosal fentanyl citrate dose at 10 µg/kg was effective in providing sedation without causing clinically significant changes in vital signs or oxygen saturation. Pruritus was present in 76% of children but Ginsberg, *et al* (1998) state that pruritus cannot be used as an endpoint for OTFC effectiveness.

Galinkin, *et al* (2000) found the use of intranasal fentanyl during halothane or sevoflurane anesthesia for myringotomy and tube placement was associated with diminished post-operative agitation without an increase in vomiting, hypoxemia, or discharge times. Borland, Jacobs and Geelhoed (2002) state that there was no significant alteration in pulse rate, respiratory rate and blood pressure or oxygen saturations when intranasal fentanyl was given to children in acute pain in the emergency department.

Patient controlled analgesia (PCA) is a system whereby, patients could administer their own intravenous analgesia and titrate the dose by using a small microprocessor controlled pump. Six studies showed PCA to be a safe method for paediatric patients (Gaukroger, Tomkins and van der Walt, 1989; Gaukroger, Chapman and Davey, 1991; Till, *et al* 1996; Marchetti, Calbi and Villani, 2000; Shin, *et al* 2001; McDonald and Cooper, 2001).

However, Kost-Byerley (2002) states that the incidence of well-known side- affects of opioid therapy do not diminish with PCA. Bray, *et al* (1996) reports that lower respiratory rates and oxygen saturations have been observed with paediatric PCA but Berde, *et al* (1991), Monitto, *et al* (2000) and Tyler *et al* (1995) report that clinically significant respiratory depression is rare. However, Berde, *et al* (1991) and Rieberer (1998) recommend that a high degree of monitoring is still required to ensure that PCA is safe in children.

d. Local Anaesthetic Agents

Lidocaine-prolocaine cream

Lidocaine-prolocaine cream, EMLA cream, contains 2.5 percent lidocaine and 2.5 percent prilocaine (5% lidoaciane-prilocaine cream). Topical formulations provide analgesia and are widely used for intact skin and for procedure related pain in neonates and children (Berde and Sethna, 2001; Lander, *et al* 2003). Topical formulations such as EMLA cream are easy to administer and painless.

A randomised controlled trial by Taddio, *et al* (1997) found EMLA cream to be safe for the prevention of pain from circumcision in neonates. Another randomised controlled trial by Cordoni and Cordoni (2001) reported that no side effects were detected when EMLA cream was used before intravenous cannula insertion in patients between the ages of 4 and 12 years. A systematic review by Taddio, *et al* (1998) reported that single doses of EMLA to be safe for application to the skin of neonates of gestational age of

more than 26 weeks. A prospective study by Essink-Tebbes (1999) showed that the application of 0.5 g lidocaine-prilocaine cream to the heel under occlusion four times a day for 30 minutes is safe. In a prospective randomised trial, Choi, *et al* (2003) found no local or systemic complications with EMLA when used as post circumcision analgesia in children. Rosen, *et al* (2000) reported minimal side effects occurred with EMLA when applied in a thick layer under occlusive covering one hour before removal of thoracostomy tube in children.

However, Steven, *et al* (2001) found EMLA cream extremely safe but contraindicated in patients who are receiving other drugs that are known to induce methemoglobinemia. Brisman, *et al* (1998) states that there is a theoretical risk of methemoglobinemia due to EMLA applied in infants younger than 3 months of age due to immaturity of the NADH reductase enzyme. Frey and Kehrer (1999) reported that concomitant application of peridural prilocaine with topical EMLA resulted in symptomatic methaemoglobinemia in preterm infants. EMLA according to Chen and Cunningham (2001) is usually well tolerated and safe in most children. However, they state that methemoglobinemia remains the most concerning and potentially life threatening complication particularly in neonates. Premature infants they state are at a greater risk, though term infants less than 3 months of age are also susceptible than older infants to develop toxic blood concentrations of methemoglobinemia.

6.1.2 Non-pharmacological modalities

Skin-to-skin contact
Gray, *et al* (2000) stated that skin-to-skin contact is a safe intervention against pain in the newborn.

6.1.3 Other modalities

Sucrose
A meta-analysis by Stevens, Yamada and Ohlsson (2001) supports the routine use of sucrose 0.012 - 0.12 g to be administered approximately 2 minutes prior to procedure of a single heel lance and venepuncture. They state sucrose has minimal side effects. However, Johnston, *et al* (2002) reported that repeated use of sucrose analgesia in infants less than 31 weeks may put infants at risk for poorer neurobehavioural development and physiologic outcomes.

Glucose
Deshmukh *et al* (2002) found concentrated glucose solution to be a safe analgesic for minor procedures in neonates. However, Carbajal *et al* (2001) found there were brief oxygen desaturations in 7 neonates during administration of glucose.

6.2 Effectiveness

6.2.1 Pharmacological agents

a. Paracetamol (Acetaminophen)
Acetaminophen is a clinically proven analgesic, elevating the pain threshold (Kost-Byerly, 2002). According to Schecter *et al* (2002) it works as an analgesic through central inhibition of prostaglandin synthesis with minimal inhibition of peripheral prostaglandin synthesis. Berde and Sethna (2002) state that acetaminophen has supplanted aspirin as the most widely used mild analgesic in children. Systematic reviews by Moore *et al* (1997, 2004) found acetaminophen to be an effective analgesia. The American Academy of Paediatrics (2001) was of the view that the effectiveness of acetaminophen is well established compared to aspirin. Perrott *et al* (2004) found that acetaminophen 7-15 mg/kg has similar efficacy for relieving moderate to severe pain as single dose of ibuprofen (4 - 10 mg/kg).

The recommended acetaminophen dose in children is 10 - 15 mg/kg orally 4 times a day (Kost Byerly, 2002; Schecter *et al*, 2002). Montgomery, *et al* (1995) found plasma concentration following a single 45 mg/kg rectal dose of acetaminophen comparable to 10 - 15 mg/kg oral acetaminophen. Based on their findings they suggest that 45 mg/kg rectal acetaminophen was roughly equivalent to a 10 - 15 mg/kg oral dose. Korpela, *et al* (1999) state that it is not good clinical practice to administer acetaminophen as an analgesic for post-operative pain at recommended rectal doses of 10 - 15 mg/kg, because the ED_{50} of rectal acetaminophen is 35 mg/kg. Anderson, *et al* (1996) compared oral and rectal acetaminophen in children aged 3 to 15 years undergoing tonsillectomy using pain scores ranging from 0 (least pain) to 10 (worst pain). They found low acetaminophen serum concentration in children receiving rectal acetaminophen compared to oral acetaminophen. Patients in the rectal group required morphine post-operatively. Bremerich, *et al* (2000) state that prophylactically administered rectal acetaminophen given in doses of 10, 20 or 40 mg/kg in children undergoing cleft palate repair had no beneficial impact on post-operative pain scores. Rusy, *et al* (1995) found rectal doses of 20 to 35/kg was unsatisfactory to treat pain after tonsillectomy in the patient group of 2 to 15 years. Pain was evaluated using standard objective pain score. Gaudreault, *et al* (1988) evaluated the effectiveness of 20 mg/kg of rectal acetaminophen given to 1 to 8 years old undergoing adenoidectomy and/or tonsillectomy at the time of induction of anaesthesia and found it unsatisfactory.

Van Lingen, *et al* (2001) studied the effects of rectally administered paracetamol on infants delivered by vaccum extraction and found it significantly improved their clinical condition but did not result in a significant change in objective pain scores. Korpela, *et al* (1999) found a single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine sparing effect in day-case surgery in children if administered at induction of anaesthesia. Van der Marcel, *et al* (2001) studied the analgesic efficacy of rectal and oral acetaminophen in children after major craniofacial surgery and found that 90% of the patients in the rectal group achieved a serum concentration greater than 10 µg/ml versus 65% in oral group.

Schecter, *et al* (2002) and Buck (2001) report that the appropriate rectal dose of acetaminophen is controversial because absorption is slow and often erratic due to several factors such as placement of the suppository, degree of lipophilicity of the vehicle and the pH within the rectum. Korpela *et al* (1999) state that rectal acetaminophen is best given with induction of anaesthesia to allow time for peak effects, achieved only 2 to 3 hours after administration of rectal acetaminophen. However, Gaudreault, *et al* (1988) found that rectal administration of acetaminophen at the induction of anaesthesia results in incomplete and delayed absorption and does not prevent the occurrence of immediate post-operative pain in children.

Barden *et al* (2004) found single doses of acetaminopehen to be effective for acute post-operative pain. Hamalainen *et al* (1997) found acetaminophen to be effective in the treatment of severe or moderate migraine attacks in children. Ho and Keneally (2000) in a study on the effectiveness of paracetamol as analgesia in the recovery room and at home, found that children aged 1 to 13 years who had herniotomy had been adequately treated, but paracetamol was not effective as analgesia in children undergoing orchidopexy as they had to be supplemented with stronger analgesics. Tay and Tan (2002) found similar analgesic efficacy of paracetamol 15 mg/kg with oral diclofenac resinate 0.5 mg/kg for control of post-operative pain in paediatric patients undergoing outpatient bilateral myringotomy and tube insertion.

Bennie *et al* (1997) compared the post operative analgesic effect of pre-operatively administered oral acetaminophen 15 mg/kg in children aged 6 months and older undergoing myringotomy and found it to be ineffective, and patients needed rescue analgesics. Watcha *et al* (1992) studied the perioperative effects of oral acetaminophen in children undergoing bilateral myringotomy and found it did not provide better post-operative control. In another RCT of children undergoing ambulatory otolaryngologic surgery Watcha, *et al* (2003) found the analgesic efficacy of oral acetaminophen (2 g) was limited to the post discharge period.

Bolton, *et al* (2002) studied the analgesic efficacy of pre-operative high dose (40 mg/kg) oral acetaminophen after bilateral myringotomy and tube insertion in children aged between 17 to 72 months found that in-hospital analgesic efficacy was 87% and the children did not require further analgesics. However, they found the 24-hour efficacy of acetaminophen was only 57% as the children required further acetaminophen. Kokki, *et al* (2004) found that paracetamol did not provide sufficient analgesia when given to children aged 3 to 15 years who had undergone strabismus surgery as most of them required rescue analgesia. Acetaminophen was not found to ameliorate either the intra-operative or the immediate post-operative pain of circumcision but Howard *et al* (1994) state it may provide some benefit after the immediate post-operative period. Shah, *et al* (1998) found that oral acetaminophen does not reduce the response to pain due to heel-lance procedures in newborns. Pappas, *et al* (2003) in a prospective randomised trial found that plain acetaminophen 10 mg/kg orally or acetaminophen 10 mg/kg with 1 mg/kg codeine orally was not the best analgesic regimes for children undergoing ambulatory surgery for myringotomy and placement equalization tubes. Similarly, Moir, *et al* (2000) found that there was no difference in the level of pain control provided by acetaminophen and acetaminophen with codeine.

Moore, *et al* (2004) found the addition of codeine 60 mg to paracetamol produced additional pain relief for post-operative pain, compared to paracetamol alone. However, they cautioned that it may be accompanied by an increase in drowsiness and dizziness. Di Craen *et al* (1996) found the combination of paracetamol-codeine to be more effective than paracetamol alone. Viitanen *et al* (2003) found that prophylactically administered rectal acetaminophen combined with ibuprofen does not improve analgesia after adenoidectomy in the immediate post-operative period compared with either drug alone, but does decrease the need for analgesia at home. Issioui *et al* (2002) found that pre-medication with rofecoxib (50 mg) was significantly more effective than acetaminophen (2 gm) in reducing the peak post-operative pain, the need for analgesic medication, and improving the quality of recovery and patient satisfaction.

b. Non-Steroidal Anti Inflammatory Drugs (NSAIDs)

NSAIDs are stated to be effective analgesics in the management of mild to moderate post-operative pain in children (Romsing and Walther-Larsen, 1997; Litalien and Jacqz-Aigrain, 2001). NSAIDs are found to be useful for post-operative pain management because of its dual effect on pain and inflammation (Kokki, 2003).

Ibuprofen

Maunuksela, Ryhanen and Janhunen (1992) studied the efficacy of rectal ibuprofen 40 mg/kg in 24 hours given in divided doses in children aged 4 to 12 years undergoing ophthalmic, orthopaedic or general surgery. The first dose was given pre-operatively and subsequent doses given for up to 3 days. They reported that the regular administration of ibuprofen decreased the need for opioid analgesic and improved pain relief on the day of operation and during recovery. Kokki, *et al* (1994) studied the efficacy of rectal ibuprofen 10 mg/kg in children aged 1 to 4 years undergoing elective umbilical surgery. The first dose was administered pre-operatively and the dose was repeated every 6 hours resulting in 40 mg/kg per 24 hours. They found that ibuprofen significantly reduced pain intensity scores and significantly reduced morphine consumption. However, they state that ibuprofen alone may not be sufficiently potent for the relief of immediate post-operative pain as it only provided effective analgesia in 40% of the patients.

A meta-analysis by Perrott, *et al* (2004) showed that single doses of ibuprofen (4 to 10 mg/kg) have similar efficacy to acetaminophen (7 to 15 mg/kg) for relieving moderate to severe pain. Autret-Leca (2003) state that ibuprofen is equally as effective as or more than paracetamol as an analgesic and has a longer duration of action. Hamalainen, *et al* (1997) report that ibuprofen is effective for the treatment of severe to moderate migraine attacks in children aged 14 to 15.8 years. When compared to acetaminophen, they state ibuprofen gave the best relief.

Viitanen, *et al* (2003) found that rectal ibuprofen 15 mg/kg alone given immediately after anaesthetic induction does not improve analgesia in the immediate post operative period after day care adenoidectomy in children aged 1 to 6 years. However, they state when given in combination with rectal acetaminophen 40 mg/kg the need for analgesia at home is decreased.

Tanabe (2002) found that oral ibuprofen 10 mg/kg alone was not an effective analgesic for children with musculoskeletal trauma. Bennie *et al* (1997) studied the effectiveness of pre-operatively administered oral ibuprofen 10 mg/kg in children aged 6 months or older who underwent myringotomy and reported it was of no benefit.

Diclofenac

A study on oral diclofenac, four studies on rectal diclofenac and a study on topical diclofenac found diclofenac to be an effective analgesia for children undergoing surgery.

Walters *et al* (1988) in a RCT involving 75 children, aged 5 to 12 years undergoing tonsillectomy done found that oral diclofenac was an effective analgesic compared to pethidine. Wennstrom and Reinsfelt (2002) studied 50 ASA class I-II children, 4 to 16 years of age who were randomised to receive either rectally administered diclofenac (Voltaren) 1 mg/kg or IV opioid (morphine) 0.05 mg/kg peri-operatively and found diclofenac to be more effective than morphine.

Sylaidis and O'Neill (1998) found twice daily diclofenac rectal suppositories provided very good analgesia in children 6 months to 9 years of age following cleft palate surgery. When combined with supplemental oral paracetamol they found that it obviates the need for opiates, resulting in alert infants who feed well and are suitable for early discharge. Baer *et al* (1992) compared rectal diclofenac (12.5 mg) administered pre-operatively with paracetamol (125 mg) on post-operative pain and behaviour after adenoidectomy in small children, and found diclofenac to be effective analgesia. A comparative study of diclofenac sodium and paracetamol for treatment of pain after adenotonsillectomy in children aged 3 to 14 years by Tawalbeh, Nawasreh and Husban (2001) showed that diclofenac sodium has a significant effect on decreasing the pain associated with swallowing post-operatively and on the general condition of the patient.

Morton, *et al* (1997) compared the use of diclofenac and oxybuprocaine eyedrops for peri-operative analgesia in paediatric patients undergoing strabismus surgery, and found both topical analgesics provided good to excellent analgesia. Bone and Fell (1988) in a study on the effectiveness of rectal diclofenac 2 mg/kg was with intramuscular papavertum 0.2 mg/kg in the prevention of pain and restlessness after induction of anaesthesia in 60 children aged between 3 to 13 years undergoing tonsillectomy, found them to be comparable. However, the use of rectal diclofenac was associated with a significantly more rapid return to calm wakefulness and significantly less effect upon respiratory rate.

Romsing, *et al* (2000) in a RCT involving 48 children, 5 to 15 years of age following tonsillectomy compared the efficacy of diclofenac 2 - 3 mg/kg per 24 hours and acetaminophen 90 mg/kg per 24 hours for the first three days after surgery, found similar efficacy. However, they found it resulted in a lower incidence of nausea and vomiting in patients following tonsillectomy.

McGowan, *et al* (1998) studied 61 children having day case circumcision, comparing penile block, penile block plus diclofenac suppository and diclofenac suppository alone, and found no difference among the three, except in the recovery area when those on diclofenac suppository alone cried more and had a higher pain score than those who had penile block plus diclofenac suppository.

A comparison between caudal bupivacaine and intramuscular diclofenac sodium on post-operative pain relief by Ryhänen *et al* (1994) found that children aged from 11 months to 7 years who were given diclofenac needed less pethidine than those who were given no analgesic pre-operatively. However, caudal bupivacaine was more effective than diclofenac for reducing the total opioid requirement during the first 24 hour after surgery.

Ketorolac

A single intravenous dose of ketorolac 1 mg/kg administered either before or immediately after surgery was found to improve post-operative analgesia in children after tonsillectomy (Romsing, 1998). Maikler (1998) who reviewed 22 studies done on children from newborn to 21 years found ketorolac was superior to placebo in 2 placebo-controlled studies. However, there was no conclusive evidence found for ketorolac in relation to other analgesics including morphine.

A prospective, randomised, observer blinded study of 120 children undergoing bilateral myringotomy and tube placement, showed ketorolac to provide superior analgesia compared with acetaminophen with codeine or plain acetaminophen (Pappas *et al*, 2004). In an RCT, Shende and Das (1999) found ketorolac in a dose of 0.9 mg/kg IV at the induction of anesthesia to be as effective as pethidine 0.5 mg/kg IV as an analgesic and is associated with significantly less PONV. Watcha *et al* (1992) found that the children undergoing bilateral myringotomy who received oral ketorolac had lower post-operative pain scores and required less frequent analgesic therapy in the early post-operative period when compared with the children who received acetaminophen or placebo.

Keiden *et al* (2004) found that intra-operative ketorolac is as effective as fentanyl in children undergoing outpatient adenotonsillectomy. An Italian study by Chiaretti *et al* (1997) showed that children treated with ketorolac in continuous infusion showed better pain relief then those treated with ketorolac in bolus. However, they found that the most efficient analgesia was obtained with the combination of fentanyl and ketorolac.

Maunuksela, Kokki and Bullingham (1992) obtained similar pain scores when morphine or ketorolac given to children between 3 and 12 years of age undergoing elective surgery. They found that the analgesic effect after ketorolac developed more slowly but was sustained longer than morphine. Rusy *et al* (1995) found that ketorolac has the same efficacy as high-dose rectal acetaminophen for analgesia in patients undergoing tonsillectomy.

No studies of the effectiveness of ketorolac to reduce pain in neonates were found.

Ketoprofen

Only two studies were found on the effectiveness of ketoprofen amongst the paediatric population. *Kokki, Nikanne* and *Tuovinen* (1998) in a dose finding study found that the post-operative analgesic effect in children aged 1 to 7 years, undergoing adenoidectomy was notable even after the lowest dose of ketoprofen (0.3 mg/kg IV). However, the higher doses (1.0 and 3.0 mg/kg) provided better analgesia with no increase in adverse events or intra operative bleeding. Salonen, Kokki and Nuutinen (2002) studied the effect of ketoprofen on recovery after tonsillectomy in children and reported that ketoprofen when combined with paracetamol-codeine seems to provide sufficient analgesia for pain treatment after discharge.

c. Opioids

Morphine

Morphine is the most commonly used opiate (Schecter *et al*, 2002; Rodriguez & Jordan, 2002). It is often used in the intravenous form, but is also available for oral, rectal, parenteral, intrathecal and epidural use. Morphine can be given IV, IM, or SC at doses of 0.08 to 0.1 mg/kg increments every 5 to 10 minutes for the desired effect. Peak effect occurs 15 to 30 minutes after IV administration and in 30 to 60 minutes after IM administration (Rodriguez & Jordan, 2002).

A retrospective study of 44 children aged 14 months to 17 years who had undergone cardiac surgery and received continuous infusion of morphine sulphate at 10 - 30 µg/kg found it provided pain relief without respiratory depression at serum morphine level less than 30 çg/mL (Lynn, Opheim & Tyler, 1984). Bouwmeester *et al* (2001) stated that morphine infusions during the post-operative period of intubated children aged 0 to 3 years undergoing major surgery was associated with low behavioural pain scores. A RCT by Kim *et al* (2002) on children aged 5 to 18 years admitted in the Emergency Department with abdominal pain found that intravenous morphine provided significant pain reduction to these children without adversely affecting the examination.

Wennstrom and Reinsfelt (2002) compared rectally administered diclofenac with morphine in children after strabismus surgery, and found no difference in pain scores. Semple *et al* (1999) comparing morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy, found no significant differences in pain scores, analgesic requirements or sedation scores between the two groups over the following 24 hours. However, with morphine sulphate there was more post-operative vomiting than codeine phosphate. Mukherjee *et al* (2001) compared fentanyl and morphine as peri-operative analgesia in children undergoing adenotonsillectomy, found that administration of rescue anti-emetics pain scores in recovery and pain scores over the next 24 hours were similar between the two groups. Rosen *et al* (2001) compared IV Morphine (0.1 mg/kg up to 10 mg IV 30 min before CTR) with topical EMLA cream (5 g per chest tube cutaneously 3 hours before CTR) in thoracostomy tube removal in children aged 1 month to 18 years found no differences in the pain score.

Three studies of continuous morphine infusion in neonates showed it to be effective in controlling post-operative pain. Farrington (1993) studied the efficacy and safety of morphine sulphate in 20 neonates and state that continuous morphine therapy was effective in controlling neonatal post-operative pain. Berde and Sethna (2002) found that morphine infusions during the post operative period in intubated neonates were associated with low behavioural pain scores. Anand *et al* (2004) studied morphine analgesia on ventilated preterm neonates and found less clinical signs of pain, but significant adverse effects.

Fentanyl

Fentanyl provides analgesia with a rapid onset and short duration of effect, although with repeated dosing or prolonged infusions, it becomes longer acting (Shafer & Varvel, 1991; Santeiro *et al*, 1997). It has been found to be the ideal analgesic for short, painful procedures (Rodriguez & Jordon, 2002) and well suited for outpatient surgery (Schecter *et al*, 2002). Manjushree *et al* (2002) found both intranasal and intravenous fentanyl provide adequate post-operative analgesia in pediatric patients, although the former required a higher drug dosage with slower onset of analgesia.

In a prospective RCT on 52 children randomly assigned to receive intravenous ketorolac and/or fentanyl, according to four different analgesic treatments, Chiaretti *et al* (1997) found the combination of ketorolac with fentanyl favourable for moderate to severe post-operative pain therapy. Mukherjee *et al* (2001) in a

study of 60 children undergoing adenotonsillectomy comparing IV fentanyl 1 µg/kg intra-operatively and IM morphine 100 µg/kg at induction, found similar pain scores in recovery and over the subsequent 24 hours. Another RCT by Saarenmaa *et al* (1999) on 163 infants, gestational age of 24 weeks and more, found fentanyl to be superior to morphine for short-term post-natal analgesia in newborns.

Two studies showed that oral transmucousal fentanyl citrate was effective for acute pain relief. Sharar *et al* (2002) compared oral transmucosal fentanyl citrate (OTFC, approximately 10 µg/kg) and oral oxycodone (0.2 mg/kg) in 22 pediatric outpatient wound care procedures (ages 5 to14 years) and concluded that OTFC was an effective analgesic. Ginsberg *et al* (1998) studied children aged 4 to 12 years undergoing surgery, who were given a 10 µg/kg oral (OTFC) and instructed to suck the OTFC until pruritis appeared or until the entire dose was consumed, found it effective without causing clinically significant changes in vital signs or oxygen saturation.

Borland, Jacobs and Geelhoed (2002) found intranasal fentanyl reduced acute pain in children between 3 and 12 years in the emergency department. Galinkin, *et al* (2000) studied the use of intranasal fentanyl in children undergoing myringotomy and tube placement during halothane and sevoflurane anesthesia, concluded that it was associated with diminished post-operative agitation without an increase in vomiting, hypoxemia, or discharge times.

Mendell *et al* (1995) studied 54 ASA I and II children 1 to 10 years of age under-going strabismus surgery who were randomised to receive in a double-blind fashion IV ketorolac (0.9 mg/kg), fentanyl (1 µg/kg), or saline placebo (2 mL) during a standardized general anesthetic. They concluded that fentanyl was not associated with less analgesic requirements compared to saline placebo administered, and advised that fentanyl be avoided, as it was associated with a significantly greater incidence of post-operative vomiting compared to ketorolac or placebo.

Keidan, *et al* (2004) in an RCT of 57 ASA I and II children aged 1.71 years undergoing outpatient adenotonsillectomy found no difference between IV ketorolac (1 mg/kg) or fentanyl (2 µg/kg) for post-operative pain control.

Patient Controlled Analgesia (PCA) is the primary mode of management of moderate to severe pain in older children and adolescents. According to Kost-Byerly (2002) children are often less anxious when they feel they have control over their pain. Morphine is the standard opioid agonist for paediatric PCA (Gillepsie *et al*, 1992). Gaukroger, Tomkins and van der Walt (1989) reported that PCA was effective for children who had undergone major orthopaedic or general surgery. Gaukroger, Chapman and Davey (1991) concluded that PCA provided good quality analgesia to children whose ages range from 4.75 to 14 years with severe burns requiring debridement and grafting. Till *et al* (1996) evaluated the feasibility of PCA following laparoscopic and open appendicectomy in 90 children and concluded that PCA is an effective and feasible method, and that consumption of analgesics was significantly reduced with PCA.

Shin *et al* (2001) found intravenous PCA to be effective for pediatric patients who have moderate to severe pain after operations such as rib cartilage graft, iliac bone graft, and large flap surgeries. An Italian study undertaken by Marchetti, Calbi and Villani (2000) also found PCA to be effective in controlling post-operative pain. McDonald and Cooper (2001) state that PCA when used with adequate monitoring is a well tolerated technique with high patient and staff acceptance and recommend PCA to be regarded as a standard for the delivery of post-operative analgesia in children aged above 5 years.

Four studies compared PCA with conventional method of using morphine. Rodriguez, *et al* (1997) compared PCA and conventional intravenous analgesia given every 6 hours following surgery in 30 patients aged 6 to 14 years and found both techniques had similar effects. They found the PCA technique to be better in treating post-operative stress response following paediatric surgery. However, Peters, *et al* (1999) found no significant difference in pain scores between PCA and conventional intravenous analgesia using morphine. According to Berde *et al* (1991) and Bray *et al* (1996) children who use PCA have better pain relief with less sedation and report higher levels of satisfaction than patients who received intermittent boluses of intravenous morphine.

A Spanish study by Moreno, Castejon and Palacio (2000) compared PCA and conventional method dispensed with Ketorolac IV and found both methods equally effective but the efficiency was higher in the PCA group.

d. Local Anaesthetic Agents

Lidocaine-prolocaine cream

A meta-analysis by Taddio (1997) showed that EMLA diminishes pain during circumcision but not for other procedures such as heel lancing, venepuncture, arterial puncture and PVC placement. However, Lander *et al* (2003) found EMLA to be effective in reducing procedure-related pain in venapuncture, intravenous cannulation, lumbar puncture and bone marrow aspiration, when applied to the skin one hour prior to the procedure. Choi *et al* (2003) in a prospective RCT found pre-operative application of EMLA cream to be an effective and simple method to produce post-circumcision analgesia. In an earlier study Lander, *et al* (1997) found EMLA to be less effective than ring block.

6.2.2 Non-Pharmacological Agents

a. Behavioural Interventions

Multisensory stimulation

An RCT on multi-sensorial stimulation showed that sensorial stimulation (tactile, vestibular, gustative, olfactory, auditory, visual) was an effective analgesic for heel prick in pre-term infants compared to glucose plus sucking (Bellieni, 2001).

Non-nutritive sucking (with pacifier)

Sucrose and pacifier

Three small RCT suggested that the combination of sucrose and pacifier is more effective than sucrose alone in term infants during heel prick (Blass *et al*, 1999), venepuncture (Carbajal *et al*, 1999) and circumcision (Herschel *et al*, 1998).

Glucose and pacifier

A study in preterm infants less than 32 weeks gestation for subcutaneous injection showed that the synergistic effect of glucose plus sucking a pacifier is less obvious in very pre-term infants than term infants (Carbajal *et al*, 2002). Another study by the same author looking at glucose and sucking a pacifier for venepuncture showed the synergistic effect in term infants measuring using both DAN (Douler Aigue Nouveau-ne) and PIPP score (PIPP score is a validated score looking at behavioral and physiological pain indicators together whereas the DAN scale has not been validated although that it can grade the degree of perception of pain) (Carbajal *et al*, 2003).

Breast feeding
2 studies showed that breast feeding is an effective analgesic in term-infants undergoing venepuncture (Carbajal *et al*, 2003) and heel prick (Gray *et al*, 2002).

Skin-to-skin contact
A study on skin-to-skin contact as an analgesic in term-infants undergoing heel prick by Gray, *et al* (2002) did not have enough evidence of its effectiveness as other comforting measure were inadvertently introduced by mothers e.g. speaking and making clicking noises.

b. Cognitive Interventions

Distraction
Distraction interventions can vary from simple things that can be manipulated such as the kaleidoscope to other distraction techniques such as music, cartoon movies, blowing air, blowing bubbles and touch.

Kaleidoscope
According to Vessey, Carlson and McGill (1994) who used kaleidoscope as a distraction technique, children perceived less pain and demonstrated less behavioral distress then the control group who received comfort by physical touch and soft voices. However, a study by Carlson, Broome and Vessey (2000) showed that the use of kaleidoscopes did not significantly reduce pain or distress during venapunctures or IV insertions.

Blowing Out Air
An RCT on 149 children by French, Painter and Coury (1994) found children who were taught to blow out air during their immunisation shots had significantly fewer pain behaviour and demonstrated a trend toward lower subjectively reported pain. Peretz and Gluck (1999) found deep breathing and blowing out air was an effective distracting technique prior to and during the administration of local anaesthetic in patients undergoing dental procedures.

Bubble Blowing
Sparks (2001) found that encouraging children needing DPT immunisation to blow bubbles decreased pain effectively.

Touch
Sparks (2001) also found touching children as a form of distraction helped to decrease the effect of injection pain during DPT immunisation.

Music
Berlin (1998) found that music therapy was effective for children undergoing invasive procedures in the emergency department. However, Aitken *et al* (2002) found music as a distraction was not effective for children ages 4 to 6 years undergoing restorative dentistry.

Fowler-Kerry and Lander (1987) also found combining suggestion and music distraction did not further enhance pain relief compared to use of distraction alone. However, they state age as an important determinant of the success of distraction.

Cartoons
Cassidy *et al* (2002) used audiovisual distraction on pre-school children who were receiving their immunisation and found watching cartoons did not distract children during needle injection nor reduce their pain. Landolt *et al* (2002) also found that cartoon movies were not sufficiently powerful in reducing burned children's distress during dressing changes.

6.2.3 Other Modalities

Sucrose

A meta-analysis by Steven, Yamada and Ohlsson (2001) showed that sucrose is effective for reducing procedural pain in neonates from single heel lance or venepuncture. The reviewers recommend the routine use of sucrose 0.012 - 0.12g to be administered approximately 2 minutes prior to single heel lance or venpunctures for pain relief in neonates. Three other small RCT also showed that sucrose to be effective as an analgesic (Ors *et al* 1999; Blass *et al* 1999; Carbajal *et al* 1999). However, the effective dose was found to vary in all the studies.

Glucose

Two studies suggest that concentrated glucose may be an effective analgesic for heel prick (Skosgdal, *et al* 1997) and venepuncture (Deshmukh, *et al* 2002) in term infants. However the two individual studies were small. Kass and Holman (2001) reported that glucose is ineffective in circumcision.

Artificial sweetener (cyclamate [10 parts] + saccharin [9 parts])

A study on artificial sweetener on heel prick in 80 term infants, age 4 days old suggested that it was an effective analgesic (Bucher *et al*, 2000).

6.3 Pain Assessment

6.3.1 Pain assessment tools

Infants display behavioural responses to painful stimuli and nurses use these as behavioural cues to help them identify children in pain. Three cross-sectional studies (Fuller & Conner, 1995; Rushforth, 1994; Grunau *et al*, 1990;) and a RCT (Taddio *et al* 1995) identified the key indicators of children's pain as the including: square, angular mouth shapes, chin quiver, closed eyes, funnel concave tongue, parted lips and stretched brow bulge, eye squeeze, nasolabial furrow and open mouth. Behavioural indicators have in common, changes in a child's behaviour such as crying, facial expressions, motor responses, body posture, activity, undue quietness, restlessness and appearance, and based on these behavioural indicators, pain assessment tools have been developed. Tesler *et al* (1991) indicates whatever scale used must be appropriate for the cognitive development of the child.

- *Premature Infant Pain Profile (PPIP)*

PPIP is a 7 indicator composite measure developed to assess acute pain in pre-term and term infants (Stevens, 1990). Nurses who implemented the flow sheet had patients who were assessed for pain more frequently and received more narcotic analgesics. Ballantyne (1999) validated the tool and reported that PPIP is a pain measure with good construct validity and excellent inter- and intra-rater reliability for assessment of procedural pain of pre-term and term infants in the clinical setting.

- *Neonatal Infant Pain Scale (NIPS)*

The Neonatal Infant Pain Scale (NIPS) is based on the measurement of facial expression, cry, breathing patterns and state of arousal. According to Lawrence, Alcock and McGranth (1993) the concurrent validity by correlation between NIPS scores at each minute of observation and scores on visual analogue scale, ranged from 0.53 to 0.84. Inter-rater reliability of the tool is stated to be high with Pearson's correlation ranging from 0.92 to 0.97 across successive minutes of observation.

Pereire *et al* (1999) found NIPS to be a suitable instrument for neonatal pain. Blauer (1998) compared NIPS with two other neonatal pain scales, the comfort scale and the SUN, and found that NIPS had a significantly larger coefficient of variation (CV 188% + 99%), and less easy to use compared to the SUN.

- *Neonatal Facial Coding System (NFCS)*

The Neonatal Facial Coding System *(*NFCS) is an anatomically based system for assessing facial expression (Grunau, 1990). According to Pereire *et al* (1999), the NFCS is a suitable instrument for evaluation of neonatal pain.

- *Crying Requires Oxygen for saturation above 95, Increased vital signs, Expression and Sleeplessness (CRIES*)

Crying Requires Oxygen for saturation above 95, Increased vital signs, Expression and Sleeplessness (CRIES) is a tool that is easy to remember, and can be used for procedural and post-operative pain assessment in infants aged 1 to 12 months. It tracks pain and the effects of analgesics in neonates down to 32 weeks gestational age. According to Krechel and Bildner (1995), the tool has inter- and intra-rater reliability of more than 0.72. However, the disadvantage of this tool is that, oxygenation can be affected by many other factors, and also, blood pressure measurements may upset babies.

- *The Liverpool Infant Distress Scale (LIDS*)

The Liverpool Infant Distress Scale (LIDS) is a scoring measure developed from analysing videotaped pain behaviours (Horgan & Choonaran, 1996). This tool is still under development.

- *Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)*

Children's Hospital of Eastern Ontario Pain Scale (CHEOPS*)* was used by Taddio *et al* (1994), to study vaccination pain in infants. They found the inter-rater reliability of the CHEOPS to be above 90% and correlations between individual and total scores to range from 0.50 - 0.86. In another study Taddio *et al* (1995) used CHEOPS to study pain in 96 healthy infants aged 4 - 6 months undergoing immunisation, and found that the tool has beginning construct and concurrent validity and inter-rater reliability. However, they suggest further testing of the measure in clinical settings to ensure its validity and reliability.

- *The Faces, Legs, Activity, Cry and Consolability (FLACC*)

The Faces, Legs, Activity, Cry and Consolability (FLACC) pain assessment scale had its validity tested by Manworren and Hynan (2003) in 147 hospitalized children aged less than 3 years, where the changes in scores were measured in response to analgesics. They found the FLACC pain assessment tool appropriate for pre-verbal children for pain from surgery, trauma, cancer and other diseases. Voepel-lewis and Merkel (2002) found FLACC a useful objective measure of post-operative pain in children.

- *Toddler Preschooler Post-operative Pain Scale (TPPPS)*

The reliability and validity of Toddler Preschooler Post-operative Pain Scale (TPPPS) was evaluated by Tarbell (1992) in 74 children aged 1 to 5 years. She found TPPPS to possess satisfactory internal reliability (Cronbach's alpha = 0.88) and good inter-rater reliability.

- *Faces Pain Scale*

The utility of the Faces Pain Scale was studied by Goodenough (1997), who compared it with 3 self-reported measures of pain intensity in 50 children 4 to 6 years old receiving intramuscular injection. She found the scale was simple to use, readily understood by the children and that it showed a realistic distribution of scores with respect to the type of pain being measured.

- *Self-reported Tools*

Self-reported tools have been found to be more appropriate for children 4 years and older, who can communicate (van Cleve & Savendra, 1993). It is considered the "gold standard" for assessing children's pain (Mc Grath *et al*, 1996). Palmero and Drotar (1996) found that childrens' self-reports provide information

on which health professionals may reliably predict post-operative pain. According to the US Agency for Health Care Policy & Research (1992), children over the age of 7 or 8 years, who understand the concept of order and numbers, can use a numerical rating scale or a horizontal word graphic rating scale. Gafne and Dunne (1986) and Savendra *et al* (1993), found children of school-going age capable of providing graphic descriptions of their pain. Tesler *et al* (1991) report strong evidence to support the use of word-graphic rating scale to measure pain intensity in children aged 8 to 17 years.

- *Coloured Analogue Scale (CAS)*

Coloured Analogue Scale (CAS) has been recommended by McGrath *et al* (1996) in children aged 5 years and above to facilitate regular documentation of a child's pain. The traditional VAS (see below) for routinely assessing children's pain, with black lines drawn on paper, may be a hassle, since the staff must measure the child's response using a ruler. However, although the CAS has been rated to be easier to use, its construct validity has yet to be ascertained.

- *Visual Analogue Scale (VAS)*

Visual analogue scales (VAS) have been used in children aged 8 years or more to assess pain (Berde & Sethna, 2002). Berde *et al* (1991), McGrath (1991), and Abu Saad (1984), state that children as young as 5 years of age are able to use the VAS, in which they mark a line where its length matches the strength of their perception of pain. Price *et al* (1983, 1991) and McGrath *et al* (1985) found that VAS pain measures has ratio-scale properties that can provide accurate estimates of ratios of pain intensity and percentage of changes in pain. However, Fradet *et al* (1990) and Tyler *et al* (1993), claim that it is less useful in younger children (3 to 8 years old) compared to older children or adults. A much better tool for these children are said to be the TPPPS (Tarbell *et al*, 1992) and CHEOPS (McGrath *et al*, 1985; Barrier *et al*, 1989).

6.3.2 Subjective assessment

A number of studies indicate the importance of children's' families, especially parents, identifying their children's pain behaviour (Coffman *et al*, 1997; Chambers *et al*, 1996; Finely *et al*, 1996; Wilson & Doyle, 1996; Reid *et al*, 1995). A positive correlation was found between mothers' perception of pain and the behavioural and physiological responses of children to painful stimuli (Stein, 1995).

However, some studies have also indicated that children's estimate of pain can differ from that of their parents (Palmero & Drotar, 1996; Jylli & Olsson, 1995) and parents may not be as accurate as their children in describing the pain (Wilson & Doyle, 1996).

6.4 Cost Effectiveness

No relevant literature on cost implications of pharmacological and non-pharmacological interventions was obtained.

7. CONCLUSIONS

7.1 Pharmacological agents

a. Acetaminophen (Paracetamol)

There is sufficient evidence to show that risk of developing toxic reactions to acetaminophen when used at therapeutic doses, is minimal, although it is hepatotoxic with inappropriate or excessive dosing, impaired liver function, ingestion of acetaminophen together with another hepatotoxic drug, as well as with rectal administration, which may produce high peak drug levels.

There is good evidence on the effectiveness of paracetamol in providing acute post-operative pain control in various surgical procedures, whether given pre-operatively or in the immediate post-operative period. Rectal acetaminophen has not been to be effective in controlling pain satisfactorily. Evidence also shows that combining paracetamol with other analgesics like codein, diclofenac, ibuprofen or rofecoxib does not provide superior pain control compared to using paracetamol alone.

b. Non-steroidal anti-inflammatory agents (NSAIDs)

Nausea and vomiting are common side effects associated with NSAIDs It may also cause mild to severe homeostasis defects peri-operatively. There is sufficient evidence to show that ibuprofen, diclofenac, ketorolac and ketoprofen are reasonably safe. There is also evidence that they are effective in relieving immediate post-operative and during recovery for various ophthalmic, ear, nose and throat surgical procedures that are administered through various routes i.e. oral, intravascular, intramuscular, rectal or topical.

c. Opoids

There is evidence that opoids can cause hypotension and respiratory depression in high doses. Fentanyl has been found to cause fewer side- effects compared to morphine. There is also sufficient evidence to show that opiods are potent analgesics for moderate to severe pain. Their sedative and analgesic effects are dose dependent. There is sufficient evidence that morphine and fentanyl are effective for relief of moderate to severe pain post-operatively in various surgical procedures like ophthalmic, ENT, cardiac procedures, and procedures carried out during the neonatal period Evidence also shows that the synthetic opiod, fentanyl, is 100 times more potent than morphine, and is effective for out-patient procedural care either in the out-patient setting or emergency department, due to its rapid onset and short duration of action. It is also effective for acute pain relief by administration through transmucosal and intra-nasal routes. Patient controlled analgesia has also been found to be effective for the management of moderate to severe pain post-operatively in older children and adolescents.

d. Local anaesthetic agents

Most evidence indicates that Lidocaine-prolocaine cream is safe as topical analgesia for pain associated with circumcision and medical procedures such as venepuncture. However, there is a risk of methemoglobinemia particularly in premature infants as well as term infants aged less than 3 months. It is effective for reducing pain during circumcision but the evidence of its effectiveness for analgesia in medical procedures is inconclusive.

7.2 Non-pharmacological modalities

a. Behavioural Interventions

There is evidence that skin-to-skin contact is a safe intervention against pain in the newborn, but there is insufficient evidence on its effectiveness. As for the other behavioural interventions, there is also insufficient evidence on their effectiveness.

b. Cognitive interventions

There is limited evidence on the effectiveness of cognitive behavioural interventions to reduce pain stimuli.

7.3 Other modalities

a. Sucrose

Evidence shows that sucrose has minimal side effects. is a safe and effective intervention against procedural pain in the term newborn. Preterm infants may be risk if repeatedly used.

b. Glucose

There is some evidence that glucose is a safe intervention against pain associated with minor procedures in neonates, but findings on its effectiveness were inconclusive.

c. Artificial sweetener

There is insufficient evidence on its effectiveness.

There was no available evidence on the cost benefits of pharmacological and non-pharmacological interventions.

7.4 Assessment tools

There are several pain assessment tools that can be used to measure pain in the different age groups i.e. pre-term infants, infants, neonates, infants and children. Children's families, especially parents, are important in identifying children's behaviour in response to painful stimuli though these may not be as accurate as that of the child.

8. RECOMMENDATIONS

a. Pharmacological agents like acetaminophen, NSAIDs like ibuprofen, diclofenac, ketorolac and ketoprofen, and opiods like fentanyl are safe and effective analgesics for use in various surgical procedures that produce mild, moderate and severe painful stimuli. However, the side effects of these need to be taken into consideration with constant monitoring carried out.

b. Pain assessment tools taking into consideration parents' assessment and/or child's self report can be used to measure pain.

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SEARCH STRATEGY: RATIONAL USE OF ANALGESICS IN PAEDIATRICS

The search sought to identify both published and unpublished studies. There was no limitation to language. Studies were limited to human subjects from 0-18 years of age.

1. Analgesics – pharmacological

Databases searched were PubMed / Medline, Austhealth, CINAHL, Biosis, Embase, The Cochrane Library, hotboot, PsycLit, Database of Abstracts of Reviews and Googles from 1980 to 2004. Handsearch of journals not included in the electronic database were also searched.

The following were the keywords used either singly or in combinantion – analgesic(s), pain, management, treatment, post operative, procedure, venesection, intravenous cannula, bone marrow aspiration, lumbar puncture patient controlled analgesics, analgesia, analgesic drugs, acetaminophen, paracetamol, NSAIDs, Ibuprofen, ketorolac, ketoprofen, opioids, morphine, fentanyl, emla cream, paed*, paediatric(s), child*, neonate, infant, juvenile, efficacy, effectiveness, adverse effects, side effects, safety,cost- benefit and cost effectiveness.

2. Analgesics – non-pharmacological

Databases searched were PubMed / Medline, Austhealth, CINAHL, Biosis, Embase, The Cochrane Library, hotboot, PsycLit, Database of Abstracts of Reviews and Googles from 1980 to 2004. Handsearch of journals not included in the electronic database were also searched.

The following were the keywords used either singly or in combinantion – pain, child*, children, paed*, paediatrics, neonates, infants, treatment, management, analgesics, , non pharmacological, distraction, music, cartoons, art, kalediscope, blow-bubbles, post operative, procedure, venesection, intravenous cannula, bone marrow aspiration, lumbar puncture, effectiveness, adverse effects, safety, cost-benefit and cost-effectiveness.

3. Pain assessment

Database searched were Embase, CINAHL and Medline /Pub Med from 1980 to 2004 using the following key words or terms: **"***pain assessment"*, "*pain scores*", child*, children, paed*, paediatrics, neonate and infants.

LEVELS OF EVIDENCE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Fair	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT, (CAHTA) SPAIN