Ketoprofen in Tonsillectomy and Adenoidectomy With Special Reference to the Effects on Surgical Time, Postoperative Pain, Adverse Events and Recovery After Surgery

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium, Kuopio University Hospital, on Friday 6th September 2002, at 12 noon

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ABSTRACT

The first aim of this study was to evaluate the effect of iv ketoprofen on operation time and length of hospital stay in 1-9 years old children undergoing adenoidectomy. Secondly, to evaluate the efficacy and safety of iv ketoprofen for pain treatment administered either before or after tonsillectomy in adults and in children. Thirdly, to evaluate severity and duration of postoperative pain and recovery after discharge following tonsillectomy in adults and in children. Finally, to evaluate the efficacy and safety of ketoprofen in pain treatment after discharge following tonsillectomy in adults and in children.

A total of 550 patients were investigated. Patient group A; 335 children underwent elective adenoidectomy in Kuopio University Hospital. Patient group B: 106 adults underwent elective tonsillectomy. Patient group C; 109 children underwent elective tonsillectomy. Treatment in patient group A was the following: subgroup I (n=99): ketoprofen 2 mg/kg and normal saline; subgroup II (n=107): ketoprofen 0.5 mg/kg and 2.0 mg/kg; subgroup III (n=129): ketoprofen 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg and normal saline. Medication was administered iv after induction of anaesthesia. Medication in the studies II and III was the following: ketoprofen 0.5 mg/kg and normal saline. Ketoprofen was administered iv after induction (pre-ketoprofen group, n= 41 adults, n= 47 children), or iv after operation (post-ketoprofen group, n= 40 adults, n=42 children) followed by iv ketoprofen 3 mg/kg infusion over 24 h. Placebo group (n= 25 adults, n=20 children) received normal saline after induction and after operation followed by normal saline infusion over 24 h. At home all patients were prescribed ketoprofen at the dose of 3-5 mg/kg/day.

Intravenous ketoprofen did not effect operation time nor delay discharge in children undergoing adenoidectomy. In adults, iv ketoprofen proved to have a significant analgesic effect immediately following tonsillectomy. In children, patients in the placebo group received 30% more oxycodone than those in the two ketoprofen groups. This difference was not, however, significant. A pre-emptive effect was not found in adults or in children. Compared to placebo iv ketoprofen did not increase the frequency of adverse events or cause clinically significant bleeding in the hospital. Pain after tonsillectomy was significant and persisted relatively unchanged for the first five days both in adults and in children. Pain lasted on average 11 days in adults and 9 days in children. After discharge ketoprofen alone did not demonstrate sufficient analgesic efficacy, but combined with paracetamol (children 14 years or younger) or paracetamol-codeine (adults and children over 14 years) it provided satisfactory pain relief for most patients. At home ketoprofen did not cause any serious adverse events after tonsillectomy.

In conclusion, within this study, ketoprofen is an effective and safe analgesic for pain treatment after tonsillectomy in adults and in children.

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To

Panu-Arttu, Sofi and Max
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ABBREVIATIONS

ASA  American Society of Anesthesiologists Physical Status Grading
CNS  central nervous system
COX  cyclo-oxygenase
ENT  ear, nose and throat
iv   intravenous
im   intramuscular
NSAID non-steroidal anti-inflammatory drug
PACU post anaesthesia care unit
PG   prostaglandin
SD   standard deviation
TE   tonsillectomy
TEA  tonsillectomy and adenoidectomy
VAS  visual analogue scale
VASr visual analogue scale at rest
VASs visual analogue scale on swallowing
VRS  verbal rating scale
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.


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1. INTRODUCTION

Tonsillectomy is one of the most common ear-, nose- and throat-surgical procedures performed in adults and in children, and in many institutions it is frequently carried out as a short-stay operation.

Morbidity after tonsillectomy is common, and it may delay the discharge and influence the patients’ ability to return to normal activity. Morbidity is most often associated with intense pain, but also poor oral intake, nausea and vomiting. Severe painful dysphagia may also aggravate dehydration, especially in children. Therefore, pain treatment after tonsillectomy should be effective and safe. Compliance is also important, because patients themselves or parents are responsible for analgesic treatment at home.

Despite increasing demands for postoperative well-being, recent studies indicate that treatment of pain after tonsillectomy is often inadequate (Toma et al. 1995, Warnock and Lander 1998). Opioids are widely used analgesics for peri- and postoperative pain. However, these drugs have adverse effects, such as emesis, excessive sedation and risk of respiratory depression, all of which may lead to under-use.

During the last two decades non-steroidal anti-inflammatory drugs (NSAIDs) are increasingly used during surgery and have proved to be effective analgesics to treat mild or moderate postoperative pain (McQuay et al. 1997). NSAIDs are used after tonsillectomy for background analgesia to decrease opioid requirements, but are often not effective enough as sole analgesics. However, the use of NSAIDs during tonsillectomy is controversial. NSAIDs can cause known side effects, such as gastric irritation and renal dysfunction. NSAIDs also prolong bleeding time by inhibiting biosynthesis of thromboxane A2, and can therefore increase blood loss during and after surgery (Kam and See 2000). The clinical significance of increased bleeding is unclear, but if haemorrhage occurs, it increases postoperative morbidity.
Ketoprofen (a NSAID) belongs to the group of phenylpropionic acid derivatives and has been in clinical use since 1973 (Fossgreen 1976). Previous studies indicate that ketoprofen has a good analgesic effect after adenoidectomy in children (Nikanne et al. 1999). The same kind of finding has been reported after tonsillectomy in adults (Tarkkila and Saarnivaara 1999). Moreover, intravenous ketoprofen appeared not only to provide analgesia and reduce opioid requirements, but significantly to decrease some adverse events of pain treatment, for example, vomiting after day case strabismus surgery (Kokki et al. 1999a). Because ketoprofen seems to disturb haemostatic function less than some other NSAIDs it may therefore be safely used during tonsillectomy (Niemi et al. 1997).

The overall purpose of studies included in this work was to evaluate the effect of intravenous (iv) ketoprofen on operation time and length of hospital stay in children undergoing adenoidectomy. The purpose was also to evaluate the analgesic effect and safety of ketoprofen in the treatment of postoperative pain after tonsillectomy and to compare the preoperative and postoperative administration of ketoprofen. Further, the aim was to evaluate the overall recovery after tonsillectomy at home and the safety and efficacy of ketoprofen during this period.
2. REVIEW OF LITERATURE

2.1. Acute pain physiology

Pain is an unpleasant sensation, but it is a protective mechanism of the body received by specialised nerve endings: it may occur when tissues are being damaged. Acute pain is a constellation of unpleasant sensory, emotional, and mental experiences and certain autonomic responses and psychological and behavioural reactions provoked by tissue damage (Bonica 1991). There has been widespread acceptance that for moral, ethical, humanitarian and physiological reasons, pain should be anticipated, and safely and effectively prevented and controlled in all age groups (Morton 1999).

Small myelinated (A-delta) and unmyelinated (C) sensory afferent fibres primarily transmit the nociceptive signals, including pain stimuli, from the site of surgery. At the peripheral inflammatory site, various endogenous analgesic substances are released after injury, including substance P and arachidonic cascade metabolites (prostaglandins, leukotrienes), histamine, and bradykinin. These substances may reduce the nociceptive threshold and facilitate afferent transport (Björkman 1995). In addition, sympathetic efferent reflexes may reduce the pain threshold. The nociceptive signal may induce functional changes within the spinal cord, leading to increased receptive fields and hyperexcitability. At the spinal level, endogenous pain inhibitory pathways from the brainstem may modulate the incoming pain stimuli, the important involved transmitters being noradrenaline, serotonin, and endogenous opioids (Kehlet and Dahl 1993).

In humans, cutaneous injury is followed by alternations in thermal and mechanical sensibility. Primary hyperalgesia refers to changes within the area of injury and secondary hyperalgesia to changes in the undamaged tissue surrounding the injury. Primary hyperalgesia is explained by sensitisation of peripheral nociceptors. A recent series of studies in humans and primates supported the suggestion that secondary
hyperalgesia is caused by altered central processing of mechanoreceptive input from the periphery (Dahl 1994).

2.2. Pain assessment

2.2.1. General aspects

Pain is a personal experience that makes it difficult to define and measure. It includes both the sensory input and any modulation by physiological, psychological and environmental factors. However, reliable pain assessment is the necessity of adequate pain treatment. Because pain is something we feel there are no objective measures for pain and its intensity, and therefore measurements of pain mostly relies on recording the patient’s report. However, there is a large group of patients who are not capable of informing the staff about their pain e.g. during the immediate postoperative period when they are under the effect of anaesthetic agents, or small children (Beyer et al. 1990). Therefore, both expressed and observed pain scales are used in adults and in children.

2.2.2. General aspects in children

Pain assessment is most accurate when the child can tell the staff about his/her pain (expressed pain assessment). It is possible for children as young as 3 years of age to self-report the location and severity of pain using words appropriate to their developmental stage (Morton 1999). The assessment can be trusted when the child has comprehended the use of the scales during the preoperative visit (Maunuksela et al. 1987), but it is not possible to use self-reporting scales in children who lack the ability to follow instructions. This inability may be due to age, disability or temporary confusion by anaesthetic agents (Beyer et al. 1990). Also, for many reasons, children may not ask for pain relief, either because they do not want to disturb the staff or because the remedy is unpleasant or induces adverse effects (Morton 1999).
To pick up the symptoms and signs of pain in the younger child, behavioural cues and physiological values are used from the neonate period up to school age (observed pain assessment). Observation of facial expression, body position and movement, crying, arterial pressure, heart rate, skin colour, oxygen saturation, ventilatory frequency and sleeplessness are all used (Kretchel and Bildner 1995). It is important that staff are trained to detect the symptoms and signs of pain in different age groups and to take a sufficiently broad view of the child to determine if the observations they are making are caused by pain or by other factors (Morton 1999).

A more clinically useful assessment is a dynamic one, where improvement in behavioural and physiological changes is sought in response to comforting, analgesia or sedation (Morton 1999).

In the hospital the accurate assessment of pain in children and medication constitutes a challenge for health professionals. At home, in the case of young children, pain assessment and the need for analgesic treatment are based on judgements made by parents. Some studies have proved a high correlation between the pain assessment performed by a medical observer and by parents (Wilson and Doyle 1996, Morgan et al. 2001). Also significant correlation has been found in older children between the child’s self-report and the parent’s or nurse’s ratings (Maunuksela et al. 1987, Kokki et al. 1999a, Kokki et al. 1999b). On the other hand, studies have concluded that parents and nurses tend to underestimate the children’s pain (Rømsing et al. 1996, Chambers et al. 1998, Kokki et al. 1999a, Kokki et al. 1999b).

2.2.3. Expressed pain scales

2.2.3.1. Visual analogue scale

The visual analogue scale (VAS) was developed for assessing chronic pain, but is often also used for assessment of acute pain. Conventional VAS is a 100 mm long horizontal line with opposite extremes at each end, the left anchor point (0 mm) indicates “no pain” and the right anchor point (100 mm) indicates “worst possible
pain” (Huskisson 1974). The patient chooses one point to reflect the pain experienced at the moment. Adding colour gradations is helpful and making the scale vertical, like a thermometer, is better understood for children under 5 years. (Morton 1999).

Tigerstedt and co-workers (1988) have proposed a modified VAS during the immediate postoperative period. The conventional 100 mm VAS can be replaced with a 50 cm long and 10 cm high scale for better illustration. This scale is also coloured with an increasing red field from the left to the right. It was found to have a good correlation with the classic 100 mm VAS.

The coloured analogue scale is an instrument to provide a practical clinical measure for assessing children’s pain intensity, and it is widely used in patients over 5 years of age. In this scale a coloured area reflects the pain intensity. The coloured analogue scale varies in three dimensions: colour, width and length. When moving from “no pain” to “most pain” on the scale, the colour changes to more intensive and the coloured area grows wider. The coloured analogue scale has been rated easier to administer and score than VAS, and thus is expected to be more practical for routine clinical use in children (McGrath et al. 1996).

A minimum clinically significant difference as measured by VAS has been discussed. Pain research outcomes involving less than 9-18 mm may have no clinical importance (Todd and Funk 1996, Kelly 1998). Powell and co-workers (2001) have found the minimum clinically significant difference in VAS pain score for children aged 8 to 15 years to be 10 mm. However, even a change of 6 mm on a 100 mm scale over the baseline is considered clinically beneficial in pain control (Hrobjartsson and Gotzsche 2001).

2.2.3.2. Categorical scales

Categorical scales use words to describe the magnitude of the pain (verbal rating scale, VRS) (Littman et al. 1985). Using this scale the patients picks the most appropriate word. A commonly used scale has four words: none, mild, moderate and
severe. For analysis, numbers are given to the verbal categories (for pain intensity, none=0, mild=1, moderate=2 and severe=3) (Maunuksela et al. 1987). Data from different subjects are then combined to produce means and measures of dispersion. Good correlation was found when comparing these two categories with concurrent visual analogue scale measurements (Scott and Huskisson 1976, Wallenstein et al. 1980, Littman et al. 1985). Also Maunuksela and co-workers (1987) proved a significant correlation between VRS, VAS and the Maunuksela pain scale (see 2.2.4.1.) in children.

Verbal numerical scales are regarded as an alternative or complement to the categorical and VAS scales. Using verbal numerical scales patients give a number to the pain intensity (0 = no pain and 10 = maximal possible pain). These scales are easy and quick to use, and correlate well with conventional visual analogue scales (Maunuksela et al. 1987, Rawal and Berggren 1994).

The faces pain scale is a self-report measure used to assess the intensity of children’s pain first described by Maunuksela and Korpela (1986). It has become a popular approach in evaluating small children’s pain, although different formats are available. The basis of this pain scale is that the child identifies the level of pain intensity using one of numerous pictures presenting faces of children (Bieri et al. 1990). Scales show different amounts of pictures (usually five or six) of a child with increasing levels of discomfort. Children select the picture that best reflects their experience of pain at the moment (Maunuksela and Korpela 1986, Beyer and Wells 1989). Faces pain scale is shown to be appropriate and valid for use in assessment of the intensity of pain in children (Hunter et al. 2000, Hicks et al. 2001).

2.2.4. Observed pain scales

2.2.4.1. Maunuksela pain scale

The Maunuksela pain scale was introduced in Finland in 1987 (Maunuksela et al. 1987). It is a behavioural pain assessment scale for children at the age of 1-17 years.
The scale is based on mimic, vocalisation, movements of limbs and body, response to handling and irritability together with measured cardiorespiratory parameters. This pain scale has later been modified by Nikanne (1997a), and the pain scores observed by a specially trained nurse are estimated 0 = no pain, 1-3 = slight pain, 4-6 = moderate pain, 7-9 = severe pain, 10 = worst pain. Features characteristics of increasing pain are: 1) distortion of face such as lowering of the brow, broadening of the nasal root, an angular and squarish mouth, tightly closed eyes, and tightening of the jaw; 2) vocalisation changing from sobbing or groaning to pain cry; 3) colour, temperature, and moisture of the skin changing pink to pale, warm to cool, dry to sweating; 4) increasing rigidity of the body and limbs and resisting movements and handling; 5) respiratory pattern changing from regular, deep, and relaxed to irregular, superficial, and jerky; 6) blood pressure and heart rate changing from normal according to age with large pulse pressure or in some cases low blood pressure or bradycardia (Maunuksela et al. 1987).

A significant correlation has been found between self-reporting scales and behavioural assessment of pain intensity in children without dependency of age (Maunuksela 1987, Kokki et al. 1999c). Kokki and co-workers (1999a) also found a high correlation between the Maunuksela pain scale and the VAS in children aged 1-12 years, undergoing strabismus surgery.

2.2.4.2. Other observed pain scales

Other observational pain scales are e.g. Objective pain Scale (Broadman et al. 1988), Children’s Hospital of Eastern Ontario Pain Scale (McGrath et al. 1987), Toddler-Preschooler Postoperative Pain Scale (Tarbell et al. 1992), COMFORT Scale (Ambuel et al. 1992) and CRIES (Krechel and Bildner 1995). They are all based on different categories of behavioural and physiological signs. In clinical routine use the pain scales mentioned above, except the Objective pain scale, are documented to be complex. Moreover, these scales cannot be used in intubated or paralysed patients.
2.3. Postoperative pain treatment

2.3.1. Background

Postoperative pain treatment has received increased attention during the last decade. New techniques for pain treatment have developed and an understanding of pathophysiology of acute pain has increased. Several studies have reported that standard surgical care does not include sufficient pain relief (Kehlet and Dahl 1993). Unrelieved acute pain produces psychological, physiological and socio-economic consequences (Justin and Richardson 1991).

The aim of postoperative pain treatment is to minimise pain throughout the recovery period, not only at rest but also during mobilisation and appropriate activity. Pain treatment should provide subjective comfort and allow patients to breathe, cough, drink, eat and move easily (Kokki and Ahonen 1997).

Pain management is suggested to begin already preoperatively, continue throughout surgery, and be fully managed postoperatively (Woodburn 1994). During the perioperative period, to ensure adequate basal analgesia, pain medication should be administered on a “timed” rather than on a “require” basis (Morton 1997). Inappropriate pain management may lead to increased incidence of nausea and vomiting, anxiety, delayed discharge, readmission to hospital and delayed resumption of normal activities (Joshi 1999).

It has been a common belief that children do not feel pain as severely as adults do. There has been much discussion about the undertreatment of pain in children, and several reports have indicated that children receive less amounts of analgesics compared to their adult counterparts (Eland and Anderson 1977, McGrath and Johnson 1988, Lloyd-Thomas 1995). However, human new-borns have been shown to have the anatomic and functional components required for appreciation of painful stimuli (Anand and Carr 1989). The development of pain pathways and stress
responses in the fetus, neonate, infant and child compared to adults has been elucidated recently, and has led to widespread acceptance that for moral, ethical, humanitarian and psychological reasons, pain should be anticipated, and safely and effectively prevented and controlled in all age groups (Morton 1999, Anand 2001).

2.3.2. Non-opioid analgesics

2.3.2.1. Non-steroidal anti-inflammatory drugs

The first non-steroidal anti-inflammatory drug (NSAID), acetyl salicylic acid (ASA, aspirin) was synthesised in 1899. A large number of NSAIDs have subsequently been developed, and all the NSAIDs have anti-inflammatory, antipyretic and analgesic properties (Björkman 1995). They have also proved reliable in relieving postoperative pain after minor procedures, and studies suggest that NSAIDs have an important role as adjuvants to other analgesics after major surgery. Several studies have shown that combining NSAIDs with opioids provides superior analgesia with less total opioid required, and possibly a reduction in adverse effects mediated by opioids (Dahl and Kehlet 1991).

NSAIDs have several advantages besides a good analgesic effect, making them suitable for postoperative treatment, such as opioid sparing effects, minimal sedation and lack of respiratory depression and emetic adverse events (Kokki et al. 1994, Brennan 1999).

2.3.2.1.1. Mechanism of action

The mechanism of action of NSAIDs is through the inhibition of prostaglandin biosynthesis by the cyclo-oxygenase (COX) enzyme. This mechanism was first proposed by Vane in 1971. After characterisation of the COX-1 enzyme in 1976, a second COX gene was discovered 1991 encoding for the inducible COX-2. COX-1 is constitutively active throughout the body and is responsible for mediating routine physiologic function, including gastric mucosal function and vascular haemostasis.
(Warner et al. 1999). In contrast, COX-2 in an inducible enzyme expressed from both polymorphonuclear leukocytes and macrophages after inflammatory stimuli (Seibert and Masferrer 1994).

Conventional NSAIDs non-specifically inhibit both the COX-1 and COX-2 isoforms (Meade et al. 1993). It is believed that therapeutic activity (anti-inflammatory, analgesic and antipyretic activity) of NSAIDs is primarily the inhibition of COX-2, whereas the toxicity results mainly from inhibition of COX-1 (Vane 1994, Hawkey 1999). Previous data have suggested that predominantly COX-2 inhibiting NSAIDs have an analgesic effect similar to those of conventional NSAIDs (Dionne et al. 2001, Cannon and Breedveld 2001), without affecting the platelet function (Hawkey 1999, Tindall 1999). They also have a good anti-inflammatory effect (Appleton et al. 1995, Tindall 1999). Adverse effects such as damage to the stomach lining and toxic effects on the kidney are due to inhibition of the constitutive enzyme, COX-1 (Vane 1994). The newest COX-1 sparing NSAIDs are celecoxib and rofecoxib and it is expected that among others, these NSAIDs may replace some conventional NSAIDs in the future.

2.3.2.1.2. Adverse effects

Data from studies on the clinical significance of NSAIDs on coagulation and bleeding are controversial. Several studies have reported increased postoperative bleeding with NSAIDs (Carrick 1984, Robinson and Ahmed 1994, Gunter et al. 1995, Smith and Wilde 1999, Schmidt et al. 2001). On the other hand, no increased bleeding during or after surgery with NSAIDs (ketorolac, diclofenac or ketoprofen) was found compared with placebo (Tarkkila and Saarnivaara 1999). Other studies support these results (Nordbladh et al. 1991, Ejnell 1992), and although diclofenac does for example increase the bleeding time, this is not above the "normal" upper limit (Power et al. 1990).
However, the prolongation of bleeding time with NSAIDs may have clinical relevance and they are suggested to be administered safely for the treatment of peri- and postoperative pain. Schaefer (1995) has found that effects of NSAIDs on the duration of platelet dysfunction depends on the specific drug dose, serum level and half-life. Also, it is well known that clinical risks of bleeding with NSAIDs are enhanced by use of anticoagulants or coexisting coagulopathies.

NSAIDs can cause some adverse effects on kidney function. In conditions where renal function is prostaglandin dependent (in patients undergoing major surgery or in patients having congestive heart failure, concurrent diuretic therapy or extracellular volume depletion), caution has been advocated in the use of cyclooxygenase inhibitors (Clive and Stoff 1984). It is also recommended that NSAIDs should be avoided in patients with renal impairment (plasma creatine above normal), during renal transplantation, hyperkalemia and hypovolemia.

Other conditions in which NSAIDs should be avoided are severe liver dysfunction, circulatory failure and aspirin-sensitive asthma. It is generally believed that increasing the dose of NSAID does not increase its analgesic effect, but the risk of adverse effects may increase markedly.

2.3.2.2. Paracetamol

Since its synthesis in the late 1800s paracetamol (acetaminophen), has become one of the most popular non-opioid analgesic agents. Currently, paracetamol is one of the first-line choices for pain management and antipyresis in a variety of patients, including infants, pregnant women, the elderly, those with osteoarthritis, simple headaches, and those with non-inflammatory musculoskeletal conditions. With proper use, paracetamol seldom causes adverse events and reports of serious adverse effects are rare. It is of particular value in the treatment of patients in whom NSAIDs are contraindicated, such as aspirin-sensitive asthmatics and people at risk for gastrointestinal complications, with doses equal or less than 2-4g/24 hours (Clissold...
1986, Mburu et al. 1990, Prescott 2000). Paracetamol, and NSAIDs, have proven to be effective analgesics for postoperative pain, and using them combined with opioids, the incidence of opioid-related adverse effects may be reduced (Mather and Peutrell 1995, Korpela et al. 1999).

The mechanism of action of paracetamol is poorly defined. It has been speculated that it may selectively inhibit prostaglandin production in the central nervous system, which would account for its analgesic and antipyretic properties (Clissold 1986). Paracetamol does not significantly inhibit prostaglandin synthesis in other tissues, and therefore does not have remarkable anti-inflammatory effects or any effect on platelet function (Clissold 1986, Mburu et al. 1990).

Paracetamol is mostly used by oral administration or per rectum. An intravenous prodrug form of paracetamol, propacetamol, has increased its feasibility during the perioperative period and among patients who cannot swallow (Granry et al. 1997). Following oral administration paracetamol is rapidly absorbed from the gastrointestinal tract, its system bioavailability being dose-dependent and ranging from 70 to 90 %. Paracetamol is also well absorbed from the rectum. It distributes rapidly and evenly throughout most tissues and fluids. Paracetamol is metabolised predominantly in the liver, the major metabolites being sulphate and glucuronide conjugates (Forrest et al. 1982).

The most serious adverse effect associated with paracetamol is hepatotoxicity. It may occur after acute overdose (usually doses greater than 10 to 15 grams in adults and 100-150 mg/kg in children) or during long-term treatment (Clissold 1986). Exposures greater than 140 mg/kg/day for several days carry a risk of serious toxicity (Cranswick and Coghlan 2000). Intravenous N-acetylcysteine is used in treatment of paracetamol overdose, and to be effective, the treatment must be initiated within 10 hours (Clissold 1986).
Because of the different mechanism of action, paracetamol has been combined with NSAIDs, providing a better analgesic effect than paracetamol or NSAID alone (Montgomery et al. 1996, Fletcher et al. 1997, Morton 1999).

2.3.3. Opioid analgesics

Opioids are the most common drugs to treat moderate and severe postoperative pain. Opioids exert analgesic effects mainly by acting on the central nervous system (CNS) (Millan 1986). Recently, evidence has begun to accumulate that opioid antinociception can be initiated also by activation of opioid receptors located outside the CNS (Stein 1993). Opioids mimic the action of endogenous opioid peptides by interacting with mu (μ), delta (δ) and kappa (κ) opioid receptors, each possessing unique pharmacological and physiological properties. Opioid receptors have been detected in the brain, brainstem, spinal cord and also in peripheral tissue (Martin 1984, Stein 1993). The opioid receptors are coupled to G1 proteins and the action of the opioids is mainly inhibitory. They close N-type voltage-operated calcium channels and open calcium-dependent inwardly rectifying potassium channels. This results in hyperpolarisation and a reduction in neuronal excitability (Bovill 1997). Opioids have also been reported to produce stimulatory effect on neurotransmission and neurotransmitter release. More recently, direct stimulatory actions of opioids have been shown in a variety of tissues: opioids increase adenosine secretion from spinal-cord synaptosomes, increase release from dopaminergic neurones, and stimulate noradrenaline release from SK-N-SH cells (Harrison et al. 1998). Except for the neonatal period, the pharmacokinetics and pharmacodynamics of opioid analgesics are not markedly different from those of adults, and the risk of using opioids in infants and children is not higher than in adults (Olkkola et al. 1995).
2.3.3.1. Morphine

Morphine is the principle active compound in opium and the standard for opioid analgesics. Main metabolites of morphine are the pharmacologically inactive morphine-3-glucuronide and pharmacologically active morphine-6-glucuronide (Olkkola et al. 1995). The adverse effects of morphine are well known and common to all opioids. These include nausea and vomiting, sedation, euphoria, dizziness, dysphoria, depression of ventilation and cough reflex, psychological and physical dependence, and tolerance. Morphine also stimulates smooth muscle causing bronchoconstriction, constipation and urine retention in addition to itching, sweating, and mouth drying (Maunuksela and Olkkola 1991, Martindale 1993).

2.3.3.2. Fentanyl

Fentanyl is the first of the present generation of potent anilino-piperidine opioids. Fentanyl citrate is a synthetic, short acting analgesic, and 100-300 times as potent as morphine, with a high therapeutic index and fewer side effects. Fentanyl is usually used during anaesthesia in the treatment of peri- and postoperative pain. Although fentanyl is considered short-acting after a single dose, the terminal half-life is 4 to 5 hours and comparable to morphine. Therefore, with higher or repeated doses, or continuous infusion of fentanyl, it becomes relatively long-acting (Rosow 1995). Fentanyl causes less histamine release than morphine, and therefore produces less change in systemic vascular resistance (Rosow et al. 1982). Furthermore, during anaesthesia the use of fentanyl has been shown to reduce the requirements for inhalation anaesthetics (Katoh et al. 2000). The introduction of fentanyl and development of various newer congeners sufentanil, alfentanil and remifentanil has allowed the clinician to use drugs with analgesic properties similar to those of morphine, but with greater potency, inactive metabolites and fewer side effects, particularly those related to histamine release (Sear 1998).
2.3.3.3. Oxycodone

Oxycodone is a commonly used semisynthetic opioid analgesic in many countries. The analgesic effect of oxycodone has been considered as good as morphine (Backlund 1997), but some studies indicate that the analgesic effect of oxycodone is even more potent with less nausea and sedation compared with morphine (Kalso and Vainio 1990, Kalso et al. 1991).

2.3.3.4. Codeine

Codeine, or methylmorphine, is an opium alkaloid about one-tenth as potent as morphine (Twycross 1999). Its use is advocated in the management of acute and chronic mild or moderate pain. Codeine appears to be a good alternative postoperative analgesic in patients in whom NSAIDs are contraindicated. Doses of codeine ranging from 0.5 to 1.5 mg/kg have been used to provide analgesia.

Codeine can be given by the intravenous, intramuscular, oral and rectal routes, but the recommended route of administration is by mouth. Because codeine also has antitussive and constipating properties, it is used in many cough, cold and antidiarrhoeal remedies (Williams et al. 2001).

Codeine is often used in combination with other drugs to improve the analgesic effect (Moir et al. 2000, Moore et al. 2000). Codeine can add significantly to the analgesic effect of drugs such as aspirin, paracetamol, and NSAIDs. This additive effect is especially prominent after repeated doses. When codeine is metabolised to morphine, accumulation of morphine has been suggested as an explanation (Williams et al. 2001).

In the multidose studies the difference in analgesic effect between a paracetamol-codeine combination and paracetamol alone has been found to be small but statistically significant. However, adverse effects were reported significantly more often with the paracetamol-codeine combination (de Craen et al. 1996).
The most common adverse effects of codeine are similar to other opioids including respiratory depression, sedation and nausea and vomiting, but also hypotension when given by the intravenous route (Williams et al. 2001). Decreased gastric motility and constipation are also well known adverse effects of codeine.

2.3.4. Prevention of postoperative pain

Pre-emptive analgesia should be a rational approach to the treatment of postoperative pain based on our knowledge of acute pain physiology (Kehlet and Dahl 1993). The theory of pre-emptive analgesia is to prevent a prolonged change in the central nervous system function by blocking afferent input before surgical stimulation by eliminating central sensitisation, and preventing amplification and prolongation of postoperative pain (Dahl and Kehlet 1991). Preoperative administration of analgesics (for example opioid or NSAIDs) may reduce the degree of pain and analgesic consumption during the postoperative period (Woolf 1993). However, recent clinical studies do not support these facts. An acute development of tolerance and delayed hyperalgesia from opioid exposure may explain this failure of a strong clinical effect by pre-emptive analgesic therapy (Eisenach 2000). In the future, more well-designed clinical studies are needed to establish the role of pre-emptive analgesia.

2.3.5. Peripheral nerve blockades

For surgical procedures peripheral nerve blockades with local anaesthetics and cryoanalgesia may be suitable (Cousins and Bridenbaugh 1988). Moreover, in addition to intraoperative analgesia, they may also be used to provide postoperative pain relief. Peripheral nerve blockades especially those utilising continuous catheter techniques in selected cases do provide excellent analgesia (Murauski and Gonzales 2002).
2.3.6. Multimodal pain treatment

Total adequate postoperative pain relief may not be achieved by a single agent or method without major expenditure on equipment and surveillance systems, or without significant adverse effects (Kehlet 1989). Multimodal analgesia techniques consist of a combination of analgesic regimens. Synergistic or additive effects have been demonstrated between NSAIDs and opioids as well as between local anaesthetics and opioids (Kehlet 1989, Dahl and Kehlet 1991). Thus, the use of multimodal pain treatment is growing, and the principles of multimodal pain treatment are of major importance in the treatment of postoperative pain (Kehlet and Dahl 1993).

2.3.7. Postoperative pain treatment at home

After surgery patients are commonly discharged within 24 hours. Therefore the treatment of postoperative pain is mostly managed by the patients or by the parents of the children. If pain treatment is not sufficient, severe pain may lead to poor oral intake and dehydration causing morbidity and delayed recovery. Occasionally readmission to the hospital may even be necessary (Blakeslee 1997).

Recent studies indicate that more than half of patients need pain medication after day case adenoidectomy (Kokki and Ahonen 1997), and more than one out of five patients experienced severe pain at home (Nikanne et al. 1999). Moreover, several studies indicate that children are often treated inadequately for pain (Finley et al. 1996, Rømsing et al. 1996).

Postoperative pain treatment in children is mostly managed by the parents. The reason for inadequate delivery of analgesia at home may be because parents underestimate their children’s pain. Parents may also have problems in administering the analgesic to their children or they may assume that medication causes adverse effects or addiction (Finley et al. 1996). However, training of medical
staff and parents have been found to improve pain management at home (Sepponen et al. 1999).

To ensure a calm recovery at home, patients should be provided with clear instructions about pain treatment both verbally and in writing. Pain following surgery is best managed by providing medication on a regular basis and preventing pain from recurring. Also, longer acting preparations should be considered for use in the evenings to allow sufficient pain relief lasting through the entire night (Toma et al. 1995). Moreover, non-opioid medication should be administered as early as possible, before the pain has broken through. When insufficient pain relief is not achieved, a multimodal technique or method should be considered.

2.4. Ketoprofen

2.4.1. Pharmacology and pharmacokinetics

Ketoprofen is a non-steroidal anti-inflammatory drug. It was synthesised in 1967 by Rhone-Poulenc Research Laboratories in Paris. Ketoprofen belongs to the group of 2-phenylpropionic acids, like ibuprofen and naproxen, and has anti-inflammatory, antipyretic and analgesic properties. Its structural formula is 2- (3- benzophenyl)-propionic acid (Figure 1) and its molecular weight is 254.29 (4.2 x 10^-22 kg) (Kantor 1986, Ballantyne and Dershwitz 1995). Ketoprofen is a clear, colourless solution, thus easily enabling blinding with placebo (0.9% saline) in clinical trials.
Figure 1
Structural formula of ketoprofen (2-(3-benzoxyphenyl)-propionic acid) (Kantor 1986).

Ketoprofen administered orally is rapidly absorbed from the gastrointestinal tract. Bioavailability of oral ketoprofen is around 90%, and the maximal plasma levels are reached approximately around an hour after ingestion (standard tablet/capsule) (Kantor 1986, Kokki et al. 2001) and 15 to 30 minutes after solution intake (Upton et al. 1980, Kokki et al. 2000a). When ketoprofen is used in an injectable form, a rapid onset of analgesic action is achieved. Administration of a single intravenous ketoprofen bolus suppresses pain within 5 to 30 minutes (Ishizaki et al. 1980, Debruyene et al. 1987). Due to rapid absorption, a peak plasma level of intramuscular (im) ketoprofen is attained within 30 minutes (Wollheim et al. 1981, Kokki et al. 2001).

The mean half-life of ketoprofen is around 2 hours in adults and it is independent of the route of administration (Depruyne et al. 1987, Ballantyne and Dershwitz 1995, Kokki et al. 2000a, Kokki et al. 2001). Ninety-nine per cent of ketoprofen is bound to plasma proteins, mostly albumin (Kantor 1986). Ketoprofen has a small volume of distribution, at steady-state, around 0.1 l/kg, and low plasma clearance, 1.2 ml/min/kg (Veys 1991, Kokki et al. 2001). Ketoprofen is extensively metabolised by microsomal enzymes in the liver and it is mainly conjugated to an inactive metabolite, glucuronic ester that is excreted in urine (Kantor 1986, Veys 1991). Only a
negligible fraction of the dose of ketoprofen is excreted as unchanged drug (Upton et al. 1980). Because the elimination half-life of ketoprofen is short it is a feasible drug for continuous intravenous infusion in acute pain treatment without evidence of accumulation after 24 hours of infusion (Kokki et al. 2000a).

In children the pharmacokinetics of ketoprofen are quite similar to those reported in adults and are not affected by age between 6 months and 7 years (Kokki et al. 2000a, Kokki et al. 2001).

2.4.2. Pharmacodynamics

Ketoprofen has shown analgesic, anti-inflammatory and antipyretic activity in both adults and in children. In comparative trials with other analgesic agents (both centrally and peripherally acting), other NSAIDs and paracetamol, ketoprofen has exhibited effective analgesic properties (Fossgreen 1976, Veys 1991, Tarkkila and Saarnivaara 1999). Compared with acetylsalicylic acid, ketoprofen is a twenty to seventy times more potent analgesic (Joulou et al. 1976). The dosage of 0.3 mg/kg ketoprofen had significant analgesic effect and it may be used safely up to a dose of 5 mg/kg/24 hours (Brewer et al. 1982, Kokki et al. 1998). Ketoprofen seems also to have a central analgesic effect. This may be achieved by inhibition of central prostaglandin synthesis. Ketoprofen injection results in a rapid and significant increase in the threshold of the nociceptive reflex (Willer et al. 1989), and it enters into the cerebrospinal fluid (Netter et al. 1985, Kokki et al. unpublished observation). This area requires further investigation (Ballantyne and Dershwitz 1995).

It is commonly accepted that the anti-inflammatory effect of NSAIDs, e.g. ketoprofen, is mainly associated with their ability to inhibit the COX enzyme, leading to a decrease in both prostaglandin and thromboxane synthesis (Kantor 1986). Ketoprofen also inhibits the action of lipo-oxygenase, although it is doubtful whether the extent of this inhibition is clinically relevant (Williams and Upton 1988). In addition, Bizzarri and co-workers (2001) have concluded that inhibition of
interleukin-8 chemotaxis could contribute to the anti-inflammatory activity of NSAIDs.

Ketoprofen has proved to be a safe and effective anti-inflammatory agent compared with other NSAIDs (Bhetty and Thomson 1978, Saxena and Saxena 1978, Brewer et al. 1982). It has produced a statistically significant relief of symptoms in rheumatoid processes and it has proved to be an effective drug in the treatment of juvenile rheumatoid arthritis (Goulton and Baker 1980, Brewer et al. 1982).

Ketoprofen has decreased antigen-induced hyperthermia in rats and rabbits to a greater extent than indomethacin, naproxen or ibuprofen (Kantor 1986). In humans, the antipyretic activity of ketoprofen has proved to be three or four times higher than indomethacin (Julou et al. 1976). NSAIDs are widely used in the treatment of fever (Keinänen-Kiukaanniemi et al. 1980).

2.4.2.1. Toxicology

Clinical trials of long term treatment have demonstrated that ketoprofen is well tolerated, and like other propionic acid derivatives, it has a low toxicity. The drug has no effect on DNA, RNA or protein synthesis. In standard screening assays there appeared to be no evidence of carcinogenicity or mutagenicity (Kantor 1986).

The acute oral toxic level ranges between 50 mg/kg and 1000 mg/kg in different animals (Kantor 1986). Maximum daily dosage for adults is 300 mg and 5 mg/kg in children (Kantor 1986, Maunuksele et al. 1993). The symptoms of poisoning have been reported to be drowsiness, abdominal pain and vomiting (Court and Volans 1984). However, human toxicity levels of ketoprofen still remain unknown.
2.4.2.2. Clinical use

Ketoprofen has been in clinical use since 1973. It is mostly used in mild or moderate pain, and it has several million patients-years of clinical exposure, primarily in arthritic conditions (Kantor 1986, Cooper 1988). Its main clinical indications are the treatment of osteoarthritis, rheumatoid arthritis, postoperative and postpartum pain, dental pain, cancer pain and dysmenorrhea (Veys 1991).

Ketoprofen is also used in severe pain with opioids in pre- and postoperative situations. Both in children and in adults, intravenous ketoprofen has proved to be a safe and effective analgesic in postoperative pain, and it has also appeared to reduce the consumption of opioids (Nikanne et al. 1997b, Tarkkila and Saarnivaara 1999, Kokki et al. 1999a, Basto et al. 2001). There is also some evidence that ketoprofen reduces the incidence of pruritus, nausea and vomiting after surgery (Kokki et al. 1999b, Basto et al. 2001).

Ketoprofen is available as oral tablets and capsules, suppositories, intramuscular and intravenous preparations, and a gel formulation (Veys 1991). However, the benefit of intramuscular injection remains open. Kokki and co-workers (2001) found that the rate and extent of absorption and the elimination of ketoprofen are comparable after intramuscular and oral administration in children, and they concluded that there is no justification for intramuscular injections in children.

In adults, the recommended daily oral or rectal dosage is 50-100 mg 2 to 3 times per day, and the intramuscularly dosage is 50-100 mg, reaching a maximum of 200 mg per day (Fossgreen 1976, Veys 1991, Martindale 1993). However, a low-dose ketoprofen 25 mg has been found to provide statistically superior analgesia compared to 90 mg codeine or to 650 mg aspirin (Mehlisch et al. 1984, Cooper 1988). In children an oral ketoprofen dosage of 5 mg/kg/24 hours divided in 2 or 3 dosages has proved to be safe and effective (Kokki et al. 2000b). Intravenously, ketoprofen has been recommended for routine use at a dose of 1 mg/kg. The dose
may be repeated 3 times per day or a continuous infusion may be used (Kokki et al. 1998).

2.4.3. Adverse effects

In long term clinical trials ketoprofen has been shown to be safe and well tolerated. Side effects of ketoprofen are similar compared to other NSAIDs: gastrointestinal disturbances, effects on kidney function and effect on platelet function being the most frequent (Veys 1991).

2.4.3.1. Effect on platelet function and bleeding

NSAIDs exert inhibitory effects on platelet function in vitro and in vivo by inhibiting platelet cyclo-oxygenase, thereby blocking the formation of thromboxane A2 (Schafer 1995, Vane and Botting 1996). These drugs produce a systemic bleeding tendency by prolonging the bleeding time. For example, Niemi and co-workers (1997) found increased bleeding time after an intravenous bolus of ketoprofen (1.4 mg/kg) and reversible platelet dysfunction measured two hours after infusion. Dordoni and co-workers (1994) found an increased bleeding time (5.0 min before vs. 8.4 min after treatment) after 100 mg intramuscular ketoprofen administration, but they did not notice any significant effect on platelet aggregation. However, the effect of ketoprofen on platelets is reversible and it inhibits platelet aggregation for a few hours only (O’Brien 1986, Niemi et al. 1997).

Ketoprofen did not increase postoperative blood loss after total hip or knee replacement (Kostamovaara et al. 1996) or after caesarean section (Sunshine et al. 1993). Tarkkila and Saarnivaara (1999) found neither increased bleeding with ketoprofen during tonsillectomy nor incidence of haemorrhage during the first 24 hours after operation. Moreover, Nikanne and co-workers (1999) reported that with ketoprofen an increase of blood loss peri- and postoperatively during adenoidectomy in children seems to be minimal. However, more controlled studies are still needed to prove ketoprofen to be safe in this respect.
2.4.3.2. Gastrointestinal adverse effects

Gastrointestinal adverse effects of ketoprofen are common and seems to be dose related and more frequently involve the upper gastrointestinal tract. Most common reported gastrointestinal adverse-effects of ketoprofen are gastritis and gastric ulcer (9%), nausea (2%), constipation and flatulation (1%), diarrhea (1%), abdominal pain (>1%), vomiting (>1%) and gastrointestinal bleeding (>1%) (Fossgren 1976).

The cause of gastrointestinal adverse effects is related to ketoprofen’s inhibition of prostaglandin synthetase; prostaglandins inhibit the secretion of gastric acid and have other protective actions such as stimulation of mucus and bicarbonate secretion and gastric mucosal blood flow (Day et al. 1987). Compared to some other NSAIDs ketoprofen has shown to be much less of a gastric irritant than e.g. acetylsalicylic acid (Veys 1991). This is supported by the COX-2/COX-1 ratio, which is suggested to correlate with adverse effects of NSAIDs. Low ratio indicate a preferential inhibition of COX-2. The COX-2/COX-1 for ketoprofen is 1 - 4.6 and e.g. for acetylsalicylic acid the ratio is 166 and for piroxicam 250 (Kankaanranta and Vapaatalo 1996, Vane and Botting 1996).

2.4.3.3. Renal adverse effects

Administration of NSAIDs, under certain circumstances, can lead to sodium retention, hyperkalemia and several different forms of acute and chronic renal failure (Hart and Lifschitz 1987). When the kidney is in a salt retaining state or when there is renal vascular damage, NSAIDs can produce acute renal failure that is usually reversible upon discontinuation of the drug. The vasodilatory prostaglandins play an important role in regulating renal homeostasis in hypovolemic patients and in those with congestive heart failure or chronic renal disease. However, renal function in normal individuals is relatively independent of the prostaglandin-system, and thus the NSAIDs don’t usually produce any renal dysfunction (Nies 1988).
In ca. 3% of patients receiving ketoprofen have been observed to have a transient decrease in renal function, such as azotaemia, increased blood urea nitrogen and serum creatinine (Kantor 1986). Only a few patients with interstitial nephritis and renal papillary necrosis related to the use of ketoprofen have been reported (Kantor 1986).

2.4.3.4. Other adverse effects

Only a few serious cases of liver toxicity have been reported with ketoprofen therapy, but slightly elevated transaminases and an elevation in alkaline phosphatase are the most commonly reported hepatic adverse effects of ketoprofen (Fossgreen 1976, Mills and Sturrock 1982, Lewis 1984). Ketoprofen has shown to have some adverse effect on the central nervous system, e.g. headache (0.6%), vertigo (0.5%) and somnolence (0.5%) (Fossgreen 1976), and dizziness (3.6%), headache (9.3%) and tinnitus (2.3%) (Kantor 1986). Erythematous rash, urticaria, pruritus, muco-cutaneous reactions, contact dermatitis and photosensitivity have been reported in less than 1% of patients (Fossgreen 1976). Ketoprofen seems also to have a low potential for allergic manifestations in aspirin intolerant patients (Kantor 1986), but some cases of a life-threatening bronchoconstriction have been reported (Frith et al. 1978).

2.5. Adenoidectomy

Adenoidectomy is one of the most common surgical procedures performed in children. In Finland more than 12 000 adenoidectomies are carried out every year (Nenonen and Rasilainen 1998). This means that annually about 2.5% of the children in the age group 0-7 years undergo adenoidectomy. Adenoidectomy has proved to be a safe procedure to be performed on a day-case basis (Mitchell et al. 1997). The main indications, relative indications and contraindications for adenoidectomy are presented in Table 1.
Table 1

The main indications, relative indications and contraindications for adenoidectomy (Paparella et al. 1991).

Main indications for adenoidectomy:
1. recurrent middle ear disease secondary to eustachian tube obstruction
2. adenoid hypertrophy obstructing respiration
3. recurrent sinusitis or its complications.

Relative indication for adenoidectomy:
1. recurrent sore throat
2. recurrent otalgia
3. recurrent or chronic rhinitis
4. recurrent upper respiratory infections
5. snoring or mouth breathing
6. failure to thrive
7. cervical lymphadenopathy
8. tuberculous adenitis
9. systemic disease secondary to beta-haemolytic streptococcal infections.

Contraindications for adenoidectomy:
1. blood dyscrasias
2. uncontrolled systemic disease
3. cleft palate
4. acute infections.

Adenoidectomy is commonly performed by curettage under indirect vision with a mirror under general anaesthesia. Remnants of the lymphoid tissue can be removed with forceps or scissors. Special attention and care should be paid removing adenoid tissue around the orifices of the eustachian tubes. Other used techniques for
adenoidectomy are e.g. adenoidectomy with suction cautery or laser, and powered instrumentation with endoscopic shaver system (Koltai et al. 1997). Haemostasis is controlled with nasopharyngeal packs or with electrocautery, when needed. In the cases of persistent bleeding, a postnasal pack can be inserted for a few hours (Paparella et al. 1991).

Pain is one of the typical complications of adenoidectomy. After day-case adenoidectomy up to 80% of the patients need pain medication also at home (Kokki and Ahonen 1997). Postoperative analgesia should be sufficient and regular medication is suggested in all children during the first 2 postoperative days after adenoidectomy (Nikanne et al. 1999).

Other typical complications following adenoidectomy are excessive haemorrhage, local infections, surgical trauma of the soft palate or eustachian tubes and velopalatal incompetence (Paparella et al. 1991, Deutsch 1996).

2.6. Tonsillectomy

2.6.1. General aspects

Tonsillectomy is a type of surgery that is commonly performed in adults and in children. In Finland more than 15 000 tonsillectomies (or adenotonsillectomies) are carried out every year (Nennon and Rasilainen 1998). Tonsillectomy has proven to be a safe operation and there is a growing trend towards day case surgery to improve health care cost efficiency (Moralee 1998, Kishore et al. 2001). Today the standard procedure for tonsillectomy (or adenotonsillectomy) in most countries is either day-case or short-stay surgery (discharge within 24 hours). This is based on low rates of serious events such as secondary haemorrhage, dehydration and infection (Rungeby et al. 1999).
The definite indications for tonsillectomy, relative indications and relative contraindications and definite contraindications for adenotonsillectomy are presented in Table 2.

Table 2
The definite indications for tonsillectomy, relative indications, relative contraindications and definite contraindications for adenotonsillectomy (Paparella et al. 1991).

Definite indications for tonsillectomy:
1. Recurrent episodes of acute or chronic tonsillitis
2. Tonsillitis resulting in febrile convulsions
3. Peritonsillar abscess
4. Diphtheria carrier
5. Tonsillar hypertrophy obstructing respiration or deglutition
6. Sleep apnoea
7. Biopsy necessary to define possible malignancy.

Relative indications for adenotonsillectomy include:
1. Recurrent sore throats
2. Recurrent otalgia
3. Recurrent or chronic rhinitis
4. Recurrent upper respiratory infections
5. Snoring or mouth breathing
6. Failure to thrive
7. Large tonsils or tonsillar debris
8. Cervical lymphadenopathy
9. Tuberculosis adenitis
10. Systemic disease secondary to beta-haemolytic streptococcal infections (rheumatic fever, rheumatic heart disease, nephritis).
Relative contraindications for adenotonsillectomy:
1. Cleft palate, frank or submucous
2. Acute infections (including tonsillitis, respiratory infections, and so on)
3. Poliomyelitis epidemic, or nonimmunized patient in endemic areas
4. Age less than 3 years.

Definite contraindications for adenotonsillectomy:
1. Blood dyscrasias – leukaemia, purpura, aplastic anaemia, haemophilia
2. Uncontrolled systemic diseases – diabetes, heart disease, seizure disorders, etc.

Mattila and co-workers (2001) have evaluated the frequency of tonsillectomies in a prospective study (n=888). The frequency of tonsillectomies increased in pre-school-aged children. Tonsillar hyperplasia was the most frequent indication among children younger than 10 years. The frequency of operations declined thereafter, and increased again in teenagers. Peritonsillar abscesses in teenagers and chronic tonsillitis among individuals older than 20 years were the most frequent indications for tonsillectomies.

2.6.2. Operation techniques

Tonsillectomy is performed either under local or general anaesthesia by a variety of techniques. The present method is dissection tonsillectomy (Homer et al. 2000).

In dissection, the tonsil is dissected carefully along the tonsillar capsule. This can be made by many different methods, including blunt dissection, bipolar or unipolar electrodissection, suction diathermy dissection, microdissection, laser dissection, bipolar scissors dissection (Leach et al. 1993, Saleh and Cain 1999), ultrasonic removal (Akural et al. 2001), or radiothermal (Bäck et al. 2001). Haemostasis is most often secured by pressure (usually with small sponges), electrocautery or ligatures (Becker et al. 1994).
2.6.3. Postoperative pain

Pain after tonsillectomy is often severe. The length of post-tonsillectomy pain varies in different studies. Toma and co-workers (1995) have reported that post-tonsillectomy pain persists relatively unchanged for the first four days and does not decrease significantly until day 7. They also noticed that even after 10 days many still suffered some discomfort. In addition, Warnock and Lander (1998) found that tonsillectomy caused considerable pain that lasted more than 7 days. The majority of patients experience most severe pain from day 5 to day 7 (Fenton and O’Dwyer 1994, Murthy and Laing 1998). In young children, it is reported that pain levels fall slightly more quickly (Rasmussen 1987, Lavy 1997).

Whether the method of tonsil removal and method of haemostasis influence the experienced pain, is controversial. Most studies examining tonsillectomy techniques are primarily concerned with speed of surgery and blood loss rather than pain control (Husband and Davis 1996). Comparing electrodissication and conventional cold-dissection methods and post-operative pain by Pinder and Hilton (2001) there were only two studies which met the inclusion criteria. In these studies, there was evidence that pain may be greater after monopolar electrodissication compared to conventional cold dissection. However, there is still insufficient data to show that one method of tonsillectomy is superior (Pinder and Hilton 2001). In adults, diathermy haemostasis seems to cause more pain than ligatures, but in contrast, in children there does not seem to be any difference (Salam and Cable 1992, Choy and Su 1992).

Oas and Bartels (1990) have compared laser with traditional cold dissection; on the day after surgery the dissected side was more painful than the laser-removed side, but at the end of the first week after surgery more than 60% of patients complained of more pain on the laser dissected side. Other studies support these findings (Auf et al. 1997, Saito et al. 1999). Bäck and co-workers (2001) did not find any difference in postoperative morbidity between bipolar radiofrequency thermal ablation and traditional cold dissection with diathermy haemostasis.
2.6.3.1. Treatment of postoperative pain

Despite the growing attention given to analgesia, several studies indicate that pain treatment after tonsillectomy has still been inadequate (Toma et al. 1995, Wexler 1996, Warnock and Lander 1998). Postoperative pain should be minimised not just for the patients comfort but also to reduce postoperative complications. The following methods have been commonly considered in the control of pain postoperatively: systemic analgesia, prophylactic antibiotic and steroid therapy, local infiltrations, and topical analgesics.

In order to achieve adequate pain control the patient undergoing tonsillectomy needs systemic analgesia. Most commonly, this is given either as opioids or NSAIDs, or as a combination of both (Husband and Davis 1996). However, the known side effects of opioids, such as emesis, excessive sedation and risk of respiratory depression, can lead to insufficient amounts of these drugs being given to patients. Also, the known adverse effects of NSAIDs such as prolonged bleeding time, may hinder use of these drugs.

NSAIDs are used after tonsillectomy for background analgesia to decrease opioid requirements, but are often not effective enough as sole analgesics. In young children and adults who have contraindications to NSAIDs, paracetamol or paracetamol-codeine are frequently used. Oral systemic analgesia with NSAIDs, paracetamol or opioids is suggested to cover at least the first five postoperative days. Consideration should also be given to longer acting analgesia, for example retard formulation, for night-time pain relief (Toma et al. 1995).

There are few studies recommending prophylactic antibiotic therapy for reducing post-tonsillectomy pain. A double-blind placebo controlled study by Telian and co-workers (1986) examined amoxicillin given intravenously during surgery followed by mouth administration for 7 days in children. Patients in the amoxicillin group had less postoperative pain, mouth odour, and returned more rapidly to a normal diet. Later, two other studies have concluded the same with peri- or postoperative
antibiotic therapy (Grandis et al. 1992, Colreavy et al. 1999). Jones and co-workers (1990) evaluated the efficacy of cefaclor vs. amoxicillin in patients recovering from tonsillectomy, but noticed no difference between these two antibiotics.

Mann and co-workers (1999) have compared topical antibiotic therapy to placebo in reducing postoperative morbidity. They noticed that mean aerobic and anaerobic oral bacterial counts were decreased in the topical treatment groups (clindamycin and amoxicillin/clavulanate). They also noticed that there was significantly less postoperative pain and mouth odour in both antibiotic study groups. Preliminary results in this study indicate a reduction in oral bacterial counts and postoperative morbidity in adult patients, but further investigation is needed (Mann et al. 1999).

A single intraoperative dose of dexamethasone has been reported to reduce pain and analgesic use after tonsillectomy (Tom et al. 1996, Carr et al. 1999), other studies have reported no significant effect with steroid use on postoperative pain scores (Catlin and Grimes 1991, Volk et al. 1993, Ohlms et al. 1995, Vosdoganis and Baines 1999, Rose et al. 1996, Palme et al. 2000). Steroid infiltration into tonsillar fossae did not reduce postoperative morbidity in patients undergoing tonsillectomy (Egeli and Akkaya 1997).

There are three aims in the injection of local anaesthetic during tonsillectomy: reduction of pain, decreased blood loss, and easier dissection. Although infiltration with local anaesthetic in addition to a general anaesthetic is common during surgery in general, the value of this practice in tonsillectomy remains uncertain. Nigam and Robin (1991) reported that the tonsil infiltrated with bupivacaine prior to removal demonstrated less pain than the other tonsil not infiltrated, but they concluded that this was not a substantial difference in terms of pain relief. A more recent study with 129 patients concluded that bupivacaine hydrochloride markedly decreased the intensity of post-tonsillectomy pain (Goldsher et al. 1996). However, in this study a large number of bupivacaine-treated patients also had medium or severe pain. In
contrary, Ørntoft and co-workers (1994) noticed that pre-emptive infiltration with 0.25% bupivacaine has no beneficial analgesic action.

Some authors have shown that infiltration with bupivacaine and adrenaline gives significantly better pain relief than infiltration with saline and adrenaline (Jebeles et al. 1993, Melchor et al. 1994, Wong et al. 1995), but others have reported no difference (Broadman et al. 1989, Schoem et al. 1993), and in one trial more pain was noticed in patients with the use of local bupivacaine (Violaris and Tuffin 1989).

Glossopharyngeal and lesser palatine nerve blocks with 0.5% bupivacaine appeared not to be effective in reducing early postoperative pain (Bell et al. 1997, El-Hakim et al. 2000).

Violaris and Tuffin (1989) investigated the analgesic effect of topical bupivacaine in 15 adult patients undergoing bilateral tonsillectomy. They found that the topical bupivacaine exposed side was more uncomfortable than the saline exposed side, and concluded that there is no place with topical bupivacaine for providing postoperative analgesia in adult tonsillectomy.

In two studies benzydamine hydrochloride spray (difflam) compared with placebo has been shown to have a significant benefit (Raj and Wickham 1986, Young 1987). Other studies have not been able to show any difference compared to placebo (Valijan 1989).

There was no benefit from topical ethanol as a neurolytic agent applied on the tonsillar bed following dissection (Purser et al. 2000).

Recently, in a study of 20 children, sprayed fibrinogen and topical bovine thrombin forming fibrin sealant was found to significantly reduce pain the evening after tonsillectomy, and also decreased the chance of experiencing emesis (Gross et al. 2001). In a larger study of 74 patients fibrin glue using 4% lidocaine chloride as
solution reduced pain compared to a control group during the postoperative period (Kitajiri et al. 2001). Both these studies are limited by a small sample size and therefore the reliability of these findings remains open.

Cryoanalgesia has been recently shown to reduce the mean of pain scores by 28% (Robinson and Purdie 2000). Unfortunately, this study was done with a small number of patients (n=59).

It is thought that promotion of saliva formation would reduce the severity of pain and facilitate early resumption to a normal diet. However, Hanif and Frosh (1999) found that chewing gum in the early postoperative period increased the average amount of pain and significantly delayed resumption of normal diet.

2.6.4. Complications

2.6.4.1. Postoperative haemorrhage

The overall incidence of post-tonsillectomy haemorrhage cited in the literature ranges from 0.1% to 33%, depending on severity (Wei et al. 2000, Liu et al. 2001, Blomgren et al. 2001). These wide and different ranges of post-tonsillectomy haemorrhage rates reflect the diversity on how to define post-tonsillectomy haemorrhage. This affects directly the recorded incidence of haemorrhage rate. Many studies with low incidence of post-tonsillectomy bleeding are retrospective, or the inclusion criteria are primarily based on the need for operative therapy (Carmody et al. 1982, Maniglia et al. 1989, Wei et al. 2000). Reports with higher rates of post-tonsillectomy bleeding also include the hospital admission and observation and those reported by patients or parents of children (Handler et al. 1986, Liu et al. 2001, Blomgren 2001). Because different authors use variations in the definitions of post-tonsillectomy haemorrhage, these results are not directly comparable.

Primary post-tonsillectomy haemorrhage is defined as bleeding that occurs within the first 24 hours after surgery, and is generally attributed to surgical technique and
reopening of small blood vessels (Krishna and Lee 2001). The primary haemorrhage rate varies between 0.1 and 3% (Handler et al. 1986, Watson et al. 1993, Conley et al. 1999, Collison and Mettler 2000, Blomgren et al. 2001). However, primary haemorrhage may even be life threatening and is the most frequent cause of post-tonsillectomy mortality (Liu et al. 2001). This is claimed to be caused by weakened reactions and airway reflexes after anaesthesia.

Secondary post-tonsillectomy haemorrhage (onset >24 hours after surgery) has its origin in the sloughing of eschar, trauma secondary to solid food ingestion, tonsil bed infection, postoperative NSAID usage, or idiopathic causes (Liu et al. 2001). Studies have reported the secondary haemorrhage rate to be more frequent compared to primary haemorrhage and it varies between 1 - 33% (Handler et al. 1986, Phillipps and Thornton 1989, Wexler 1996, Randall and Hoffer 1998, Collison and Mettler 2000, Wei et al. 2000, Ghufoor et al. 2000, Blomgren et al. 2001). Secondary haemorrhages occur mainly as minor bleedings, presenting mostly on 5 to 7 postoperative days, but can also be life threatening, especially in children (Wei et al. 2000).

Several risk factors for post-tonsillectomy haemorrhage have been presented. Although factors such as intraoperative blood loss volume and recent viral illness have been postulated to be associated with primary postoperative haemorrhage, neither factor has been proven to be statistically significant (Wei et al. 2000). The older age (>10 years), prolonged procedure, excessive intraoperative blood loss, the use of intraoperative vasoconstrictors, history of chronic tonsillitis, and elevated postoperative mean arterial pressure may increase the risk of haemorrhage. Also the patients sex (female) and the time of year the surgery is performed (winter) are associated with increased bleeding (Myssiorek and Alvi 1996, Collison and Mettler 2000). On the other hand, Wei and co-workers (2000) concluded from 4662 tonsillectomy patients that age was the only factor found to be statistically significant among the bleeding patients and the control group: the highest incidence (4%) of post-tonsillectomy haemorrhage occurred in patients 21 to 30 years of age. Liu and
co-workers (2001) have concluded in a retrospective study with 1438 patients that 12 years and older were most likely and those 3 years and younger were least likely to have post-tonsillectomy haemorrhage.

To avoid peri- and postoperative bleeding, tonsil dissection should be performed in the plane between the capsule and fossa musculature to avoid leaving tonsil remnants and to prevent muscular tears. It is reported that general anaesthesia and the use of diathermy or a electrodisssection method reduced the rate of immediate post-tonsillectomy haemorrhage (Carmody et al. 1982, Kennedy and Strom 1990). A “cold-knife” technique and prophylactic cautery of the tonsil fossa decreased primary haemorrhage from 3% to 0.2% (Williams and Pope 1973). Moreover, Handler and co-workers (1986) have concluded that overall adenotonsillar bleeding occurs less frequently than in the past, possibly because of electrocautery.

There is an agreement that laser offers good cutting and haemostasis, but its effect on post-tonsillectomy bleeding is controversial (Oas and Partels 1990, Auv et al. 1997, Saito et al. 1999). In the recent study with fibrin glue, Stoeckli and co-workers (1999) did not notice any beneficial effect of fibrin glue in postoperative haemostatic action.

The use of intraoperative injection of local anaesthetic, with or without adrenaline or perioperative antimicrobial therapy have not been shown to significantly reduce postoperative bleeding (Wei et al. 2000).

The use of NSAIDs during and after tonsillectomy has been controversial because of fear of increased postoperative bleeding complications. Earlier studies have indicated that perioperative use of some NSAIDs, for example ketorolac, is associated with a two- to five-fold higher incidence of postoperative haemorrhage compared to those patients using opioid analgesia only (Gallagher et al. 1995, Splinter et al. 1996, Judkins et al. 1996). In a study of 712 patients with tonsillectomy Carrick (1984) found that haemorrhage occurred in 4% of the patients receiving aspirin compared to 0.3 in the control group receiving paracetamol. Moreover, Stage and co-workers (1988) found a significantly higher incidence of late postoperative bleeding in
patients treated with acetylsalicylic acid (3\%) than in patients treated with paracetamol (0.5\%) in a study of 832 patients.

Diclofenac administered pre- and postoperatively to patients undergoing uvulopalato-pharyngoplasty and tonsillectomy did not result in increased bleeding time when compared with placebo (Ejnell et al. 1992). Using the same type of surgery, Virtanen and co-workers (1999) did not find any increase in bleeding complications with ketoprofen compared to fentanyl. Tarkkila and Saarnivaara (1999) did not notice any difference in bleeding complications with ketorolac, diclofenac or ketoprofen compared to placebo during the first 24 hours after tonsillectomy. Rømsing and co-workers (2000) reported no bleeding episodes in a study of diclofenac prescribed for the first 72 hours after tonsillectomy. Even though NSAIDs have been proven to be effective analgesics for peri- and postoperative pain, the safety of NSAIDs during and after operations with risk of bleeding, e.g. tonsillectomy is still questioned, and more large and controlled studies are needed.

When significant bleeding occurs, the evaluation and required intervention should be made in the emergency department. Most haemorrhages can be stopped by electrocautery or ligations. In the case of severe or continuous bleeding re-operation should be made and blood transfusion considered. However, mostly bleedings after tonsillectomy are considered as minor, and the evaluation can be made at home.

2.6.4.2. Other complications

Nausea and vomiting are frequent after tonsillectomy (Lee and Sharp 1996). In addition to general anaesthesia and swallowed blood, nausea and vomiting can be caused by opioid analgesics. However, a recent study indicates that these opioid-related adverse effects may be reduced by using ketoprofen as a background analgesic (Kokki et al. 1999a). If this is caused by the reduction of the amount of opioids used, or possibly by an antiemetic effects of ketoprofen, remains open.
There are some studies reporting that a single-dose of dexamethasone given during tonsillectomy (or adenotonsillectomy) reduces nausea and vomiting for 24 hours after surgery (Vosdoganis and Baines 1999, Steward et al. 2000). Tom and co-workers (1996) have found that the percentage of patients vomiting was reduced significantly from 48% to 4%. However, other studies have not noticed any benefit from dexamethasone in that respect (Catlin and Grimes 1991, Volk et al. 1993).

Several factors can cause dehydration after tonsillectomy. General anaesthesia and swallowed blood may induce nausea and vomiting and induce dehydration. Odynophagia may reduce the ability to maintain liquid intake by mouth. Fever can also increase excessive fluid losses and aggravate dehydration. Sore throat, a smaller volume reserve and lack of co-operation increases the risk of dehydration in small children (Randall and Hoffer 1998). Otalgia frequently accompanies sore throat, and it represents referred pain, most likely via the glossopharyngeal nerve. Minor uvular and pharyngeal oedema are common and may aggravate postoperative pain.
3. AIMS OF THE PRESENT STUDY

The aims of the present study were:

1. To evaluate the effect of iv ketoprofen on operation time and length of hospital stay in 1-9 year old children undergoing adenoidectomy. (I)

2. To evaluate the efficacy and safety of iv ketoprofen for pain treatment before discharge, administrated either before or after tonsillectomy in adults and in children. (II, III)

3. To evaluate postoperative pain and recovery after discharge following tonsillectomy in adults and in children. (IV, V)

4. To evaluate the efficacy and safety of ketoprofen in pain treatment after discharge following tonsillectomy in adults and in children. (IV, V)
4. PATIENTS AND METHODS

4.1. Patients

A total of 550 patients were investigated in three different patient groups. Patient group A, 335 children underwent elective adenoidectomy in Kuopio University Hospital between September 1995 and February 1998. Other results of this same patient population have been described earlier (Nikanne et al. 1997a, Nikanne et al. 1997b, Kokki et al. 1998). In patient group B, 106 adults underwent elective tonsillectomy (or adenotonsillectomy) in Kuopio University Hospital between September 1998 and December 1999. In patient group C, 109 children underwent elective tonsillectomy (or adenotonsillectomy) in Kuopio University Hospital (n=75) or Päijät-Häme Central Hospital (n=34) between September 1998 and June 2000.

Inclusion criteria were:
1. Elective adenoidectomy (patient group A), tonsillectomy or adenotonsillectomy (patient groups B and C)
2. ASA (American Society of Anesthesiologists) physical status I (patient group A, B and C) or II (patient group A)
3. No contraindications to NSAIDs (patient groups A, B and C), paracetamol or codeine (patient groups B and C)
4. Written informed consent given by the patients and by the parents of the children

Exclusion criteria were:
1. Allergy to ketoprofen or other NSAIDs (patient groups A, B and C), paracetamol or codeine (patient groups B and C)
2. Asthma, if symptoms have been exacerbated with NSAIDs
3. Haemorrhagic diathesis
4. Kidney disease
5. Liver disease.
4.2. Pain medication

4.2.1. In the hospital

Three different patient groups (A, B and C) were studied:

**Patient group A (adenoidectomy group, n= 335) (I)**

Patients were divided into three subgroups.

**Subgroup I (n=99)**

*Ketoprofen group*, 1.0+1.0 mg/kg (n=54):

Children who received a 1.0 mg/kg ketoprofen bolus iv (Orudis®, Rhone-Poulenc-Rorer, Helsinki, Finland ) after induction followed by a 1.0 mg /kg ketoprofen infusion over two hours.

*Placebo-subgroup (n=45):*

Children who received normal saline in the same manner.

**Subgroup II (n=107)**

*Two ketoprofen groups*, 0.5 mg/kg (n=54) and 2.0 mg/kg (n=53):

Children who received ketoprofen after induction of anaesthesia made up to 10 ml with normal saline injected iv over 10 min.

**Subgroup III (n=129)**

*Three ketoprofen groups*, 0.3 mg/kg (n=33), 1 mg/kg (n=29) and 3.0 mg/kg (n=32):

Children who received ketoprofen after induction of anaesthesia made up to 10 ml with normal saline injected iv over 10 min.

*Placebo-subgroup (n=35):*

Children who received normal saline in the same manner.
Rescue analgesia:
All children were given fentanyl 1 µg/kg iv for rescue analgesia if the pain score at rest was ≥3 on a scale 0-10.

**Patient groups B and C (tonsillectomy groups) (II-V)**
Patients (n=215, 106 adults and 109 children) were allocated randomly to one of two ketoprofen groups or a placebo group as described below.

*Pre-ketoprofen group* (n=41 in adults, n=47 in children):
Patients were given ketoprofen 0.5 mg/kg (Ketorin®, Orion, Espoo, Finland) intravenously made up to 10 ml with normal saline and injected over 5 min after induction of anaesthesia but before surgical incision, and placebo (10 ml normal saline) injected over 5 min in the postanaesthesia care unit (PACU) followed by a continuous intravenous ketoprofen infusion of 3 mg/kg over 24 h.

*Post-ketoprofen group* (n=40 in adults, n=42 in children):
Patients were given placebo (10 ml normal saline) after induction, and ketoprofen 0.5 mg/kg intravenously in the PACU followed by a ketoprofen infusion of 3 mg/kg over 24 h.

*Placebo group* (n=25 in adults, n=20 in children):
Patients were given normal saline after induction and in the PACU, followed by a normal saline infusion.

Rescue analgesia:
Rescue analgesic medication, which consisted of oxycodone 0.05 mg/kg iv or 0.1 mg/kg im, was given if the observed pain score at rest was ≥ 3 on a scale of 0-10. The oxycodone dose was repeated at 15-30 min intervals until the pain had diminished to slight (the observed pain score at rest <3).
4.2.2. At home

Patient groups B and C (II-V):
For postoperative pain relief at home, all patients were given ketoprofen 25 mg tablets, or 50 or 100 mg capsules (Ketorin®, Orion, Espoo, Finland) and were instructed to take 2 or 3 tablets a day (3-5 mg/kg/day) for 5 to 10 days. Thereafter, patients were instructed to take ketoprofen on an as required basis. For rescue analgesia, adults and children older than 14 years were prescribed paracetamol-codeine tablets up to 4-8 tablets a day (Panacod®, Sanofi-Winthrop, Solna, Sweden, paracetamol 500 mg - codeine 30 mg/tablet) and children 14 years or younger were prescribed paracetamol 250 or 500 mg tablets at a dose of 15-20 mg/kg up to four times a day (Panadol®, SmithKline Beecham, Helsinki, Finland). Rescue analgesics were instructed to be taken when pain relief with ketoprofen was insufficient.

4.2.3. Trial plan for ketoprofen

<table>
<thead>
<tr>
<th>Patient group A</th>
<th>Adenoidectomy</th>
<th>Hospital: iv ketoprofen vs. placebo</th>
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<tr>
<td>335 children</td>
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<table>
<thead>
<tr>
<th>Patient group B</th>
<th>Tonsillectomy or adenotonsillectomy</th>
<th>Hospital: iv ketoprofen vs. placebo (pre- and postoperative administration) Home: oral ketoprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>106 adults</td>
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<tr>
<th>Patient group C</th>
<th>Tonsillectomy or adenotonsillectomy</th>
<th>Hospital: iv ketoprofen vs. placebo (pre- and postoperative administration) Home: oral ketoprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>109 children</td>
<td></td>
<td></td>
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</table>
4.3 Anaesthetic and surgical technique

Patient group A:
The same anaesthetic technique was used in all children. Each child was premedicated with diazepam 0.5 mg/kg orally up to a maximum of 10 mg, 30-45 min before induction of anaesthesia. An eutectic mixture of prilocaine and lidocaine (EMLA®, Astra, Södertälje, Sweden) was applied to the skin 60 minutes before venepuncture. Atropine was injected iv and anaesthesia was induced with thiopental, and tracheal intubation was facilitated with atracurium. All children received fentanyl 1 μg/kg iv at induction. Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen. All children were given normal saline 5-10 ml/kg/h iv for intraoperative fluid maintenance.

The adenoids were removed using a curettage technique under indirect visual control. The operations were performed by five experienced ENT- resident surgeons, of whom the present author was one, working in the day-care surgery centre. Haemostasis was controlled with temporary nasopharyngeal packs. Suction-electrocautery was used if needed. After the operation children were transferred to the PACU for continuous monitoring of vital signs and assessment of pain and adverse events. A study nurse recorded the operation time from the first incision to the time when the surgeon finished the operation.

Patient groups B and C:
The same endotracheal anaesthetic technique was used in all patients. Each patient was premedicated with diazepam 60 minutes before induction. EMLA cream was applied to the skin of children 60 minutes before venepuncture. Fentanyl 2 μg/kg was given intravenously and anaesthesia was induced with thiopental 5 mg/kg. Neuromuscular blockade was achieved with cis-atracurium 0.1 mg/kg. Anaesthesia was maintained with 2-3 % sevoflurane (inspired concentration) in 65 % nitrous oxide in oxygen with intermittent positive pressure ventilation. On completion of surgery, neuromuscular block was reversed with neostigmine and glycopyrrolate.
For intraoperative fluid maintenance all patients were given normal saline 10 ml/kg/h and after surgery 5% glucose until they were able to tolerate fluids by mouth.

All tonsillectomies were performed between 08.00 and 14.00 hours by five resident otorhinolaryngologists with a previous experience of over 50 procedures. Bilateral tonsillectomy was performed with an electrodissection technique using unipolar electrocautery set 75W cut and 25W coagulation (Martin ME 200, Martin Medicine Technic, Germany, Erbotom ACC 450, ERBE electromedicin company, Germany), and haemostasis was controlled with temporary packs or electrocautery. The handpiece used was a pin dissection tip (E 1552-6, Valleylab PTY, Ltd., Australia). After the operation patients were transferred to the PACU for continuous monitoring of vital signs and assessment of pain and adverse events. An anaesthesia nurse recorded the operation time from the first incision to the time when the surgeon finished the operation.

4.4. Discharge criteria and the length of stay

Patient group A:
Each child was observed in the PACU for at least 2 hours. Thereafter, the children were discharged when vital signs were stable for 60 minutes, they were awake or easily aroused, had no pain or only mild pain, were able to tolerate clear fluids by mouth, had no bleeding, and had not vomited for 60 minutes. The length of stay was defined as the time from the first incision to the actual discharge from the hospital. A delayed discharge was defined as a child leaving the hospital later than 4 hours after the surgery. Time from the incision to the first urination was also recorded.

Patient groups B and C:
Patients were discharged 24-30 h after the surgery when they had no pain or mild pain, were able to tolerate clear fluids and soft food, had no bleeding, and had no
nausea or vomiting. On discharge, all patients received a ketoprofen tablet or capsule (2 mg/kg).

4.5. Assessment of postoperative pain

4.5.1. In the hospital

Patient groups B and C:
The pain intensity after surgery was assessed by five specially trained research nurses using the Maunuksela pain scale (Maunuksela et al. 1987, 0 = no pain, 10 = worst possible pain) and by asking patients to express their pain on a 100 mm visual analogue scale (VAS, 0 = no pain, 100 = worst possible pain). Pain scores were recorded at rest and on swallowing at 1, 2, 3 and 4 hours following the surgery in the PACU. Thereafter, on the ward, pain scores were recorded at 20.00 and 08.00 hours, and just before discharge. At discharge patients were also asked the worst pain and the average level of pain they had experienced on the ward.

4.5.2. At home

Patient groups B and C:
Postoperative pain at home was assessed by the patients or by the parents of the children. At discharge all patients were given a questionnaire (appendix 1 and 2) which consisted of structured and open-ended questions dealing with the intensity and duration of pain at rest and during swallowing.

During the first seven days pain intensity was assessed twice daily at 0800 h in the morning before analgesic and 1800 h in the evening after taking ketoprofen. Patients also recorded worst pain and average pain daily for the first week. Pain was expressed using a visual analogue scale (VAS; 0= no pain, 100=worst possible pain) and a four-point verbal rating scale (VRS; 1=no pain, 2=mild pain, 3=moderate pain and 4=severe pain). The efficacy of pain medication with ketoprofen, paracetamol
and paracetamol-codeine was evaluated by asking whether medication was sufficient or not. The number of ketoprofen and rescue analgesic doses was recorded daily.

Three weeks after surgery, the patients were mailed a second questionnaire (appendix 3). Patients were asked a series of questions concerning postoperative pain and its duration, adverse events and complaints, and time to return to normal daily activities after surgery. Patients were asked to report all adverse events and additional problems during the second and third week after surgery and then to return the questionnaire. If the questionnaire was not returned within a week or if some details needed to be verified, the patients were contacted by telephone.

### 4.6. Assessment of bleeding

#### 1. Intraoperative bleeding

*Patient group A:*

Surgeons estimated the amount of intraoperative bleeding using a five-point verbal rating scale (1= no bleeding, 2=less than normal, 3=normal, 4=more than normal, 5=profuse), and this was recorded (I).

*Patient groups B and C:*

The intraoperative blood loss was assessed by making a visual estimation of blood lost on sponges and collected in suction bottle (ml) (II-V).

#### 2. Postoperative bleeding

*Patient group A:*

Research nurses observed and recorded postoperative bleeding of each patient in the PACU. Bleeding was classified as minor if the patient was discharged after normal observation, and significant, if discharge was delayed or any intervention was needed to stop the bleeding from the adenoid area.
Patient groups B and C:

Bleeding was classified as minor if medical attention was required and intravenous fluid or suction of the clot was initiated, and major, if electrocautery, re-operation or blood transfusion was required.

4.7. Recording of adverse events

Patient group A:

Research nurses recorded all adverse events and time to the first voiding of each patient in the PACU.

Patient groups B and C:

Time to the first voiding, nausea (the feeling as about to vomit) and vomiting, and all adverse events were recorded for each patient.

The diary at one week (appendix 1 and 2) and at three weeks (appendix 3) contained structured and open-ended questions dealing with adverse events of ketoprofen, postoperative bleeding, need for further medical contact and problems in administering drugs.

4.8. Statistical methods and study design

The statistical analyses were made by the research group with the help of Computing Centre of Kuopio University.

In patient group A (adenoidectomy group) (I), analysis of continuous data was performed using the Mann-Whitney U test in subgroup I and II, and the Kruskal-Wallis test in subgroup III. In patient groups B and C (tonsillectomy groups) (II-V), the statistical analysis of continuous variables was performed using the Kruskal-Wallis test. Patients (n=215, 106 adults and 109 children) were allocated randomly to one of two ketoprofen groups or placebo group as described below. The estimation
of the required sample size in studies B and C was made using data from our pilot study which reported a need of three doses (SD 1.5) of rescue analgesia during the first 24 hours after tonsillectomy. Using this data a sample size of 40 patients in pre-operative and postoperative group was calculated to provide over 80% power to detect a 35% difference in the need of rescue analgesia between the two groups with a 0.05 level of significance. For post hoc analysis the Mann-Whitney U test with Bonferroni correction was used. For categorical variables the chi-square test was used. Correlation between independent variables was tested with the Pearson correlation coefficient. As the study population was collected from three different subgroups with eight groups altogether in patient group A, the association of independent variables on operation time and actual length of stay was analysed by linear regression analysis. Differences were considered statistically significant when the p-value was less than 0.05. Results are presented as number of cases (%), mean (SD) with 10th and 90th percentiles, correlation coefficient (R) or mean difference (95% confidence intervals) as appropriate.

In patient group A a retrospective study design was used. In patient groups B and C at the hospital, a prospective, randomised, double-blind, double-dummy, parallel-group study design was used. Results in patient group A, subgroups I and III, and patient groups B and C were placebo controlled. After discharge in patient groups B and C the study design was prospective, longitudinal, open and descriptive.

4.9. Ethical aspects

The studies were approved by the Ethics Committee of Kuopio University Hospital (no. 3/95, 73/98) and the Ethical Committee of Päijät-Häme District Hospital (no. 115/99) and were conducted in accordance with the latest revision of the Declaration of Helsinki (World Medical Association 2000). The patients or the parents of the children gave a written informed consent. The National Agency for Medicines was notified of the use and the doses of ketoprofen in children less than 12 year-old.
All the manuscripts included in this study are original. However, the outcome before and after discharge have been reported from the same patient group in articles II and IV, and in articles III and V. This has been informed openly to the editors and readers.

**4.10. Interest of conflict**

This study was financially supported by an EVO-grant of Kuopio University Hospital, the Otologic Research Foundation and Kymenlaakso Medical Society. Ketoprofen injections, tablets and capsules were kindly donated by Orion Pharma (Espoo, Finland), but the company did not participate in the trial planning or the analysis of the results.
5. RESULTS

5.1. Patients

In patient group A 335 patients were studied. There were no differences between the treatment groups in sex distribution, age, height, weight or ASA physical status. The patient characteristics are presented in Table 3.

Table 3
Patients and surgery characteristics in patient group A: mean (SD) or number of patients. There were no significant differences between the study groups. (N = 335)

<table>
<thead>
<tr>
<th></th>
<th>Subgroup I</th>
<th>Subgroup II</th>
<th>Subgroup III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0+1.0</td>
<td>2.0</td>
<td>0.5</td>
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<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age (months)</td>
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<tr>
<td>Height (cm)</td>
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<td>96 (16)</td>
<td>95 (15)</td>
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<tr>
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<td>ASA I/II</td>
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</tbody>
</table>

In patient group B 106 adults and in patient group C 109 children were studied. The patient characteristics are presented in Tables 4 and 5. There were no differences between the different treatment groups in sex distribution, age, height or weight. One patient in the placebo group in group C was given ketoprofen during surgery and was therefore withdrawn from further analysis.
Table 4
Patient group B: mean (SD) or number of patients. TE = tonsillectomy, TEA = tonsillectomy and adenoidectomy. There were no significant differences between the study groups. (N=106)

<table>
<thead>
<tr>
<th></th>
<th>Pre-ketoprofen group (n=41)</th>
<th>Post-ketoprofen group (n=40)</th>
<th>Placebo group (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>17 / 24</td>
<td>20 / 20</td>
<td>12 / 13</td>
</tr>
<tr>
<td>Age (yr.)</td>
<td>31 (12)</td>
<td>29 (10)</td>
<td>29 (14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (9)</td>
<td>173 (9)</td>
<td>172 (11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72 (14)</td>
<td>74 (15)</td>
<td>70 (14)</td>
</tr>
<tr>
<td>Operation type (TE/TEA)</td>
<td>34 / 7</td>
<td>33 / 7</td>
<td>20 / 5</td>
</tr>
<tr>
<td><strong>Indication for operation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic tonsillitis</td>
<td>29</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Recurrent tonsillitis</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tonsillar hypertrophy</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5
Patient group C: mean (SD) or the number of patients. TE = tonsillectomy, TEA = tonsillectomy and adenoidectomy. There were no significant differences between the study groups. (N=109)

<table>
<thead>
<tr>
<th></th>
<th>Pre-ketoprofen group (n=47)</th>
<th>Post-ketoprofen group (n=42)</th>
<th>Placebo group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>23 / 24</td>
<td>19 / 23</td>
<td>7 / 13</td>
</tr>
<tr>
<td>Age (yr.)</td>
<td>10 (1)</td>
<td>12 (3)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>143 (24)</td>
<td>153 (20)</td>
<td>148 (22)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40 (19)</td>
<td>48 (16)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>Operation type (TE/TEA)</td>
<td>24 / 23</td>
<td>20 / 22</td>
<td>8 / 12</td>
</tr>
<tr>
<td><strong>Indication for operation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic tonsillitis</td>
<td>9</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Recurrent tonsillitis</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Tonsillar hypertrophy</td>
<td>34</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>
5.2. Indications and type of surgery (II-V)

Indications for surgery are presented in Tables 4 (patient group B) and 5 (patient group C).

Among the adults 87 patients underwent tonsillectomy (TE) and 19 patients adenotonsillectomy (TEA) with a similar distribution across the three study groups (Table 4). There was no difference between these two groups in total rescue analgesic consumption during the first 24 hours, the mean (SD) was 3.6(3.0) doses in patients with TE and 4.1(2.9) doses in patients with TEA. Also the analgesic consumption in the first three weeks was similar between the two groups, 32(16) ketoprofen doses and 22(19) paracetamol+codeine doses in patients with TE vs. 34(14) ketoprofen doses and 20(19) paracetamol+codeine doses in patients with TEA.

Among the children 52 patients underwent tonsillectomy and 57 patients adenotonsillectomy with a similar distribution across the three study groups (Table 5). However, there was no difference between these two groups in total rescue analgesic consumption in the first 24 hours, the mean(SD) was 4.3(2.9) doses in children with TE and 4.0(2.5) doses in children with TEA. In addition the analgesic consumption in the first three weeks was similar between the two groups, 22(11) ketoprofen doses and 13(12) paracetamol+codeine doses in children with TE vs. 22(12) ketoprofen doses and 13(12) paracetamol+codeine doses in children with TEA.

5.3. Duration of surgery, intraoperative blood loss and length of hospital stay

Duration of surgery and actual length of stay at the hospital following incision in the subgroups in patient group A are presented in Table 6. There was no difference between the treatment groups on the duration of surgery, but in subgroup I, the actual length of stay was significantly longer in the placebo group compared to the ketoprofen group 1.0+1.0 mg/kg (P=0.006). In the other subgroups there were no differences between the groups in actual length of stay (Table 6).
Table 6

Duration of surgery and actual length of stay at the hospital following incision in the subgroups (patient group A): mean (SD). (N= 335)

<table>
<thead>
<tr>
<th>Subgroup I</th>
<th>Subgroup II</th>
<th>Subgroup III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0+1.0</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>n=54</td>
<td>n=45</td>
<td>n=53</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>13(5)</td>
<td>13(5)</td>
</tr>
<tr>
<td>Actual length of stay (minutes)</td>
<td>225(44)</td>
<td>251(46)*</td>
</tr>
</tbody>
</table>

* p = 0.006 , placebo compared to ketoprofen 1.0+1.0 mg kg⁻¹ (Mann-Whitney test).

Duration of surgery and intraoperative blood loss in patient group B (II) and patient group C (III) are presented in Table 7. Ketoprofen administration before incision did not increase the duration of surgery or the amount of blood loss in patient groups B and C. In the whole patient population in both studies the amount of intraoperative blood loss correlated positively with the duration of surgery (patient group B, R=0.45, p=0.001, Table 6 and patient group C, R=0.45, p<0.01, Table 6).
Table 7

The duration of surgery and intraoperative blood loss in tonsillectomy (adults, n=106 and children, n=109): mean (SD). There were no significant differences between treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Patient group B (adults)</th>
<th>Patient group C (children)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ketoprofen (n=41)</td>
<td>Post-ketoprofen (n=40)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>24 (15)</td>
<td>23 (13)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>22 (26)</td>
<td>30 (40)</td>
</tr>
</tbody>
</table>
5.4. Regression analysis

In addition to the primary analysis a multiple regression analysis was performed in patient group A to see if gender, weight, height or age of the children, number of ketoprofen dose, subgroup of the study or administration of ketoprofen/placebo affected operation time. In the multiple regression analysis of the whole study group only 9% of operation time was explained with these variables.

Actual length of stay was tested between the same variables and in addition with the number of doses of rescue analgesic, estimated intraoperative bleeding and worst pain in the PACU (at rest and during swallowing). Eighteen percent of actual length of stay was explained by the variables tested. Of significance were the number of doses of rescue analgesics and the phase of the study (p<0.05).

5.5. The need for rescue analgesics

The need for rescue analgesics was investigated in all three patient groups. In patient group A ketoprofen proved to be an effective analgesic: in subgroups I and III patients in the placebo groups needed significantly more rescue analgesics and fentanyl doses than patients in ketoprofen groups during the stay in the PACU (p<0.05).

Number of oxycodone doses during the first 24 hours after tonsillectomy in adults is presented in Table 8. Patients in the placebo group received significantly more oxycodone doses than did patients in the two ketoprofen groups (P=0.001). The mean difference between the placebo group and the pre-ketoprofen group was 2.6 (95% CI: 1.3 to 3.9) doses, and between the placebo group and the post-ketoprofen group 2.6 (95% CI: 1.1 to 4.0) doses. There was no difference between the study groups in the proportion of patients receiving oxycodone in the PACU. During the next 20 h significantly more patients in the placebo group (24 patients (96%)) received oxycodone compared with the pre-ketoprofen group (27 patients (66%)) (difference
30%, 95% CI: 14 to 47%) and with the post-ketoprofen group (22 patients (55%))
difference 41%, 95% CI: 24 to 58%) (P=0.002). We however, did not notice a pre-
emptive effect with ketoprofen, because recovery was similar whether ketoprofen
was administered before or after the operation.

Table 8

Number of oxycodone doses during the first 24 hours after surgery in adults (patient
group B): mean (SD), (N=106)

<table>
<thead>
<tr>
<th></th>
<th>Pre-ketoprofen (n=41)</th>
<th>Post-ketoprofen (n=40)</th>
<th>Placebo (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early: 0 to 4 h</td>
<td>1.5 (1.2)</td>
<td>1.5 (1.4)</td>
<td>2.7 (2.0) *</td>
</tr>
<tr>
<td>Late: 5 to 24 h</td>
<td>1.5 (1.8)</td>
<td>1.5 (2.0)</td>
<td>2.9 (1.7) **</td>
</tr>
<tr>
<td>Total</td>
<td>3.0 (2.5)</td>
<td>3.1 (2.9)</td>
<td>5.6 (1.7) **</td>
</tr>
</tbody>
</table>

*Significantly different from pre-ketoprofen (p=0.03) and post-ketoprofen (p=0.036).
**Significantly different (p=<0.01) from pre-ketoprofen and post-ketoprofen (Mann-
Whitney test with Bonferroni correction).

In children (patient group C) ketoprofen did not reduce the number of patients
receiving rescue analgesic. However, patients in the placebo group received 30%
more oxycodone doses than those in the two ketoprofen groups, but this difference
was not statistically significant (mean difference 1.2 doses, 95% CI: - 0.1 to 2.5 doses,
p=0.074).
5.6. Pain after surgery

In patient group A (children with adenoidectomy), worst pain at rest and during swallowing in subgroup I was higher in the placebo group than in the ketoprofen group (p<0.01). No other difference was noticed. (I)

In patient group B (adults), patients in the two ketoprofen groups experienced less pain after tonsillectomy at rest and on swallowing than did those in the placebo group. (II) Pain at rest and on swallowing in the PACU and 24 h after operation are presented in Figure 2a and 2b. The occurrence of insufficient pain relief, defined as a VAS score of average level of pain ≥30 mm at rest and ≥50 mm on swallowing, was significantly more common in patients receiving placebo than in those receiving ketoprofen (p=0.001).
Figure 2a and 2b

Mean (SD) visual analogue scale (VAS) pain scores in adults at rest and during swallowing for the study groups at various postoperative times. * p < 0.05 Placebo group compared with both ketoprofen groups (Mann-Whitney test with Bonferroni correction).
The experienced average and worst pain at rest and on swallowing recorded on the ward in adults are presented in Figure 3. The mean pain scores at rest and on swallowing were less in both ketoprofen groups than in the placebo group ($p=0.001$). A similar difference was observed in worst pain at rest and on swallowing (Figure 3).

Figure 3

The proportion of patients in adults with insufficient pain relief, defined as visual analogue scale (VAS) pain score $\geq 30$ mm at rest and $\geq 50$ mm during swallowing, in the study groups. * $p = 0.001$ Placebo group compared with both ketoprofen groups (chi-square test).

In patient group C (children), we did not find any significant difference in pain scores between the three treatment groups (Figure 4a and 4b). (III) Pain relief at rest was sufficient in all treatment groups (defined as a VASr $<30$), so was the average level of pain on swallowing (defined as a VASs $<50$). In contrast, at discharge over half of the patients suffered severe pain on swallowing. In all three treatment groups the worst pain experienced in the 24 hour period after surgery was also high both at
rest (VASr ≥ 30) and on swallowing (VASs ≥ 50). In patient group C, there was a significant positive correlation between the expressed and observed pain scores (R=0.63 to 0.88, P= 0.01). (III)

Figure 4a and 4b

Mean (SD) visual analogue scale (VAS) pain scores in children at rest and during swallowing for the study groups at various postoperative times. No significant difference between study groups.
5.7. *Adverse events in the hospital*

After adenoidectomy (patient group A) only two children had a delayed discharge. One child in the ketoprofen group 1.0 mg/kg had a swollen uvula after a difficult intubation and he was observed on the ward overnight. One child in the ketoprofen group 0.3 mg/kg had low oxygen saturation on room air in the PACU and his discharge was delayed for a few hours. Thereafter the recovery was uneventful in both of them.

The amount of intraoperative bleeding was estimated to be similar in the study groups. Three (4%) children in the placebo groups and 16 (6%) children in the ketoprofen groups vomited before discharge.

Seventy-six percent of the children voided before discharge, and there were no differences between the study groups. In those children who voided, there were no significant differences in the time to the first voiding between the study groups.

Adverse events in adults (II) and children (III) after tonsillectomy are presented in Table 9. Thirty-seven (35%) adults and forty-seven (43%) children developed one or more adverse events. The incidence of adverse events in both studies was similar in the three treatment groups and no serious adverse events were noticed. There was no difference between the study groups in the time to first voiding after surgery.
Table 9

Adverse events in adults (n=106) and in children (n=109) after tonsillectomy in the treatment groups (number (%)).

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th></th>
<th></th>
<th>Children</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ketoprofen</td>
<td>Post-ketoprofen</td>
<td>Placebo</td>
<td>Pre-ketoprofen</td>
<td>Post-ketoprofen</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=41)</td>
<td>(n=40)</td>
<td>(n=25)</td>
<td>(n=47)</td>
<td>(n=42)</td>
<td>(n=20)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early: 0 to 4 h</td>
<td>7 %</td>
<td>3 %</td>
<td>4 %</td>
<td>13 %</td>
<td>12 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Late: 5 to 24 h</td>
<td>27 %</td>
<td>18 %</td>
<td>20 %</td>
<td>30 %</td>
<td>33 %</td>
<td>35 %</td>
</tr>
<tr>
<td>Recurrent ≥3 episodes</td>
<td>5 %</td>
<td>5 %</td>
<td>4 %</td>
<td>11 %</td>
<td>19 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Total</td>
<td>29 %</td>
<td>18 %</td>
<td>20 %</td>
<td>36 %</td>
<td>36 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Nausea without vomiting</td>
<td>7 %</td>
<td>13 %</td>
<td>8 %</td>
<td>11 %</td>
<td>12 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>-</td>
<td>4 %</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 %</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Excessively sedated</td>
<td>-</td>
<td>-</td>
<td>8 %</td>
<td>4 %</td>
<td>-</td>
<td>5 %</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 %</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 %</td>
</tr>
<tr>
<td>Flushing on face</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 %</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 %</td>
</tr>
<tr>
<td>Stomach ache</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 %</td>
<td>-</td>
</tr>
<tr>
<td>Patients with one or more adverse events</td>
<td>37%</td>
<td>33%</td>
<td>36%</td>
<td>47%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>
5.8. Postoperative haemorrhage

In patient group A there occurred no clinically significant postoperative haemorrhage after adenoidectomy. (I)

Clinically significant primary haemorrhage after tonsillectomy occurred in two adult patients (5 %) in the pre-ketoprofen group and in one patient (3%) in the post-ketoprofen group, but none in the placebo group. (II) In children, clinically significant primary haemorrhage after tonsillectomy occurred in two patients (5 %) in the post-ketoprofen group and none in the pre-ketoprofen or in the placebo group. All five patients needed electrocautery under local anaesthesia to stop bleeding, but no blood transfusions were needed. (II,III)

5.9. Recovery from tonsillectomy after discharge

A total of 102 adult (patient group B, response rate 96%) and 102 children (patient group C, response rate 94%) were studied. There were no significant differences between the three treatment groups in adults or in children in recovery after discharge and therefore the results are presented for the whole study group.

5.9.1. First week after surgery (IV,V)

Pain scores at rest and during swallowing during the first week and at three weeks after tonsillectomy are presented in Figure 5a and 5b (adults), and 6a and 6b (children). All adults and children reported pain during the first week after surgery. Pain scores were higher in the mornings before the first analgesic dose than in the evenings after ketoprofen administration. Moreover, 50% or more patients had significant pain (at rest VAS ≥30 mm and during swallowing VAS ≥50 mm) in the first six (adults) and in the first five (children) mornings after surgery.
Figure 5a and 5b

Pain scores at rest and during swallowing in adults during the first week and at three weeks after tonsillectomy on a 100 mm VAS in the mornings before the first analgesic dose and in the evenings after ketoprofen administration. Data are means (SD).
Figure 6a and 6b

Pain scores at rest and during swallowing in children during the first week and at three weeks after tonsillectomy on a 100 mm VAS in the mornings before the first analgesic dose and in the evenings after ketoprofen administration. Data are means (SD).
Pain disturbed the sleep of the patients because most patients woke up due to pain at least once during the first seven (adults) and the first six (children) postoperative nights.

Need for rescue analgesic during the first week after tonsillectomy in adults and in children are presented in Figure 7a and 7b. Most patients used ketoprofen for the first five postoperative days as defined in the protocol. At the end of the first postoperative week, 85 out of 102 adults (83%) and 84 out of 102 children (82%) continued to need regular ketoprofen treatment. In addition to ketoprofen, 99 adults (97%) and 87 children (85%) used paracetamol-codeine or paracetamol for rescue analgesia at home. More than 50% of them required 1-3 rescue analgesic doses daily during the first postoperative week.

Figure 7a and 7b

Need for rescue analgesics in adults and in children during the first week after tonsillectomy. Data are proportion of patients.
5.9.2. Three weeks after surgery (IV,V)

At three weeks after tonsillectomy 55 out of 102 adults (54%) and 40 out of 102 children (40%) still had some pain at rest and 86 and 76 patients (84% and 75%) during swallowing, respectively. Therefore 76 adults (75%) and 82 children (80%) continued the analgesic treatment. The patient satisfaction with the analgesic treatment was high, because 82 patients (80%) in both studies reported that the analgesic efficacy of ketoprofen combined with paracetamol-codeine or paracetamol was sufficient.

The median time for pain cessation (pain at rest or on swallowing) in adults was 11 days (range, 3 to 24 days) and in children 9 days (1 to 20 days). The median duration of analgesic treatment in adults was 12 days (5 to 25 days) and in children 10 days (4 to 19 days), respectively. The median of ketoprofen doses during the three weeks in adults was 30 capsules (6 to 102 capsules) and in children 25 capsules (7 to 55 capsules), and the median of rescue analgesic doses in adults was 17 tablets (0 to 110 tablets) and in
children 11 tablets (0 to 60 tablets). Cessation of significant pain on drinking in adults occurred after 7 days (1 to 18 days) and on eating solid food after 11 days (1 to 20 days), and in children after 6 days (0 to 21 days) and 9 days (2 to 22 days), respectively. Adults reported the first normal night sleep at 7 days (0 to 18 days) and children at 6 days (0 to 21 days) after surgery. Adults were able to return back to normal daily activities after 12 days (2 to 24 days) and children after 9 days (2 to 26 days).

5.9.3. Complaints at home (IV,V)

Adverse-events after tonsillectomy at home during recovery in adults and in children are shown in Table 10. Twelve adults out of 102 and 8 children out of 102 contacted the hospital because of secondary postoperative bleeding, and 9 adults and 5 children needed electrocautery under local anaesthesia to stop the bleeding. None of the adults or children needed re-operation. One child had to receive a blood transfusion.

Nineteen of the adults and 19 of the children reported to having had problems in administering the analgesics at home. The most common encountered problems were difficulties in swallowing a tablet or capsule (9 patients in adults and 12 patients in children). Two of the adults and 3 children described the drugs as tasting unpleasant. Eight adults reported short duration of analgesic action.
Table 10

Adverse-events during the three weeks after tonsillectomy. Data are numbers of cases.

<table>
<thead>
<tr>
<th>Event</th>
<th>Adults (n=102)</th>
<th>Children (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>Significant bleeding in the tonsillar bed</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Sedation</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gastric distress</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Numbness of extremities</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal rumbling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Irregular bleeding</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Flu</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total number of adverse-events</strong></td>
<td><strong>91</strong></td>
<td><strong>53</strong></td>
</tr>
<tr>
<td><strong>Number of patients with one or more adverse events</strong></td>
<td><strong>50 (49%)</strong></td>
<td><strong>48 (47%)</strong></td>
</tr>
</tbody>
</table>
5.9.4. Influence of age (V)

Since children younger than 10-years-old are expected to recover faster after tonsillectomy than those older than 10 years (Lavy 1997), a post hoc analysis of the outcome of these two age groups was compared. Forty-four children were 10-years-old or younger and 58 were older. A significant difference was found in favour of the younger age group in pain duration (p=0.003), length of analgesic treatment (p=0.001), cessation of significant pain on drinking (p=0.02) and eating (p=0.002), and pain at three weeks on swallowing (p=0.009). The median of rescue analgesic doses was 8 doses (0-41 doses) in the younger age group and 14 (0-60 doses) in the older age group (p=0.006).
6. DISCUSSION

6.1. Effect of ketoprofen on duration of surgery and discharge time after adenoidectomy

Earlier studies (Nikanne et al. 1997a, Nikanne et al. 1997b, Kokki et al. 1998) reported that ketoprofen is a safe and potent non-opioid analgesic after adenoidectomy in young children. Ketoprofen did not cause any serious side-effects or increase bleeding. In the present study a further analysis of the same sample of young children with adenoidectomy showed that pre-incisional ketoprofen does not prolong the operation time or delay discharge. No clinically significant bleeding or other serious adverse effects occurred. This proves that ketoprofen is a safe analgesic for children undergoing adenoidectomy.

6.2. Pain and analgesic effect of ketoprofen after tonsillectomy

Pre-emptive analgesia should be a rational approach to the treatment of postoperative pain based on our knowledge of acute pain physiology (Kehlet and Dahl 1993). Pre-emptive or proactive administration of NSAIDs is justified because of the delayed action of these drugs. In the present study we did not notice a pre-emptive effect with iv ketoprofen. Recovery and rescue analgesic consumption was similar when ketoprofen was administered either before or after surgery. Our study is in accordance with other studies (Kehlet and Dahl 1993, Zacharias et al. 1996).

Intravenous ketoprofen was an effective analgesic in adults for 24 hours after tonsillectomy, whereas in children this effect was not seen so clearly. Adult patients in the two ketoprofen groups experienced less pain at rest and on swallowing than did those in the placebo group. Also, the use of ketoprofen significantly reduced the number of oxycodone doses needed after the operation in adults. In children we did not find a
significant difference in pain scores between the three study groups. However, patients in the placebo group received 30% more oxycodone doses than those in the two ketoprofen groups.

In the present study we gave ketoprofen 0.5 mg/kg pre- or postoperatively and continued with an infusion of 3 mg/kg over 24 hours. The same opioid sparing effect and less painful immediate recovery after tonsillectomy have been observed with a bolus of 100 mg iv given preoperatively in adults (Tarkkila and Saarnivaara 1999). Our chosen amount of ketoprofen for children turned out to be rather small. Previous studies have reported that much higher doses, up to 3.0 mg/kg of a single administration and 5 mg/kg infusion over 24 hours, have proved to be safe without any increase in adverse events in children (Kokki et al. 1998, Kokki et al. 1999b). However, because we did not have any previous experience with the use of ketoprofen in children during tonsillectomy, where the risk of bleeding is high, we decided to use a rather small dose of ketoprofen. We conclude, that the used amount of ketoprofen provided effective analgesia in adults, whereas children need a higher dose of ketoprofen to reach a good analgesic effect. On the other hand, children also seem to tolerate higher doses of ketoprofen than adults (Nikanne et al. 1999). A study in children with higher than 0.5 mg/kg dose of iv ketoprofen is needed to show the analgesic efficacy immediately after tonsillectomy.

The present study shows that pain after tonsillectomy is significant and persists relatively unchanged for the first five days. This is also supported by other studies (Toma et al. 1995, Lavy 1997, Murthy and Laing 1998). Despite using proactive pain treatment, tonsillectomy was still associated with significant pain that lasted on average for 11 days in adults and 9 days in children. We found that the age of children had minor clinical influence on the recovery because the median cessation was one day shorter in children younger than 10 years compared with older children. This may be caused by the fact that pain is difficult to measure precisely and reliably in small
children. In this post hoc analysis, however, it should be noticed that smaller children were treated with paracetamol and older children were treated with paracetamol-codeine for rescue analgesic. This was, because during the time of the study, codeine was not commonly used in small children in Finland.

Ketoprofen as a sole analgesic for pain after tonsillectomy did not demonstrate sufficient efficacy, because the use of rescue analgesics was high both in adults and in children. However, when combined with paracetamol or paracetamol-codeine tablets ketoprofen provided satisfactory pain relief for most patients. Since over half of the patients in both studies experienced severe pain during swallowing, it is obvious that it may be difficult to achieve satisfactory pain management at home. Severe pain may lead to poor oral intake and dehydration causing morbidity and delayed recovery, occasionally readmission to the hospital may even be necessary (Blakeslee et al. 1997). Unrelieved pain has been reported to be a predominant reason for postoperative consultations after tonsillectomy (Runyby et al. 1999).

Severe pain affects not only daytime functions, but also sleeping patterns are disturbed, and the control of pain during the night seemed to be a problem. This was also found by Toma and co-workers (1995). In their study many patients commented on the difficulty in controlling night-time pain, as no oral analgesia lasted long enough to provide uninterrupted sleep. In the present studies 50% of the patients woke up every night because of pain during the first six nights after surgery, and pain scores were also highest in the mornings. This may be explained by the preparations used. Clinically significant analgesic action of standard ketoprofen tablets and capsules is around six hours and that of paracetamol or paracetamol-codeine tablets just four hours (Turek and Baird 1988). Therefore longer acting preparations of these drugs, or an analgesic with a longer action should be considered for use in the evenings to allow uninterrupted sleep during recovery.
The present studies indicate that pain treatment at home should be improved. An appropriate pain assessment tool is essential to provide optimal analgesia, particularly in children. Pain assessment should be repeated regularly in response to analgesic interventions (Brennan 1999). The patients and the parents should be educated in giving postoperative analgesia on a regular proactive basis rather than waiting for a patient to become excessively uncomfortable. In children, a recent study has shown that even trained nurses tend to underestimate children’s pain (Rømsing et al. 1996). Finley and co-workers (1996) have reported that when parents recognize that their children are in pain, most give inadequate doses of medication to control the pain. It is therefore important that patients and parents are provided with clear instructions about pain treatment both verbally and in writing, that analgesics should be used on a scheduled basis and that regular pain treatment should cover at least the first five days after tonsillectomy.

6.3. Perioperative haemorrhage

One of the major concerns of tonsillectomy is bleeding. In both adults and children the perioperative bleeding was not increased by given ketoprofen preoperatively. Ketoprofen administration before incision did not increase the duration of surgery.

Ketoprofen, as other NSAIDs, inhibit platelet cyclo-oxygenase, thereby blocking the formation of thromboxane A2 and this leads to a systemic bleeding tendency (Schafer 1995, Vane and Botting 1996). However, the clinical significance of increased intraoperative bleeding with NSAIDs is unclear. There have been several clinical studies reporting increased perioperative bleeding associated with NSAIDs (Gunter et al. 1995, Schmidt 2001). Other studies have also concluded that the risk of bleeding varies between different NSAIDs. Ketorolac has been associated with a higher incidence of bleeding than propionic acid derivatives (ibuprofen, naproxen or ketoprofen) (Rusy et al. 1995, Bailey 1997). More recent studies however, have not reported such increased
perioperative bleeding effects with ketoprofen (Kokki et al. 1998, Tarkkila and Saarnivaara 1999, Basto et al. 2001). In these studies ketoprofen has been used safely in different kinds of operations e.g. adenoidectomy, tonsillectomy and thyreoidectomy. Our studies with patients undergoing tonsillectomy support these recent findings, and we conclude that ketoprofen could be safely used during tonsillectomy in healthy patients. In children, however, the safety of larger doses of ketoprofen than used in this study should be tested, because the effect on pain after tonsillectomy appeared to be insufficient. On the other hand, because we did not notice a pre-emptive effect with ketoprofen, we suggest that the first dose of ketoprofen is administered after completion of surgery.

6.4. Postoperative haemorrhage

The overall significant post-tonsillectomy haemorrhage rate in adults was 12% and in children 7%. The incidence of significant post-tonsillectomy haemorrhage cited in the literature ranges from 0.1% to 33%, depending on severity and how to define post-tonsillectomy haemorrhage (Wei et al. 2000, Liu et al. 2001, Blomgren et al. 2001, Windfuhr and Ulbrich 2001). However, comparing haemorrhage rates between different studies is difficult, because an inclusion criterion for haemorrhage varies a lot. In some studies, only those haemorrhages that needed re-operation under general anaesthesia were recorded (Windfuhr and Ulbrich 2001). Other studies have reported high haemorrhage rates (33%) when all major and minor bleedings were evaluated (Blomgren et al. 2001). We defined major or significant post-tonsillectomy haemorrhage as that which was so profuse that it required electrocautery, re-operation or blood transfusion, and minor haemorrhage as all other bleedings reported in the questionnaires.
6.4.1. Primary haemorrhage

In the study on adults the primary haemorrhage rate was 3% whereas in children 2%, and there was no difference between the study groups. In the literature, the primary haemorrhage rate varies between 0.1 and 4% (Handler et al. 1986, Tami et al. 1987, Watson et al. 1993, Conley et al. 1999, Collison and Metler 2000, Blomgren et al. 2001, Pickering et al. 2002). Thus, the incidence of primary post-tonsillectomy haemorrhage in our studies did not differ from those previously reported. On the other hand, there are recent reports where no postoperative bleeding in patients undergoing tonsillectomy using ketoprofen is recorded (Tarkkila and Saarnivaara 1999, Virtaniemi et al. 1999). However these studies have studied a rather small number of patients.

The use of NSAIDs can lead to prolonged bleeding time and increased blood loss during and after surgery even in healthy patients (Kam 2000). However, the effect of NSAIDs for primary haemorrhage and its clinical significance during tonsillectomy is controversial. Several studies have reported an increased risk of haemorrhage with NSAIDs, particularly with ketorolac (Gunter et al. 1995, Rusy et al. 1995, Judkins et al. 1996). Kotorolac has also been associated with a higher incidence of bleeding than propionic acid derivatives (ibuprofen, naproxen or ketoprofen) (Kristensen et al. 1988, Gallagher et al. 1995, Rusy et al. 1995, Kokki et al. 1998, Smith and Wilde 1999). Thus, the studies suggest that the risk of bleeding varies with different NSAIDs. However, all studies have not found any risk of primary haemorrhage with different NSAIDs (Tarkkila and Saarnivaara 1999). Moreover, there is no difference in the incidence of post-tonsillectomy bleeding when paracetamol (or paracetamol-codeine) is used comparing with NSAIDs (St Charles et al. 1997). Haemorrhages are also reported when opioids are used alone (Bailey et al. 1997, Agrawal et al. 1999, Tarkkila and Saarnivaara 1999). In the present studies with ketoprofen, three adult patients and two children experienced primary post-tonsillectomy haemorrhage. None of them were serious, but all needed electrocautery. According to our present studies, it seems that ketoprofen
does not increase the risk for primary post-tonsillectomy haemorrhage. However, a comprehensive review of NSAID use recommended that NSAID should be withheld from patients after tonsillectomy if there has been increased perioperative blood loss or if there is evidence of reduced platelet function (Maunuksela et al. 1993).

6.4.2. Secondary haemorrhage

In the present studies, minor postoperative haemorrhages were reported in 36% of adults, and in 32% of children. The percentages of major secondary post-tonsillectomy haemorrhage were 9% in adults and 5% in children, respectively. These results are supported by the recent study by Blomgren and co-workers (2001). However, most studies have reported that a secondary haemorrhage rate varies between 1% and 11% (Handler et al. 1986, Lavy 1997, Randall and Hoffer 1998, Collison and Mettler 2000, Wei et al. 2000, Ghufoor et al. 2000, Pickering et al. 2002), and between 2% and 5% in patients not using NSAIDs (Segal et al. 1983, Smith and Wilde 1999, Wei et al. 2000).

NSAIDs are effective analgesics, but they are recommended to be prescribed with caution for post-tonsillectomy pain, because of the fear of increased postoperative bleeding. These fears have mainly been concerned with reactionary and primary haemorrhage. In a previous study, diclofenac did not increase bleeding after tonsillectomy in a three day follow up study (Rømsing et al. 2000). However, Smith and Wilde (1999) have reported a seven-fold higher secondary haemorrhage rate (11%) for those of using NSAIDs compared with those not using NSAIDs (1.5%). A higher incidence of secondary haemorrhage with NSAIDs compared with patients not using NSAIDs are supported by several other studies (Carrick 1984, Stage et al. 1988, Harley and Dattolo 1998). This increased secondary haemorrhage rate could be due to the fact that minor bleedings, which have not previously required attention, are now bleeding more due to anti-platelet activity of the NSAIDs (Smith and Wilde 1999).
In our studies all haemorrhages including the grade and need for treatment were recorded in the questionnaire. Most often, only haemorrhages that needed treatment have become evaluated, and most of these studies are retrospective. In our studies, these post-tonsillectomy haemorrhage rates are soundly based and may be closer to reality, because of the prospective nature of the present study and the high response percentage for the questionnaire.

These studies with adults and children demonstrate, that regular use of ketoprofen seems not to increase significantly the incidence of secondary haemorrhage rate during recovery after tonsillectomy. The incidences reported here are similar to those reported previously (Segal et al. 1983, Carithers et al. 1987, Ghufoor et al. 2000, Blomgren at al. 2001, Pickering et al. 2002). However, a trial with a much higher number of patients and controls would be needed before any firm conclusions regarding the safety of ketoprofen for post-tonsillectomy pain treatment could be made.

6.5. Adverse events

6.5.1. In the hospital

In the present studies 35% of adults and 43% of children developed adverse events in the hospital, the most common being nausea and vomiting. There were no differences in the incidences of nausea and vomiting between the treatment groups.

Vomiting is a common problem following tonsillectomy. The incidence of vomiting in the immediate postoperative period varies between 40% and 75% (Litman et al. 1994, Mather and Peutrell 1995, Gunter et al. 1995, Panarese et al. 1999). In the present studies on adults (23%) and children (37%) the incidence of vomiting during the hospital stay was less than previously reported. The aetiology of vomiting appears to be multifactorial: opioid administration, swallowed blood, pain, and direct oropharyngeal
Irritation all contribute to postoperative vomiting (Panarese et al. 1999). However, the use of opioid analgesics has been considered the most important factor in post-tonsillectomy emesis (Mather and Peutrell 1995). The need for opioids may be reduced by using ketoprofen as a background analgesic. Kokki and co-workers (1999a) reported that ketoprofen administered during the operation reduced opioid consumption and the incidence of vomiting after strabismus surgery, which is associated with a high risk of vomiting. Mather and Peutrell (1995), comparing morphine and intraoperative NSAIDs during tonsillectomy, reported significantly less vomiting in the NSAID group. In contrast to our expectations, although patients in all the ketoprofen groups in the present studies received less opioids, vomiting was not less common in the ketoprofen groups than in the placebo groups.

Opioids may have different emetic properties. Kokki and co-workers (1999a) have proposed that fentanyl may induce less vomiting than morphine. The present study in adults suggests that oxycodone is also associated with a fairly low incidence of vomiting. However, this was not noticed so clearly in children in the present study.

Although vomiting is common, Hamid and co-workers (1998) have suggested caution concerning vomiting and the use of prophylactic antiemetics in children undergoing adenotonsillectomy. Occult blood loss may become evident to the parents only when the child vomits. If vomiting is suppressed by prophylactic antiemetics, the blood loss may continue with serious consequences. In the study by Hamid and co-workers (1998), the incidence of vomiting after adenotonsillectomy was over 80% without antiemetics. In the present study antiemetic drugs were not used. As in the previous studies on children undergoing adenoidectomy (Nikanne et al. 1997b, Kokki et al. 1998) and in the present studies on patients undergoing tonsillectomy, it seems that the incidence of vomiting may be reduced and kept on an acceptable level with carefully planned anaesthesia and a pain treatment protocol without the use of prophylactic antiemetics.
6.5.2. At home

In previous studies the incidence of adverse events with ketoprofen has varied between 0 and 50% of patients (Fossgreen 1976, Sunshine et al. 1993). In the present studies, 49% of adults and 47% of children reported one or more adverse events at home. In adults the most common adverse event besides minor bleeding was sedation and constipation, which is common with the use of codeine. It is known that ketoprofen also has a central action (Netter et al. 1985, Willer et al. 1989), but we consider that sedation was mainly attributable to codeine (Rasmussen 1987). On the other hand, the incidence of nausea and vomiting was fairly low both in adults (4%) and in children (2%). Overall, with the exception of 9 cases in adults and 5 cases in children of postoperative bleeding, the adverse events were classified as mild, e.g. no cases of gastric bleeding occurred.

6.6. Limitations of the study

There are certain limitations that should be considered when evaluating these results.

Pain is something that we feel and there is no tool to measure it objectively, particularly in children. However, a wide knowledge of pain was obtained by questionnaires; response rates were high and missing data was collected by telephone. Thus it may be assumed that a good general view of pain after tonsillectomy was obtained.

Pain intensity in the hospital was assessed slightly lower by medical observers than what children graded themselves. However, the nurse’s ratings and the child’s self-reports correlated significantly. Therefore we believe that the results concerning pain are soundly based.

The optimal dose of ketoprofen has not been defined in children. In our tonsillectomy study, the dose of 0.5 mg/kg followed by 3 mg/kg infusion over 24 hours was used,
which may have been too small. A dose finding study, comparing different amount of ketoprofen, had perhaps revealed an optimal ketoprofen dose. This kind of study can not be done, however, without considering an increased bleeding risks in children. Therefore, we considered it safe to perform the present study with doses found effective and safe in previous trials (Nikanne et al. 1997b).

The number of patients was low for the purpose of evaluating the safety of ketoprofen. Especially when evaluating bleeding complications, larger series are needed to draw statistically significant conclusions. To show a two-fold difference in bleeding complications (for example an increase from 5% to 10%) 600 patients are required in each arm at 5% significance level to achieve 90% power. To perform this kind of a clinical trial in children, a profound ethical consideration is needed.
7. CONCLUSIONS

1. Intravenous ketoprofen does not affect the operation time nor delay the discharge in 1-9 years old children undergoing adenoidectomy. (I)

2. Intravenous ketoprofen 0.5 mg/kg followed by 3 mg/kg ketoprofen infusion has a clear analgesic effect immediately after tonsillectomy in adults, but does not have a preemptive effect. Among children the same dose of ketoprofen immediately after tonsillectomy does not provide a significant analgesic effect. Ketoprofen does not increase the frequency of adverse events or cause clinically serious perioperative or primary postoperative bleeding compared to placebo. (II, III)

3. Pain after tonsillectomy is significant and persists relatively unchanged for the first five days. Post-tonsillectomy pain lasts on an average for 11 days in adults and 9 days in children. The age of children has just a minor influence on the recovery. (IV, V)

4. Ketoprofen administered by mouth alone after tonsillectomy does not demonstrate sufficient analgesic efficacy. Combination of ketoprofen and paracetamol or ketoprofen and paracetamol-codeine provides satisfactory pain relief in most patients. Use of ketoprofen at the doses studied after tonsillectomy does not cause any serious adverse events. (IV, V)
8. REFERENCES


Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998; 5: 1086-90.


Kokki H, Nikanne E, Ahonen R. The feasibility of pain treatment at home after adenoidectomy with ketoprofen tablets in small children. Paediatr Anaesth 2000(b); 10: 531-5.


Nikanne E, Kokki H, Tuovinen K. Comparison of perioperative ketoprofen 2.0 mg/kg with 0.5 mg/kg i.v. in small children during adenoidectomy. Br J Anaesth 1997a; 79: 606-8.


9. APPENDIX

FOLLOW-UP DIARY FOR PATIENT/PARENTS OF PATIENT USED AFTER TONSILLECTOMY
(appendix number 1)

This diary is to be filled in 1 through 7 days after tonsillectomy

Name of patient: ________________________________

This sheet is to be filled in 1./2./3./4./5./6./7. day after operation.

Please, evaluated pain in the morning before the first analgesic at 08.00 h and in the evening at 18.00 h. Pain is evaluated at rest and during swallowing. Make a vertical line on the place that best describes the incidence of pain.

<table>
<thead>
<tr>
<th></th>
<th>at rest</th>
<th>during swallowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.00h</td>
<td>no pain</td>
<td>worst possible pain</td>
</tr>
<tr>
<td>18.00h</td>
<td>no pain</td>
<td>worst possible pain</td>
</tr>
</tbody>
</table>

Evaluate here the worst pain and the least pain, and the average pain at rest and during swallowing during the day. (Circle the answer)

The worst at rest 1) severe pain 2) moderate pain 3) mild pain 4) no pain
during swallowing 1) severe pain 2) moderate pain 3) mild pain 4) no pain
The least at rest 1) severe pain 2) moderate pain 3) mild pain 4) no pain
The average at rest 1) severe pain 2) moderate pain 3) mild pain 4) no pain

Did the analgesic treatment result in: 
1) complete pain relief 2) significant pain relief 3) some pain relief 4) no pain relief

Did you wake up during night due to pain? 1) no 2) yes, ___ times

Adverse events or other comments: 

---

FOLLOW-UP DIARY PATIENTS/PARENTS OF PATIENT USED AFTER ELECTIVE TONSILLECTOMY (appendix number 2)

This diary is to be filled one week after tonsillectomy

Name of the patient: ________________________________

Is the patient able to:

Drink normally? 1) no 2) yes drinking normally after ____ days

Eat normally? 1) no 2) yes eating normally after ____ days

Did the patient wake up due to pain last night? 1) no 2) yes, ____ times
Has the patient returned to normal daily activity such as to play, day care, to school or to work?
1) no  2) yes, _______ days after operation

Has there been any bleeding from the operated area? 1) no  2) little  3) a lot

Has there been any contact to health care centre/hospital due to bleeding?
1) no  2) yes, where ________________________________

Did the bleeding demand any treatment? 1) no  2) yes, what ________________________________

<table>
<thead>
<tr>
<th>Pain at the moment</th>
<th>at rest</th>
<th>worst possible pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
<td></td>
<td>worst possible pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>during swallowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
</tr>
</tbody>
</table>

Does patient use analgesics:
Ketorin
1) no  2) when needed  3) regularly
Panacod/Panadol
1) no  2) when needed  3) regularly

Adverse events and other comments _______________________________________

______________________________________________  Thank you!
FOLLOW-UP DIARY PATIENTS/PARENTS OF PATIENT USED AFTER TONSILLECTOMY
(appendix number 3)

This diary is to be filled three weeks after tonsillectomy

Name of the patient: _______________________

How many days patient was in pain? _______ days after operation

When was pain the worst? _______ days after operation

How many days was the analgesic used? _______ days regularly

in addition _______ days when needed

all together _______ days

<table>
<thead>
<tr>
<th>How many days after operation was able</th>
<th>drinking after</th>
<th>_______ days</th>
</tr>
</thead>
<tbody>
<tr>
<td>to drink, eat, and sleep normally?</td>
<td>eating after</td>
<td>_______ days</td>
</tr>
<tr>
<td></td>
<td>sleeping after</td>
<td>_______ days</td>
</tr>
</tbody>
</table>

Patient returned to normal daily activities such as to play, to day care, to school or to work? _______ days after operation

During how many nights did you wake up after operation? 1) no
2) woke up _______ nights

Evaluate here the worst pain and the least pain, and the average pain at rest and during swallowing after your operation. (Circle the answer)

**The worst**

<table>
<thead>
<tr>
<th>at rest</th>
<th>during swallowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) severe pain</td>
<td>1) severe pain</td>
</tr>
<tr>
<td>2) moderate pain</td>
<td>2) moderate pain</td>
</tr>
<tr>
<td>3) mild pain</td>
<td>3) mild pain</td>
</tr>
<tr>
<td>4) no pain</td>
<td>4) no pain</td>
</tr>
</tbody>
</table>
### Pain at Rest and during Swallowing

<table>
<thead>
<tr>
<th>Least at Rest</th>
<th>1) Severe pain</th>
<th>2) Moderate pain</th>
<th>3) Mild pain</th>
<th>4) No pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>during swallowing</td>
<td>1) Severe pain</td>
<td>2) Moderate pain</td>
<td>3) Mild pain</td>
</tr>
</tbody>
</table>

### Did the Analgesic Treatment be Sufficient?

- 1) Complete pain relief
- 2) Significant pain relief
- 3) Some pain relief
- 4) No pain relief

### How Long Did the Patient Need Analgesic Treatment?

<table>
<thead>
<tr>
<th></th>
<th>Ketorin</th>
<th>Panadol/Panacod</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Severe pain</td>
<td>days, together doses</td>
<td>days doses</td>
</tr>
</tbody>
</table>

### Was there any problems taking analgesics?

1) No 2) Yes, what

### Where there any adverse events?

1) No 2) Yes, what

### Has there been any contact made with health care centre/hospital because of bleeding?

1) No 2) Yes, where

### Did the bleeding demand any treatment?

1) No 2) Yes, what

### Other comments about pain or pain treatment after your operation:

---

Thank you for your co-operation!