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PAIN MANAGEMENT OPTIONS AFTER TONSILLECTOMY AND THIRD MOLAR EXTRACTION

UNIVERSITY OF OULU GRADUATE SCHOOL, UNIVERSITY OF OULU, FACULTY OF MEDICINE
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Abstract

The purpose of this study was to investigate the clinical implications of a combination of a peripheral opioid, paracetamol (APAP) and ketoprofen (KTP) on the intensity of acute postoperative pain by focusing on tonsillectomy (TE) and third molar extraction. A second focus in the study was to assess the utility of the surgical ultrasonically activated scalpel (HS) technique for TE.

In Study I, TE was performed on one side using the HS and on the contralateral side using a “blunt dissection technique”. The first TE study (I) demonstrated that - based on NRS pain scores during the first 10 postoperative hours - intra-operative blood loss and need for haemostasis were greater on the blunt dissection side than on the HS side. Pain scores were higher on the HS side than on the cold dissection side during the second postoperative week.

Study III assessed the analgesic effect of a peripheral dose of 4 mg morphine. The peritonsillar infiltration of morphine locally did not significantly decrease pain compared to the control side.

Studies (II and IV) included patients who were scheduled for third molar extraction. In Study II, patients received 1000 mg APAP or 100 mg KTP or both or a placebo to evaluate pain relief after third molar extraction. This study demonstrated that the mean sum of pain intensity differences scores up to the 1.5 h mark and the mean time to onset of pain relief at rest and on swallowing were favoured in the combination group more than in the APAP, KTP, and placebo groups.

In Study IV, patients were assigned for a submucosal injection of 2 mg morphine or NaCl into either the non-inflamed (Trial I) or the inflamed (Trial II) peridental tissue, while the active control group received the same drugs in reverse order intramuscular (IM). Postoperative pain intensity at rest and on swallowing was assessed in all studies using the numerical rating scale (NRS). Pain scores in the peripheral morphine group at rest (Trials I and II) and on swallowing (Trial I) were not associated with any further pain reduction. Pain scores on swallowing during the 2–6 hours postoperative period (Trial II) were greater in the IM morphine group.

HS TE was associated with decreased pain in the early postoperative period, but there was increased pain and otalgia during the second postoperative week. Locally administered peripheral morphine was not associated with any benefit during the postoperative period after TE.

The multimodal analgesia combination of a single dose of KTP and APAP demonstrated the same benefit during the early postoperative period without an increase in side effects. Locally administered peripheral morphine produced significant analgesia on swallowing during the early postoperative stage in inflamed tissue after third molar extraction.

Keywords: nonopioid analgesics: ketoprofen; acetaminophen = paracetamol, opioid analgesics: peripheral morphine, oral, pain: postoperative, surgery: otorhinolaryngology, surgical equipment: surgical instruments; ultrasonics
Akural, Ibrahim Ethem, Nielurisan ja viisaudenhampaan poistoleikkausen jälkeisen kivun hoidon mahdollisuudet.

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Tiivistelmä


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To my family
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pay tribute to my grandparents, my father, uncle and father-in-law who have already passed away

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Oulu, September 2016

Ibrahim Ethem Akural
Abbreviations

ADE  Adverse drug event
APAP  N-acetyl-p-aminophenol = Acetaminophen = Paracetamol
AUC  Area Under the Curve
CNS  Central nervous system
COX  Cyclo-oxygenase
ENT  Ear, nose and throat = Otorhinolaryngology
IBP  Ibuprofen
IM  Intramuscular
IV  Intravenous
KTP  Ketoprofen
NSAID  Nonsteroidal anti-inflammatory drug
NRS  Numerical rating scale
ORADE  Opioid-related adverse drug event
Panacod®  Paracetamol 500 mg + codeine 30 mg
PID  Pain intensity difference
PIDR  Pain intensity difference at rest
PIDS  Pain intensity difference on swallowing
POD  Postoperative day
PONV  Postoperative nausea and vomiting
PTH  Post-tonsillectomy haemorrhage
RCT  Randomized controlled trial
SPID  Sum of pain intensity difference
SPIDR  Sum of pain intensity difference at rest
SPIDS  Sum of pain intensity difference on swallowing
SM  Submucosal
TE  Tonsillectomy
tNSAID  Traditional nonsteroidal anti-inflammatory drug
List of original publications

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


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1 Introduction

The relief of pain has been designated as a human right (Brennan et al. 2007). Postoperative pain is still undertreated, as obstacles to efficient pain management still exist. The prevention and control of postoperative pain are unresolved challenges after oral cavity procedures such as tonsillectomy (TE) and third molar extraction.

The intensity and duration of pain, the consumption of analgesics and the incidence of adverse drug events (ADEs) in some new surgical and analgesic treatment modalities after TE and third molar extraction are the topics of this thesis. Even small procedures such as TE and third molar extraction are associated with tissue damage and most patients will experience some degree of postoperative pain after surgery despite conventional pain treatment (Gerbershagen et al. 2014).

It has been shown that 90 percent of all patients claimed to have postoperative pain (Fletcher et al. 2008) and 25 percent declared severe or moderate pain at rest on the day after surgery (Sommer et al. 2010). It has been reported that 42 to 79 percent of patients claimed a maximal numerical pain score over 3 on the first postoperative day (POD1), depending on the type of otorhinolaryngologic (ENT) surgery (Guntinas-Lichius et al. 2014).

Efficaciously managed ambulatory surgery requires multimodal pain treatment because poorly controlled pain and postoperative nausea and vomiting (PONV) are the most usual reason for delaying a patient’s discharge. Nowadays there is an increasing requirement for short stays in hospital after TE and third molar extraction are performed in outpatient clinics, which means that the time period to titrate the analgesic effect is shorter. This set a challenge for adequate pain management in everyday practice (Schug & Chong 2009). It has been recognized that pain was the most common reason for unplanned hospital admission (Mattila et al. 2001). At the same time, concerns over opioid-related adverse drug events (ORADEs), misuse and addiction frequently limit the use of opioids (Wu et al. 2002, Smith et al. 2008). ORADEs were the second most important reason after pain for unplanned hospital admission (Wu et al. 2002). Thus, the further development of safe and effective pain management techniques is essential (Segerdal et al. 2008).

The most common analgesics used postoperatively are nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (Acetaminophen = APAP). They have fewer restrictions on short term use, but they have ADEs which are more likely to occur when used in high doses or over long courses of treatment. Although
opioids and NSAIDs are commonly used analgesics in the postoperative period, they have a number of undesirable side effects which limit their clinical usefulness. NSAIDs and APAP are often combined with opioids, such as codeine and tramadol, in the postoperative phase (Segerdahl et al. 2008). APAP and codeine combination formulas have been in use for many decades.

APAP is not always sufficient for pain relief after TE or for pain on swallowing after third molar extraction. A combination of analgesics may increase effectiveness without an increase in dose and ADEs. NSAIDs are often combined with APAP, particularly for treating postoperative pain after TE and third molar extraction. NSAIDs, and APAP and locally acting analgesics may decrease systemic opioid consumption and thus reduce ORADEs.

The purpose of the present work was to investigate the intensity of TE and third molar extraction pain. Furthermore the thesis aims to find answers to the questions of whether a combination of APAP with ketoprofen (KTP), locally administered morphine, and an ultrasonically activated scalpel technique can improve postoperative analgesia.
2 Review of the literature

2.1 Consequences of postoperative pain after tonsillectomy and third molar extraction

Pain transpires in response to the activity in a specific subset of high threshold peripheral sensor neurons, the nociceptors. The detection of noxious stimuli is a complicated and multi-factorial physiological experience known as nociception. Central and peripheral sensitization may play a role during the postoperative period and enhance postoperative pain. Immediately after surgery the production of an “inflammatory soup” may sensitize the nociceptors in the tissue, A-delta and C fibers peripherally as well as the central nervous system (CNS) through several mediators including cyclo-oxygenase (COX) (Costigan & Woolf 2000, Finnerty et al. 2013, Juhl et al. 2006). Subsequent to third molar extraction, prolonged peripheral sensitization may last up to 30 days despite the pain having disappeared (Juhl et al. 2008). In the clinical setting, postoperative pain can be either somatic or visceral. Somatic pain can originate in deep structures, such as muscles, joints, and ligaments; or in superficial structures, such as the skin, subcutaneous or mucosal tissues. As an example, third molar extraction and TE represent mostly somatic pain. Postoperative pain commonly depends on the type of the surgery, the quantity of tissue damage, inflammation and ischemia (Gerbershagen et al. 2013, Singla et al. 2014, Loveridge & Patel 2014). The timing and indication for surgery can determine postoperative pain. Third molar extraction and TE can be performed when the patients are in pain and inflammation is present or preventively when preoperative pain and inflammation are minimal. Therefore the pathophysiological background of pain can predict postoperative pain levels and pharmacological treatment efficacy (Gramke et al. 2009).

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Bonica 1979). Surgery is a powerful stress stimulator in itself. Many other factors including postoperative pain, concern about complications, prognosis, and socioeconomic issues - either alone or in combination - can increase levels of patient stress. As part of the sensory system, pain is closely connected with spiritual and psychological feelings, which often results in analgesic dissatisfaction when traditional pharmacological methods and doses are used (Gramke et al. 2009, Burns et al. 2015). For example it has been demonstrated in breast cancer patients...
that those with high-anxiety levels have significantly higher mean pain scores (Kaunisto et al. 2013).

Pain has a protective function after TE and third molar extraction procedures, when oral cavity mucosal tissue damage has already occurred, and this function is to allow undisturbed healing (Pogrel 2012). It is controversial as to whether postoperative oral pain should be completely eliminated or whether it is sufficient to reduce it to a level where it is no longer distressing and allows eating and drinking while still serving a protective function (Gewandter et al. 2015).

### 2.2 Principles of postoperative pain treatment

Kehlet and Dahl first described multimodal analgesia (Kehlet & Dahl 1993). Multimodal analgesia involves the simultaneous use of a combination of medications with different mechanisms or techniques that are associated with preferable pain relief and opioid-sparing effects. At present, this is the strategy which is most commonly recommended for pain relief following surgery (McDaid 2010, Kontinen & Hamunen 2015). The multimodal approach contributes a logical basis for improved postoperative pain control, enhanced patient satisfaction and a decrease in ADEs after TE and third molar extraction (McDaid 2010, Devin & McGirt 2015, Dahl et al. 2014, Mathiesen et al. 2014).

Postoperative pain involves multiple mechanisms, which will ideally respond to a multimodal approach by combining analgesics that act at different sites within the central and peripheral nervous systems. Combinations of drugs of high efficacy include APAP and codeine, APAP and oxycodone, ibuprofen (IBP) and codeine, IBP and oxycodone, and IBP and APAP (Stein 2010, Ong et al. 2010, Dahl et al. 2014, Au et al. 2015).

#### 2.2.1 Opioid Analgesics

Opioid analgesics are still a mainstay and the gold standard for postoperative pain management. The goal with opioids is to achieve a balance between pain relief and ORADEs. Opioid receptors belong to the superfamily of seven transmembrane G-protein coupled receptors. A fourth opioid receptor, the nociceptin opioid receptor, is the most recently discovered member of the family of the opioid receptors (Muñoa et al. 2015). The majority of the clinically used opioids stimulate activity at the “μ-receptors” and are considered “μ-agonists” (Trescot et al. 2008, Rittner 2012).
Opioid efficacy depends to some extent on the type of pain being treated. Inflammatory pain is usually associated with enhanced opioid efficacy (Busch-Dienstfertig & Stein 2010). Furthermore, multiple distinct opioid receptor subtypes have been identified, and interactions between them may change the opioid response (Mercadante S. 2014). The µ-agonists bind to a large number of µ-opioid receptor subtypes. Several opioids produce subtly different responses based on the distinct activation profiles of the µ receptor subtypes (Stein C. & Machelska H. 2011, Mercadante S. 2014). The opioid receptors show an epigenetic regulation and use different epigenetic regulation forms (Muñoa et al. 2015). In theory, different opioids can be used simultaneously with improved effectiveness and decreased dose-related ADEs. The clinical benefit of combining different opioids remains, however, controversial (Richards et al. 2013, Mercadante 2014).

Opioid receptors are located chiefly in the CNS, but peripheral opioid receptors have also been demonstrated (Tescot et al. 2008, Stein & Kühler 2013). Opioid agonists with a preference for µ-receptors are the most potent inducers of peripheral analgesia, but δ- and κ-opioid agonists are effective as well. (Stein C. & Machelska H. 2011). Peripheral opioid receptors can interact with exogenous or endogenous opioid ligands both in animals and in humans (Ferreira & Nakamura 1979, Joris et al. 1987, Zhou et al. 1998, Koppert et al. 1999, Stein et al. 2001, Labuz et al. 2007, Khalefa et al. 2012, Stein & Kühler 2013). The peripheral effect of opioids has long been a focus of pain treatment. One hundred and forty years ago, peripheral opioids were used for pain relief in Finland by Knut Fellix von Willebrand (Tammisto & Tammisto 2000).

The antinociceptive effect of peripheral opioids has been demonstrated in experimental (Ferreira & Nakamura 1979, Mikami & Miyasaka 1979) and clinical models (Antonijevic et al. 1995, Koppert et al. 1999). Several reviews summarizing peripheral opioid analgesic efficacy generally concluded that peripheral opioids have the potential to decrease pain, even though positive clinical trials had small sample sizes (Kalso et al. 1997, Picard et al. 1997, Nielsen et al. 2015). At the same time, locally applied opioids have been shown to demonstrate controversial analgesic effects, but no significant adverse effects have been reported so far (Farley P. 2011, Stein C. & Machelska H. 201, Rosseland 2005). Hence, the American Pain Society’s current postoperative pain management guidelines recommend intra-articular opioids for total hip and knee replacements as a part of the multimodal pain therapy (Chou et al. 2016).

The meta-analysis by Nielsen which included 26 studies (excluding intra-articular opioid studies), 1531 patients and 13 different surgical interventions
(mainly dental, cholecystectomy and inguinal hernia surgery), has suggested that locally applied morphine has an analgesic effect for from between 6–8 and 12 h postoperatively (Nielsen et al. 2015). An analysis of data from a subgroup of five dental comparisons showed similar results (Likar et al. 2001, Kaczmarzyk & Stypulkowska 2005) and the trials with a preoperative inflammation reported more significant effects (Table 1). The expression of peripheral opioid receptors depends on the duration of inflammation (Stein C. & Machelska H. 2011). For example, third molar extraction in subjects with pericoronitis and preoperative pain induced clinically relevant peripheral opioid analgesia (Likar et al. 2001, Kaczmarzyk & Stypulkowska 2005). However, a short-lasting inflammatory stimulus may not change opioid expression on the sensory nerve terminal (Labuz et al. 2007). A large number of clinical studies have shown that peripherally applied opioids do not readily produce analgesic effects in tissue without preoperative inflammation (Picard et al. 1997, Stein et al. 2003). Therefore, a peripheral opioid analgesic effect may be diminished during the early stage of the postoperative period in many clinical acute pain trials.

Many current clinical investigations focus on the new peripheral opioid agonists, which are unable to penetrate the blood brain barrier (Stein & Küchler 2013). These peripherally restricted opioids - such as morphine-6-glucuronide - have been found to reduce postoperative pain in a manner similar to morphine with limited ORADEs (Dahan et al. 2008). Few trials have researched the peripheral opioid effect after TE (Elhakim et al. 1997, Nikandish et al. 2008)).

The peripheral effects of many different opioid agonists were investigated for third molar extraction (over 500 patients) and the side effects were generally not significant (Likar et al. 2001, Dionne et al. 2001, Kaczmarzyk & Stypulkowska 2005, Likar et al. 2005, Pozos et al. 2006, Ceccheti et al. 2014, Gönül et al. 2015). These studies are summarized in Table 1.
Table 1. Variables related to pain in randomised controlled trials comparing peripheral opioids with systemic opioids or a placebo after third molar extraction. NA, Not available; N, number of patients; Mo, Morphine; LA, local anaesthesia; NaCl, Sodium chloride; IV, intravenously; VAS, Visual Analog Scale; SM, submucosal injection; SC, subcutaneous injection; Inf, Inflammation. Adapted with permission from Nielsen and colleagues (Nielsen et al. 2015).

<table>
<thead>
<tr>
<th>Study</th>
<th>First author, year / trial</th>
<th>N active / control</th>
<th>Peripheral opioid group</th>
<th>Control group</th>
<th>Pain intensity score (VAS) after surgery</th>
<th>Analgesic consumption after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likar, 2001 / I</td>
<td>14 / 13 + 1 mg Mo + LA SM</td>
<td>LA SM</td>
<td>8–24 h¹</td>
<td>Didlofenac (0–24 h)¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likar, 2001 / II</td>
<td>24 / 26 - 1 mg Mo SM</td>
<td>1 mg Mo SC</td>
<td>0–24 h²</td>
<td>Didlofenac (0–24 h)²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likar, 2001 / III</td>
<td>19 / 16 + 1 mg Mo + LA perineural</td>
<td>LA perineurally</td>
<td>0–24 h²</td>
<td>Didlofenac (0–24 h)²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dionne, 2001 / I</td>
<td>12 / 15 - 1.2 mg Mo SM</td>
<td>1.2 mg Mo IV</td>
<td>0–3 h²</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dionne, 2001 / II</td>
<td>12 / 16 - 1.2 mg Mo SM</td>
<td>NaCl SM</td>
<td>0–3 h²</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Dionne, 2001 / III</td>
<td>19 / 32 - 50 μg Fentanyl SM</td>
<td>50 μg Fentanyl IV</td>
<td>0–3 h (p &lt; 0.05 prefer IV group)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dionne, 2001 / IV</td>
<td>19 / 20 - 50 μg Fentanyl SM</td>
<td>Placebo</td>
<td>0–3 h²</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaczmarzyk, 2005</td>
<td>30 / 30 + 1 mg Mo + LA SM</td>
<td>LA SM</td>
<td>0–12 h¹</td>
<td>Mefanamic (0–48 h)¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likar, 2005</td>
<td>29 / 30 - 2 mg Mo + LA spray</td>
<td>LA spray</td>
<td>0–24 h²</td>
<td>Didlofenac (0–24 h)²</td>
<td></td>
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<tr>
<td>Pozos, 2006</td>
<td>24 / 24 NA 1 mg/kg tramadol SM</td>
<td>NaCl SM</td>
<td>1–12 h¹</td>
<td>Initial Analgesic Intake¹ Metamizole¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cecchetti, 2014</td>
<td>52 / 52 NA 100 mg tramadol SM</td>
<td>NaCl SM</td>
<td>0–72 h¹</td>
<td>Initial Analgesic Intake¹ Total Analgesic Intake¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gönul, 2015</td>
<td>30 / 30 NA 1 mg/kg tramadol SM</td>
<td>NaCl SM</td>
<td>1–12 h¹</td>
<td>Initial Analgesic Intake¹ Total Analgesic Intake¹</td>
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¹ Significant difference prefer to peripheral opioid group; ² No significant difference
Opioid treatment causes a number of side effects which may interfere with their analgesic effects and create discomfort postoperatively, including urinary retention, pruritus, somnolence, dizziness and depression of CNS functions (Wheeler et al. 2002). The most important ORADEs are suppression of gastrointestinal and respiratory drive and opioid-induced hyperalgesia (Benyamin et al. 2008), and the most common ORADEs are constipation and PONV. Many recent studies have reported that opioids are being used in lower than optimal doses, resulting in inadequate analgesia (Gerbershagen et al. 2013). The reason for less than optimal doses could be concern over possible ORADEs and opioid overuse, as well as the opioid-related safety profile.

It has been reported that 11.5 percent of patients have ORADEs during postoperative opioid treatment (Minkowitz et al. 2014), and overall hospital costs were higher in patients suffering from ORADEs compared to those with no ORADE (Oderda et al. 2007). The risk factors for ORADE involved age (over 65 years), male sex, prior opioid use, chronic obstructive pulmonary disease, cardiac dysrhythmias, diverticulitis, and ulcerative colitis. Hospital costs were over 80 percent higher when the patient had several ORADE risk factors and over 20 percent when patient had only one. (Minkowitz et al. 2014). Opioids have a good analgesic effect and low costs, but the cost of postoperative ORADEs could be a notable economic burden for hospitals. One of the most frightening ORADEs is respiratory depression leading to death. Therefore, the FDA issued a public warning and the labelling of all codeine-containing drugs regarding “increased risk in postoperative pain management in children following TE and/or adenoidectomy” (Benyamin et al. 2008).

2.2.2 Nonsteroidal anti-inflammatory agents (NSAIDs)

COX inhibitors, commonly called NSAIDs, have a long history of safe and effective use as both analgesics and antipyretics. NSAIDs have been used consistently as first-line agents in treating postoperative pain after TE and third molar extraction (A van de Ketterij-de Ridde, Martina.A. 2014, TD 2004, Paganelli et al. 2014, Riggin et al. 2013, Hamunen & Kontinen 2005, Costa et al. 2015, Esquivel-VelAsquez 2014, Barden et al. 2004). NSAIDs act by inhibiting COX-1 and COX-2 isoenzymes, which are involved in the formation of prostaglandins. COX isoforms have different functions and the inhibition of these results in distinct therapeutic properties and side effects (TD 2004, Brune & Patrignani 2015). The analgesic effects of NSAIDs mostly result from COX-2 inhibition at the site of
inflammation. However, COX-2 inhibition also contributes to renal physiology, reproductive function, bone resorption, and neurotransmission. COX-1 participates in gastro protection and thromboxane formation by platelets. NSAIDs are associated with an increased risk of cardiovascular, gastrointestinal, respiratory and renal events (TD 2004, Moore et al. 2015, Carson & Rees Willett 1993). During the inflammatory response, COX-dependent prostanoids increase the sensitivity of nociceptors in the periphery, thereby contributing to the development of central hyperalgesia (Vardeh et al. 2009).

Differences in the efficacy and tolerability of NSAIDs have been observed between individuals resulting from genetic factors that affect the pharmacokinetics and pharmacodynamics of NSAIDs (Wyatt et al. 2012, Lee et al. 2006).

The analgesic and side effects of NSAIDs depend on their absorption, distribution, elimination and dose. It is commonly recommended that NSAIDs be taken with food or after meals to reduce gastrointestinal ADEs, but this probably also reduces the analgesic effectiveness for a given dose (Moore R.A. et al. 2015).

Bhala and colleagues suggested that all NSAIDs evaluated increased the early risk of upper gastrointestinal complications, and diclofenac and IBP - especially at high-doses - increase the cardiovascular risks similar to COX-2 selective NSAIDs (Bhala 2013). Overall, it is crucial to understand the pharmacogenetics/pharmacogenomics of NSAIDs in order to treat patients with the most appropriate agents that will have enhanced therapeutic outcomes with fewer side effects (Wyatt et al. 2012).

KTP belongs to the group of 2-arylpropionic acid or profen class of NSAIDs. It represents a racemic mixture. The S-enantiomer possesses most of the beneficial pharmacological activity, whereas the R-enantiomer is considered to be an impurity or a pro-drug: approximately 10–15% of the R-isomer undergoes chiral inversion upon oral administration (Rudy et al. 1998). KTP analgesic activity is affiliated with the inhibition of COX and prostaglandin synthesis, but it also inhibits the lipoxygenase pathway of the arachidonic acid cascade and leukotriene synthesis (Fossgreen 1976, Jamali & Brocks 1990). In addition to its peripheral effects, KTP may also affect CNS action through the inhibition of central prostaglandin biosynthesis.

As an acidic drug, KTP binds intensively to protein and selectively accumulates at inflammation sites; thus KTP with its short plasma half-life may provide a satisfactory analgesic effect even at lower dosing levels (Brune & Patrignani 2015). Clinical studies suggested that KTP is as effective as other NSAIDs in the reduction of postoperative pain and discomfort after third molar
extraction (Seymour et al. 1996, Kaczmarzyk et al. 2010). Bjornsson and colleagues found a reduction in swelling on the third and sixth PODs for KTP compared to APAP after third molar extraction (Bjornsson et al. 2003). The analgesic effect of KTP was speculated to be greater than that of IBP or diclofenac at their therapeutic doses (Sarzi-Puttini et al. 2014). R- and S-ketoprofen elimination undergoes metabolism in the liver and is excreted predominantly in the urine (Grubb et al. 1999). ADEs are more likely associated with the S-enantiomer (Grubb et al. 1999).

2.2.3 Paracetamol (Acetaminophen = APAP)

APAP (N-acetyl-p-aminophenol, acetaminophen, also named paracetamol) is the most widely used and well-established analgesic for postoperative practice worldwide. It is the first-line pharmacological therapy for a multitude of acute and chronic painful conditions and the first step on the WHO pain ladder (Ventafridda et al. 1987). At the same time, APAP can also be a dangerous analgesic, which can cause acute liver failure and death (Roberts et al. 2015). The pain-relieving mechanism of APAP is still unclear (Anderson 2008).

It has been suggested that APAP possesses a central effect as well as a weak inhibition of prostaglandin synthesis. It was reported that APAP inhibited both COX isoforms (Schwartz et al. 2015), and prostaglandin synthesis in the CNS and peripheral tissues (Hinz et al. 2008). APAP analgesic action could be mediated via the central anti-inflammatory pathways and act as a selective COX-2 inhibitor in the CNS. APAP’s analgesic effect may also be mediated via the interference of APAP with brain-derived neurotrophic factor, neurotransmitter systems (including serotonergic, dopaminergic, adrenergic, as well as the endogenous endocannabinoid systems) (Bjorkman et al. 1994, Miranda et al. 2006, Anderson 2008, Kumpulainen 2007, Graham et al. 2013, Tiippana et al. 2013, Twycross et al. 2013). It was suggested that the co-administration of a 5-hydroxytryptamine type 3 antagonist with APAP completely blocked the analgesic effect of APAP in healthy volunteers (Tiippana et al. 2013). Therefore, APAP may affect descending inhibitory pathways (Pickering et al. 2015). The indirect activation of cannabinoid receptors can explain part of the analgesic action of APAP, as well as some of its subjective effects, such as euphoria and relaxation (de Fays et al. 2015).

Altogether, these data support the proposition that APAP has a weak NSAID profile with COX-2 inhibition. Even though APAP is considered to be a safer analgesic than NSAIDs, a systemic review demonstrated a dose–response
relationship between APAP with increased ADEs at standard analgesic doses (Roberts et al. 2015). Overall, it was speculated that the use of APAP is associated with the same problems as NSAIDs, including increases in blood pressure, aggravated risk of GI ulcers and myocardial infarction (Hinz et al. 2008). The hazardous side effect of APAP-induced hepatotoxicity is dose-related. It has been reported that overuse of APAP and APAP with an opioid combination has caused a substantial burden of hepatotoxicity in United States, with an increasing trend during the study follow-up period between 2000–2007 (Bond et al. 2012).

Preoperative APAP has been found to reduce the risk of PONV (Doleman et al. 2015). It was speculated that reductions in PONV were associated with reductions in pain scores rather than reductions in morphine consumption, and APAP may have a direct antiemetic effect, such as reuptake of the cannabinoid agonist anandamide (Apfel et al. 2013). APAP may also cause antidepressant-like and anticonvulsant-like effects, which might be a result of its CNS effects - possibly through the serotonergic or endocannabinoid system. The mood-elevating properties of APAP were found at low doses, alone or in combination with an antidepressant drug (Manna & Umathe 2015). APAP has recently been shown to blunt individuals’ reactivity to a range of negative stimuli in addition to physical pain (DeWall et al. 2010, Nathan DeWall et al. 2015, Randles et al. 2013). APAP attenuates volunteers’ evaluations and emotional reactions (Durso et al. 2015). Similarly, APAP can also blunt the intensity of negative experiences (DeWall et al. 2010, Randles et al. 2013) and empathy for pain (Mischkowski et al. 2016). Overall, a better designation for APAP may be as an all-purpose emotion reliever rather than as simply a pain reliever (Durso et al. 2015).

The use of APAP during pregnancy is generally considered safe and effective. Prenatal exposure to APAP, however, is speculated as increasing the risk for developing attention-deficit–hyperactivity disorder and similar behavioral problems in children (de Fays et al. 2015, Liew et al. 2014)

### 2.2.4 Analgesic effect of a combination of NSAID and paracetamol

The practice of combining analgesics with different mechanisms of action or pharmacokinetic properties has contributed to more satisfactory pain relief. The combination of an NSAID with APAP can provide more analgesia than either single analgesic in the combination. Synergistic analgesia means that the effect of a combination of two analgesics is greater than the summation of each analgesic
Additive analgesia occurs if the analgesic combination effect equals the summation of the analgesic effect of each (Moore et al. 2012).

Many TE studies showed that combining APAP and an NSAID might provide superior analgesia than either analgesic alone (Pickering et al. 2002, Hiller et al. 2004). Many third molar extraction studies also confirm the same results (Breivik et al. 1999, Haglund & Von Bültzingslöwen 2006, Menhinick et al. 2004, Gazal & Mackie 2007, Daniels et al. 2011, Atkinson et al. 2015). As Table 2 shows, the effects of a combination of APAP and an NSAID were generally greater than APAP after third molar extraction. There has been a trend in recent years for combining NSAIDs with APAP for postoperative pain management, and several recent meta-analyses have shown the therapeutic superiority of the combination over either drug alone after different kinds of surgery (Ong et al. 2010), including third molar extraction (Derry et al. 2013, Bailey et al. 2014, Alexander et al. 2014).

IBP and APAP, the most widely studied analgesic combination, has displayed promising outcomes after third molar extraction (Moore et al. 2011, Derry et al. 2013, Bailey et al. 2014). Derry and colleagues showed in a Cochrane review that a combination of IBP 400 mg + APAP 1000 mg has a superior analgesic effect when compared to either drug alone (Derry et al. 2013).
Table 2. Single dose studies in which paracetamol (APAP) was combined with NSAID after third molar extraction. IBP, Ibuprofen; NA, Not available or not applicable; NSD, No significant difference; G, treatment group; VAS, Visual Analog Scale; SPID, Sum of pain intensity difference; TOTPART, total pain relief; ADEs, Adverse drug events. Adapted with permission from Ong and colleagues (Ong et al. 2010).

<table>
<thead>
<tr>
<th>Study, First author, year</th>
<th>Sample size</th>
<th>Treatment groups</th>
<th>Outcome measures and analgesic results</th>
<th>ADEs (significant difference between groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breivik, 1999</td>
<td>115</td>
<td>1. Diclofenac 100 mg</td>
<td>Pain intensity during 8 h: G3, G4 and G5 superior to G1,G2; G5 superior to G1,G2, G3</td>
<td>Nausea and drowsiness higher G5 and G3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. APAP 1 g</td>
<td></td>
<td>Nausea and drowsiness: 25%–33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. APAP 1 g + Codeine 60 mg</td>
<td>TOTPAR: G4 and G5 superior to G1, G2; G5 superior to G3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Diclofenac 100 mg + APAP 1 g</td>
<td>Rescue medication: G4,G5 less frequently than G1, G2,G3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. APAP 1 g + Codeine 60 mg + Diclofenac 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haglund, 2006</td>
<td>107</td>
<td>1. Rofecoxib 50 mg + APAP 1 g</td>
<td>Pain intensity at 0.5, 1, 1.5 h: G1 superior to G2</td>
<td>NSD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Rofecoxib 50 mg</td>
<td>Pain relief at 0.5, 1 h: G1 superior to G2</td>
<td>Headache: 3%–12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. APAP 1 g</td>
<td>TOTPAR: G1,G2 superior than G3,G4</td>
<td>Drowsiness: 3%–10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Placebo</td>
<td>Fatigue: 11%–12%</td>
<td></td>
</tr>
<tr>
<td>Mehlisch, 2010</td>
<td>226</td>
<td>1. IBP 400 mg + APAP 1 g</td>
<td>Pain relief and pain intensity difference: G1 superior to others.</td>
<td>NSD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. IBP 200 mg + APAP 0,5 g</td>
<td>TOTPAR / SPID: G1 superior to G3, G4 G5</td>
<td>Nausea (26.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. IBP 400 mg</td>
<td>G2 superior to G4</td>
<td>Vomiting (18.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. APAP 1 g</td>
<td></td>
<td>Headache (10.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Placebo</td>
<td></td>
<td>Dizziness (8.1%)</td>
</tr>
<tr>
<td>Study, First author, year</td>
<td>Sample size</td>
<td>Treatment groups</td>
<td>Outcome measures and analgesic results</td>
<td>ADEs (significant difference between groups)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------------</td>
</tr>
</tbody>
</table>
| Mehlisch, 2010           | 676         | 1. IBP 400 mg + APAP 1 g  
2. IBP 200 mg + APAP 0.5 g  
3. IBP 100 mg + APAP 0.25 mg  
4. IBP 400 mg  
5. IBP 200 mg  
6. APAP 1 g  
7. APAP 0.5 g  
8. Placebo | SPID8 / Pain relief: G1 superior to G3,G4,G6,G8  
G2 superior to G5,G6,G7,G8 | G1 less than G4,G6,G8 / G2 less than G5,G7,G8 |
| Daniels, 2011            | 678         | 1. IBP 200 mg + APAP 0.5 mg  
2. IBP 400 mg + APAP 1 g  
3. IBP 400 mg + Codeine 25.6 mg  
4. APAP 1 g + Codeine 30 mg  
5. Placebo | SPID12 / TOTPAR: G1 superior to G4,G5  
G2 superior to G3,G4,G5 | ADEs prevalence G1, G2 less than G3,G4,G5 |
| Atkinson, 2015           | 159         | 1. IBP 300 + APAP 1 g  
2. IBP 150 + APAP 0.5 g  
3. IBP 75 + APAP 0.25 g  
4. Placebo | SPID12 / Time to rescue medicine and meaningful pain relief: G1,G2, G3 superior to G4 | Higher at placebo group (G1 mostly) (40.8 %) |
2.3 Tonsillectomy

Tonsillectomy (TE = surgical excision of the tonsils) is one of the most common ENT operations performed world-wide. Koskenkorva and colleagues reported that adult patients who have had three or more acute pharyngitis episodes during the previous year benefit subjectively from TE (Koskenkorva 2015, Koskenkorva 2014). TE incidence in the US increased from 126 per 100 000 in 1970–1974 to 153 per 100 000 in 2000–2005 (Erickson et al. 2009). TE rates differ among different age groups and genders. For example, the proportion of females undergoing TE is higher than males (Mattila et al. 2001, Erickson et al. 2009).

2.3.1 Procedure and techniques

Many studies and meta-analyses have compared different surgical techniques in order to reduce postoperative pain and post-tonsillectomy haemorrhage (PTH), but these have produced ambivalent results (Kamal et al. 2006). It is an unresolved challenge to develop a new surgical technique which is safe, cost efficient, easy to use and reduces intraoperative bleeding with minimal PTH and postoperative pain.

TEs have developed from blunt/cold dissection and guillotine excision to the more recent electrocautery, coblation, cryosurgery, ultrasonic, laser and vessel sealing techniques (Anonymous 2005, Alexiou et al. 2011, Sayin & Cingi 2012). The traditional “blunt/cold” dissection TE technique, which is considered the gold standard, removes the tonsil by dissecting with metal instruments, with continuous haemostasis obtained through the ligation of blood vessels. Blunt/cold dissection TE preserves good protection of the pillar mucosa. Mono- or bipolar diathermy (electrosurgical) dissection of the peritonsillar space is the most common “hot” TE technique and is often used for haemostasis during cold dissection TE because thermal injury can postpone pharyngeal mucosa healing and the duration of postoperative pain. New “hot” or powered instrument techniques (e.g. Coblation, Radiofrequency, Harmonic scalpel (HS), Vessel sealing systems) can decrease postoperative morbidity and the risk of PTH (Anonymous 2005, Alexiou et al. 2011, Sayin & Cingi 2012). Blunt/cold dissection and electrocautery techniques are, however, still the most commonly used TE techniques (Chen et al. 2014, Gallagher et al. 2010). It was reported that the bipolar technique was least associated with early PTH, and the blunt/cold technique related with the least delayed PTH (Gysin & Dulguerov 2013), while hot techniques (except for coblation) were associated
with a higher rate of late PTH and re-operation rates compared with cold dissection + cold haemostasis (Söderman et al. 2015). HS resulted in a lower risk for early PTH (Söderman et al. 2015). In different studies, PTH rates have fluctuated between different techniques based on the surgeon and the surgical practice routine. The perioperative use of intensive diathermy for haemostasis may cause severe thermal damage to the surrounding tissue and create a large slough area and late PTH (Anonymous 2005).

In the Harmonic Scalpel technique, an ultrasonic dissector simultaneously coagulates and cuts through tissue. The tissue is cut by the instrument’s sharp blade, which vibrates at an ultrasonic frequency of 55 kHz, and haemostasis is achieved by the vibration of the blade causing superficial denaturation and coagulation of the proteins by the production of low temperature (55 ºC to 100 ºC) causing less thermal damage to the operation wound. The advantages of the HS technique are minimal as regards intra-operative blood loss and time of operation. This has been noted in several studies, which have compared HS with conventional cold dissection or electrosurgical techniques (Collison & Weiner 2004, Cushing et al. 2009, Ji et al. 2012, Kamal et al. 2006, Kemal 2012, Lachanas et al. 2007, Leaper et al. 2006, Walker & Syed 2001, Willging & Wiatrak 2003, Sheahan et al. 2004, Oko et al. 2005, Leaper et al. 2006, Parsons et al. 2006, Khan et al. 2012, Zhou et al. 2012, Ragab 2012, Pajic-Penavic et al. 2013, Slouka et al. 2016).

In general, modern TE is a safe procedure. However, postoperative morbidity in terms of pain, bleeding, and recovery to normal activity and diet is notable. Although new devices may result in less intraoperative blood loss, intraoperative time, postoperative pain and bleeding, there is a still a general lack of consensus regarding the ideal method for TE (Alexiou et al. 2011, Chen et al. 2014, Sayin & Cingt 2012).

HS TE has been compared to traditional operation techniques and reported to have some differences between the groups regarding average postoperative pain and side effects (Table 3).
Table 3. Harmonic Scalpel technique compared with conventional cold steel (CS) and/or electrocautery dissection (EC) techniques. NA, not applicable; POD, postoperative day; OD, operation day; A, adult; C, child; S, comparing sides. Data are express as median or mean as appropriate. Adapted with permission from Alexiou and colleagues (Alexiou et al. 2011).

<table>
<thead>
<tr>
<th>Study First author, year</th>
<th>N = HS/(CS/EC)</th>
<th>Age</th>
<th>Pain Score HS/(CS/EC)</th>
<th>Other HS/(CS/EC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker, 2001</td>
<td>97 / 75 C NA</td>
<td></td>
<td></td>
<td>Return to regular diet: POD 1(^{2}): 44% vs 23%, POD 3(^{2}): 74% vs 47% Return to normal activity: POD 1(^{2}): 28% vs 12%, POD 3(^{2}): 49% vs 23%</td>
</tr>
<tr>
<td>Sheahan, 2004</td>
<td>28 S A POD 1(^{1}), POD 2(^{1}), POD 7(^{1}) and POD week 3(^{1})</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Willing, 2003</td>
<td>117 C POD 1(^{2}), POD 2(^{2}), POD 3(^{2}), POD 14(^{2})</td>
<td></td>
<td></td>
<td>Ability to eat, drink, or swallow and amounts consumed(^{1}), Level of daily activity: POD1(^{2})</td>
</tr>
<tr>
<td>Collison, 2004</td>
<td>28 S A + C OD 3 hours(^{2}): 3.5 vs 4.4, POD 7(^{1}): 2.7 vs 2.6</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Oko, 2005</td>
<td>45 / 48 C POD 1–9(^{3}), POD 1(^{3}): 2 vs 1.7, POD 3(^{3}): 2.2 vs 1.8</td>
<td></td>
<td></td>
<td>Dietary intake scores: POD 1(^{2}): 0.6 vs 0.4, POD 3(^{1}): 0.6 vs 0.5, POD 5(^{1}): 0.6 vs 0.4, POD 7(^{2}): 0.6 vs 0.3, POD 9(^{2}): 0.3 vs 0.1</td>
</tr>
<tr>
<td>Kamal, 2006</td>
<td>180 / 100 A + C HS group required mild and CS group needed stronger analgesia.</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Parsons, 2006</td>
<td>44 / 43 C POD 1–10(^{1}): 4.7 vs 4.3</td>
<td></td>
<td></td>
<td>POD10, 80% of patients achieved normal food intake(^{1}) / 92% reached normal activity level(^{1})</td>
</tr>
<tr>
<td>Study</td>
<td>N = HS/(CS/EC)</td>
<td>Age</td>
<td>Pain Score</td>
<td>Other</td>
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<tr>
<td>--------------------</td>
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<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Leaper, 2006</td>
<td>103 / 101</td>
<td>C</td>
<td>POD 1–6 at rest: 4.7 vs 4.2,</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 1–6 at worst pain: 6.9 vs 6.2,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 1–6 on swallowing: 5.9 vs 5.2</td>
<td></td>
</tr>
<tr>
<td>Lachanas, 2007</td>
<td>43 / 37</td>
<td>A</td>
<td>POD 1: 4.9 vs 8,</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 3: 4.5 vs 7.8, POD 5: 4.2 vs 6.1,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 7: 3.3 vs 5.3, POD 10: 1.3 vs 3,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 1–10: 3.6 vs 6</td>
<td></td>
</tr>
<tr>
<td>Cushing, 2009</td>
<td>114 S</td>
<td>A + C</td>
<td>POD 1–14 pain at rest and on swallowing</td>
<td>Delayed postoperative haemorrhages / readmission for dehydration / poor oral intake</td>
</tr>
<tr>
<td>Khan, 2012</td>
<td>100 / 100</td>
<td>C</td>
<td>POD 1: 3.4 vs 5, POD 3: 4.6 vs 6.3,</td>
<td>Return to regular diet 5.1 vs 7,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 5: 3.2 vs 4.9, POD 10: 1.7 vs 2.8</td>
<td>Days required for complete healing 13.6 vs 13.7</td>
</tr>
<tr>
<td>Kemal, 2012</td>
<td>63 / 81</td>
<td>C</td>
<td>POD 1: 3.9 vs 4.3, POD 4: 3.6 vs 3.8,</td>
<td>Immediate bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 7: 3.1 vs 3.6, POD 14: 1.1 vs 1.4</td>
<td></td>
</tr>
<tr>
<td>Zhou, 2012</td>
<td>42 / 46</td>
<td>A</td>
<td>Operation day (first 10 hours) less pain with HS</td>
<td>Return to regular diet 8.5 vs 8.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 1–3 more pain with HS and most patients lasted longer</td>
<td>Return to work 9 vs 8.9</td>
</tr>
<tr>
<td>Ragab, 2012</td>
<td>50 / 50</td>
<td>A</td>
<td>POD 1: 8.2 vs 9.2</td>
<td></td>
</tr>
<tr>
<td>Paji, 2013</td>
<td>50 / 50</td>
<td>C</td>
<td>POD 1: 3.7 vs 3.5, POD 2: 3.4 vs 3,</td>
<td>Return to regular diet 3.5 vs 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 3: 3.2 vs 2.9, POD 4: 3 vs 2.6,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 5: 2.9 vs 2.6, POD 6: 2.7 vs 2.4,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>POD 7: 2.3 vs 2</td>
<td></td>
</tr>
<tr>
<td>Slouka, 2016</td>
<td>10 S</td>
<td>A</td>
<td>Maximal pain reduction of 7%</td>
<td>NA</td>
</tr>
</tbody>
</table>

1 nonsignificant difference, 2 significant difference prefer to HS group, 3 significant difference prefer to CS/EC group
2.3.2 Postoperative care

Achieving adequate postoperative care remains challenging after TE, especially for children, as prolonged pain and pain-related poor oral intake can lead to dehydration and poor outcomes. The appropriate management of postoperative pain reduces perioperative complications, hospital stay, re-hospitalization and costs after minor surgical procedures such as TE (Savoia et al. 2010).

TE was ranked 24th for pain severity out of 179 different surgical procedures (Gerbershagen et al. 2014), with patients reporting relevant or severe pain within 24 hours after ENT surgery. A significant number of patients expressed a desire for more pain medication (Guntinas-Lichius et al. 2014). A systemic review showed that children experienced significant pain, and a single prophylactic dose of analgesics was not enough to provide analgesia on the day of the TE (Hamunen & Kontinen 2005). Pain scores remained higher between POD4-POD7 during the two weeks after TE in adults (Kamarauskas et al. 2013, Sarny et al. 2012).

Evidence-based, procedure-specific multimodal analgesic protocols are still needed to improve the quality of postoperative pain management and to meet the needs of individual patients with fewer side effects after TE (White & Kehlet 2010). In order to attain this goal, general non-medical management for multimodal TE analgesia treatment has been described including behavioral therapy, acupuncture and vocal exercises (Gilbey et al. 2015, Sertel et al. 2009, Fayoux & Wood 2014, Vayisoglu et al. 2010).

2.3.3 Complications

Complications after TE most often include pain, dehydration, and bleeding. PTH is one of the most feared and life threatening complication of TE. The database of a large insurance company suggested that 20% of adult patients had complications after TE and needed to contact the hospital. Six percent of the patients were treated for PTH and 11 percent had postoperative pain during the two-week postoperative period. Pain and PTH have increased mean healthcare expenditures over 20 and 60 percent, respectively, after TE (Seshamani et al. 2014).

The incidence of mortality was estimated to be from 0.01 to 0.0024 after TE, (Østvoll et al. 2015, Goldman et al. 2013, Gysin & Dulguerov 2013). A cohort study showed that the 30-day reoperation, complication and mortality rates were 3.2, 1.2 and 0.03 percent, respectively, indicating the safety of adult TE (Chen et al.
The incidences in early and delayed PTH were reported to be 0.1–1.5 percent and 0.8–40 percent, respectively, depending on patient age and the definition of bleeding and operation technique (Gysin & Dulguerov 2013, Tolska et al. 2013, Ruohoalho et al. 2015, Söderman et al. 2015). Several coincident factors may affect PTH occurrence, including surgical technique, PONV and pain medications. Patients with increasing pain during early PODs had a higher risk for PTH after TE and showed the relation of pain management and PTH after TE (Sarny et al. 2012).

The concern over increased bleeding has made practitioners reluctant to use NSAIDs in patients undergoing TE. On the other hand, untreated pain could increase bleeding. Some reviews have suggested that the use of NSAIDs is associated with an increased rate of reoperations (Møiniche et al. 2003) while others reported no significant impact on bleeding in children (Cardwell et al. 2012, Riggin et al. 2013). The co-administration of NSAID and dexamethasone was suggested to be safe in adults undergoing TE (Tolska et al. 2013). The co-administration of IBP and APAP offered an effective postoperative pain management after TE in children and did not increase the bleeding rate (Liu & Ulualp 2015). The use of a combination of IBP + APAP, however, was reported to increase PTH compared to an APAP + codeine/hydrocodone combination after intracapsular TE in children (D'Souza et al. 2015).

Sleep apnoea, aspiration, anaesthesia, and opioid analgesics (codeine) may all contribute to respiratory failure, and thereby increase mortality after TE. Therefore, an understanding of mortality risk is important for conducting convincing patient counselling and maximizing patient safety before TE (Ciszkowski et al. 2009, Goldman et al. 2013).

### 2.4 Third molar extraction

The surgical removal of impacted third molars is considered to be the most common outpatient procedure of oral and maxillofacial surgery. Third molar extraction induces an inflammatory reaction with pain, swelling, and trismus. Third molar extraction is commonly related to a change in quality of life—especially over the first three PODs (McGrath et al. 2003).

Third molar extraction, especially in the mandible, causes predictable, unavoidable and self-limiting side effects such as discomfort, swelling, bruising, and jaw stiffness. Most morbidities are relatively mild and short-lived, and most patients can return to work after 2 to 3 days, even though it takes 4 to 6 weeks
before patients are fully recovered with a full range of jaw movements and the ability to chew food well. More serious complications occur in 10% of patients. The greatest degree of discomfort occurs on the first POD. The rate of discomfort will decrease by POD7 and will almost disappear by POD14 (Pogrel 2012).

Various surgical flap designs can be used to gain better surgical access to the operation area and to decrease periodontal problems, as well as to minimize postoperative discomfort for the patient. Studies as to the superiority of any design have, however, displayed conflicting results (Steel 2012, Cetinkaya et al. 2009). Depending on the degree of impaction, the tooth is exposed by removing bone around the crown and the tooth is extracted after splitting it in several pieces if necessary. It is of utmost important to avoid unnecessary removal of bone (Steel 2012). In cases where nerve damage to the mandibular nerve is estimated to be of high risk, only the crown of the tooth can be extracted and the roots may be left in situ. Proper primary closure of the flap avoids suture dehiscence, improves wound healing and thus decreases postoperative pain (Cetinkaya et al. 2009).

The third molar extraction pain model has been claimed to have high success, recruiting rates and cost effectiveness. Third molar extraction had higher pain sensitivity than joint replacement- and soft tissue surgery models (Singla et al. 2014). Third molar extraction studies provide the opportunity to test multiple doses, combinations of analgesics, and preemptive interventions. The third molar extraction model has been applied to estimate different compounds, e.g. traditional NSAIDs, COX-2 selective NSAIDs, opioids and combination of these analgesics, as well as some adjuvant drugs with different mechanisms of action (Cooper & Desjardins 2010).

As an example, Moraschini found that the submucosal (SM) injection of dexamethasone reduced oedema and pain after third molar extraction (Moraschini et al. 2016). In the same manner, an immediate cooling effect was tested after third molar extraction (Ibikunle & Adeyemo 2016, Zandi et al. 2016). Isiordia-Espinoza showed that a single dose of tramadol has a poorer analgesic efficacy and safety profile than administering an NSAID after third molar extraction (Isiordia-Espinoza et al. 2014).
3 Aims and hypothesis of the study

The aims of this study were to investigate the intensity of acute postoperative pain associated with TE and third molar extraction.

The specific aims were as follows:

I To assess the efficacy of the Harmonic scalpel in tonsillectomy and its possible benefits for postoperative pain compared to the blunt/cold dissection technique. (I)

II To study the efficacy and tolerance of a combination of paracetamol and ketoprofen compared to either drug used alone in treating pain after third molar extraction. (II)

III To study the role of a peritonsillar morphine infiltration as a part of multimodal analgesia after tonsillectomy in adult patients. (III)

IV To evaluate the analgesic effect of peripherally administrated morphine and compare its efficacy on the inflammatory and non-inflammatory teeth after third molar extraction. (IV)

The hypotheses tested in the original studies were:

1. That the Harmonic scalpel in tonsillectomy reduces postoperative pain compared with the blunt/cold dissection technique. (I)

2. That the combination of APAP and NSAID is potentially more effective and safe for acute post-operative pain control after third molar surgery than either drug alone. (II)

3. That a local administration of opioid after TE and third molar extraction could provide a peripherally mediated opioid analgesia without the undesirable side effects associated with the use of systemic opioids. (III and IV)

4. That the analgesic effects of local morphine depend on whether or not it is injected into inflamed tissue. (IV)
4  Patients and Methods

4.1  Patients

Studies I and III included patients (n = 72) who were scheduled to undergo bilateral TE operations at the Oulu University Hospital, Department of Otorhinolaryngology. Studies II and IV included patients (n = 172) who were scheduled to undergo an extraction of the third molar at the Department of Oral and Maxillofacial Surgery in the Finnish Student Health Service Oulu branch (Study II) and Oulu University Hospital (Study IV). A detailed description of the patients and surgeries in Studies I–IV is given in Table 4. Exclusion criteria included having an allergy to the drugs under study, acute infection, major organ disease, drug or alcohol abuse and sleep apnoea syndrome.

The patients were admitted to the Oulu University Hospital and the Finnish Student Health Service Oulu branch during the years 1998–2007.

Table 4. Different clinical studies (I–IV), The number of patients included and type of surgery in each study. (American Society of Anesthesiologists (ASA) sorted the category physical status classification system 1 = Healthy person, 2 = Mild systemic disease).

<table>
<thead>
<tr>
<th>Study</th>
<th>N recruited</th>
<th>Age</th>
<th>ASA</th>
<th>Elective Operation</th>
<th>Pain compared between</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>32</td>
<td>17–48</td>
<td>1–2</td>
<td>bilateral tonsillectomy</td>
<td>sides</td>
</tr>
<tr>
<td>II</td>
<td>84</td>
<td>18–40</td>
<td>1</td>
<td>third molar extraction</td>
<td>groups</td>
</tr>
<tr>
<td>III</td>
<td>40</td>
<td>19–50</td>
<td>1–2</td>
<td>bilateral tonsillectomy</td>
<td>sides</td>
</tr>
<tr>
<td>IV</td>
<td>88</td>
<td>18–40</td>
<td>1</td>
<td>third molar extraction</td>
<td>groups</td>
</tr>
</tbody>
</table>

4.2  Ethical Issues

The protocols of the studies were accepted by the Ethics Committee of the Oulu University Hospital Studies I, II, and IV) and the Northern Ostrobothnia Hospital District (study III). The National Agency for Medicine was notified of the study protocols (Studies II, III, and IV). Written informed consent was obtained from all patients prior to their recruitment to the studies.

4.3  Study design

All studies were clinical randomized controlled trials (RCTs).
Study I was designed to compare the bilateral TE sides with one side operated using HS and the other side using a blunt/cold dissection technique (Figure 1). Study III was designed to compare the bilateral TE sides with one side infiltrated morphine and the other side infiltrated NaCl into tonsillar bed and peritonsillar tissues (Figure 2). The side was chosen randomly using a sealed envelope protocol. The surgeon opened the envelope after the induction of general anaesthesia. Operating theatre personnel and the surgeon did not take part in the patient’s postoperative pain management. Neither the patient nor the postoperative personnel knew which side had been operated on using the HS technique / injected morphine. TE was performed with the blunt/cold dissection technique on both sides in Study III. In Study I, bleeding was managed with HS, if possible; otherwise in Studies I and III haemostasis was managed with electrocoagulation.

Fig. 1. Consort flowchart of Study I.
Studies I and III were designed to assess the postoperative pain and side effects of the HS technique (I) or a single dose of morphine injection (III) at bilateral TE. The schedules of Studies I and III are shown in Figures 1 and 2, respectively.

Study II was designed to compare the pain relief efficacy and ADEs of KTP and APAP alone or in combination after third molar extraction. Patients were enrolled to undergo extraction of one or two impacted third molars, of which at least one was the mandibular third molar. The patients were randomly assigned to one of four different groups: KTP 100 mg + APAP 1000 mg, KTP 100 mg, APAP 1000 mg, or a placebo tablet. Patients were instructed to take the study medicine postoperatively if they had pain over three on a numerical rating scale (NRS, 0 = no pain, 10 = worst pain imaginable). Rescue medication was available to be used 1 hour after the study medication was taken. Patients were discharged with 20 IBP 800 mg tablets and the maximum recommended dose for rescue medication was 2400 mg per day.
Study IV was a single-dose active controlled RCT to compare the analgesic effect and ORADEs of peripheral IM morphine injection after extraction of one impacted mandibular third molar. This study also consisted of two trials. Peripheral morphine was infiltrated into non-inflamed SM (Trial I) and inflamed (Trial II) SM tissue. The patients who received 2 mg morphine hydrochloride (2 mg/ml) intramuscular (IM) in the upper arm were concomitantly given a SM injection of 1 ml sodium chloride NaCl. The patients who received morphine peripherally as a SM injection of 2 mg morphine hydrochloride were concomitantly given an IM injection of 1 ml of NaCl in the upper arm. Third molar extraction was performed with standardized procedure (buccal approach with bur) by the same surgeon (K.A.). The schedules of Studies II and IV are shown in Figures 3 and 4, respectively.

Fig. 3. Consort flowchart of Study II.
Fig. 4. Consort flowchart of study IV.

Each patient’s postoperative data was collected and analysed by the principal researcher (E. A.) (Studies I–IV). Important help was received from the operation theater nurses and personnel of the day care and outpatient departments at the Oral and Maxillofacial Surgery and Otorhinolaryngology Departments.

### 4.4 Anaesthesia and analgesia

Tonsillectomies (Studies I and III) were carried out under general anaesthesia with endotracheal intubation. Propofol (2–3 mg/kg), fentanyl (2 μg/kg) and mivacurium were administered IV for general anaesthesia induction. Fentanyl 50 μg was administered intravenously (IV) at the start of the operation. Anaesthesia was
maintained with isoflurane 1 ± 2 percent (Study I) or sevoflurane 1 ± 4 percent (Study III) with 70% nitrous oxide in O2 at an end-tidal concentration.

In the immediate postoperative period, IV and IM oxycodone (Study I) or IV fentanyl (Study III) and subsequently IV KTP were given for analgesia after TE.

Orally administered APAP (Panadol®, GlaxoSmithKline, Study I) or KTP (Ketorin® Orion, Finland, Study III) and APAP in combination with codeine (Panacod®, Sanofi, APAP 500 mg + codeine 30 mg, Studies I, II, and III) were used for postoperative pain management. Impacted third molar extraction was performed under local anaesthesia (4% Ultracaine with 1 : 100 000 epinephrine; Sanofi, Vienna, Austria).

4.5 Outcome measures

4.5.1 Measurement of pain

The patients and all-postoperative investigators involved in pain assessment and management were unaware of the perioperative management. Postoperative pain was assessed using NRS at rest and on swallowing for the operation side of each tonsil (Studies I and III).

In Study II, the analgesic efficacy of the treatment medicine was expressed as the reduction of the pain scores compared to baseline values among the treatment groups at rest and on swallowing. Baseline pain values were determined as the level at which the patient decided to take the study medication. Pain intensity difference (PID) and summation of PID (SPID) were defined as observations at each time point and period. Distinguishable pain relief was expressed as one category in NRS change (PIDR ≥ 1) in PID at rest and on swallowing.

The duration of the analgesic effect was evaluated using the median time to the use of rescue analgesia.

In all four studies the patients were asked to record pain levels, all analgesic consumption and any side effects in their pain diary postoperatively (Table 5). The patients visited the outpatient clinic after two weeks and at that visit the pain diaries were collected and sealed in Studies I, II, and IV. In Study I the tonsillar fossae were examined for slough and healing at the same postoperative visit.

In Study I and III, patients were asked to record individual pain levels on each operation side at rest and on swallowing (after swallowing 50 ml of water) in the morning and evening after discharge from hospital until the 14-day POD.
Meanwhile, each day's least, average and worst (only in Study I) levels of pain and worst level of otalgia throughout the day were recorded in the evening for both operation sides individually during the two postoperative weeks in Studies I and III. In Study III, patients returned the pain questionnaire to the clinic by post.

In Studies II and IV, the patients rated pain levels at rest and on swallowing without differentiating between operation sides (Table 5). In all four studies, pain intensity was self-rated first at rest and then on swallowing (dry in Studies II and IV; with water in Studies I and III). In Studies II and IV the patients were asked to rate restriction from daily activity due to pain, and absence from work due to pain at 2 weeks after the operation.

In Study III, the patients measured their weight over the following two weeks after TE.

Table 5. Schedule for the assessment of pain in Studies I–IV. Postoperative pain assessment after arrival in recovery room (studies I, III, IV) and treatment medication was taken (Study II), Postoperative day (POD).

<table>
<thead>
<tr>
<th>Time point for pain at rest and swallowing</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>15 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1 h 15 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h 30 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h 45 min</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6 h (hourly)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>8 h</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–14 days morning and evening</td>
<td></td>
<td>X</td>
<td>X (POD1–4)</td>
<td>X (POD1–7)</td>
</tr>
<tr>
<td>Day's least and average pain in evening daily</td>
<td>X</td>
<td>X (POD1–4)</td>
<td>X (POD1–7)</td>
<td></td>
</tr>
<tr>
<td>Day's worst pain in evening daily for 2 weeks</td>
<td>X</td>
<td>X (POD1–4)</td>
<td>X (POD1–7)</td>
<td></td>
</tr>
<tr>
<td>Worst level of otalgia in evening daily for 2 weeks</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.5.2 Measurement of the consumption of analgesics

In all four studies, postoperative pain medicines were available free of charge for the patients when it was feasible to take medicine orally, and the names of all other analgesics were documented in the pain diary during the 14-day period (Figures 1–
The patients were instructed to take APAP (Study I), IBP (Studies II and IV) and KTP (Study III), when their pain scores were over three. In Studies I, III and IV, the patients were instructed to take one Panacod® when their pain scores were five or over. In Studies I and III, the patients were asked to record all analgesics, including self-care analgesics taken during the 14-day post-operative period. This follow-up period was shorter in Studies II and IV (Table 5). In Study I, the use of NSAID was represented as APAP consumption. A dose of 50 mg KTP, 400 mg IBP or one Panacod were expressed as a dose of 500 mg APAP. In Study III, the use of NSAID was represented as KTP consumption. A dose of 500 mg APAP, 400 mg IBP or one Panacod were expressed as a dose of 50 mg KTP. In Studies II and IV, the use of NSAID was represented as IBP consumption. A dose of 500 mg APAP or one Panacod were expressed as a dose of 400 mg IBP. In the TE studies, we compared pain between sides. Therefore, analgesic consumption did not provide an opportunity to compare groups.

4.5.3 Measurement of adverse effects

The presence and intensity of side effects and pain medication consumption were estimated concurrently with pain intensity assessments (Table 5). In Study I, bleeding was monitored on the POD1 and later during the two-week period by the surgeon and by patients in their pain diary. Bleeding was reported as the level of bleeding using a three-point categorical verbal rating scale (3 = severe, 1 = mild, 0 = none). In the third molar extraction studies, the patient assessed bleeding at 1–3 PODs with a four-point categorical verbal rating scale (3 = severe, 2 = moderate, 1 = mild, 0 = none). Postoperative sedation was evaluated on the operation day on a four-point categorical verbal rating scale. In Studies I and III, side effects were assessed during 14 PODs. In Studies II and IV, patients were asked to record the effect of the local anaesthesia and adverse effects such as PONV, trismus, bleeding, and oedema, at the same time as their pain assessment on the first three PODs.

4.6 Statistical analysis

The definition of the sample size was performed by approximation to the normal distribution. The number of patients included in each of the studies was determined using power analyses (Table 7). In the prospective power analysis, an $\alpha$-level of 0.05 and $\beta$-power of 0.9 were used in all studies. For the TE studies (Studies I and...
III) the calculation of the sample size was based on data from the Campbell and colleagues study (Campbell & Kendrick 1997) with a comparable methodology. We calculated that at least thirty subjects would be needed to define a difference of ten percent in NRS pain scores.

In the TE studies (I, III) sample sizes were sufficient to give a statistically significant difference between the two different treatments because the patients acted as their own controls.

In Study I, the pain diaries were collected during each patient’s postoperative outpatient department visit after two-weeks. We assumed a low number of dropouts and recruited 32 patients. However, in Study III, we asked patients to send their pain questionnaires to the clinic by post, and consequently we assumed a 25 percent dropout and recruited 40 patients. In the third molar extraction studies, based on a previous trial of Hyrkäs (Hyrkas et al. 1992) and colleagues, the standard deviation of the change in pain scores over time could be assumed to be approximately two. With a two-sided significance level of 5 percent and a power of 90 percent, we approximated that sixteen patients should be included in each treatment arm. We proposed to treat twenty-one patients in each treatment arm, with a 23 percent dropout margin, and 84 cases were recruited in Study II. To compensate for imbalance in group sample sizes due to a congruent randomization list and dropouts, 88 patients were recruited in Study IV.

In all studies, the distribution of data was assessed with frequency histograms, and summary measurements are presented as means with standard deviation or as medians with 25th–75th percentiles unless otherwise stated. Between-group comparisons were performed by Student’s t-test or Mann-Whitney U-test (continuous variables) and by Pearson’s χ²-test or Fisher’s exact test (categorical variables). Paired samples t-test or the Wilcoxon signed rank test were used in the case of paired data (e.g. pain day 0 vs day 1). Kendall’s correlation test was used for correlation.

Data with more than two measurements were analyzed by calculating Area Under the Curve (AUC) or by using the Linear Mixed Model (LMM). The p-values reported with LMM are: p_time for the change over time, p_group for the average difference between sides, and p_time x group for the interaction between time and side. In the case of a significant time effect (p_time < 0.05), the comparison between time points was performed using the Wilcoxon matched-pair signed rank test for skewed data and the paired-samples t-test for normally distributed data. The comparison was taken in LMM if the measurements were taken from the same individual. Kaplan-Meier survival curves were drawn for time to event data and the
log rank test was performed to estimate the statistical difference between the treatment groups. Two tailed p-values are reported. SPSS for Windows (version 9, 14.01, 17.0, 22.0) and SAS (version 9.3) were used in statistical analysis.
5 Results

5.1 Patients

The main characteristics of the patients included in the analyses are summarized in Tables 6 and 7. In Study I, the reasons for four drop outs were the need for a re-operation due to haemorrhage and protocol noncompliance. In Study II, the reason for dropouts was protocol violation: inadequately filed pain questionnaire and no reported pain over NRS level 3. In Study III, eleven cases were excluded as the pain questionnaires were not returned by post. Nine patients were withdrawn for protocol non-compliance and loss of follow-up in Study IV (Table 6). The patients’ demographic and baseline characteristics were very similar in all studies (Table 7).

Table 6. Patients and reasons for withdrawal in Studies I–IV.

<table>
<thead>
<tr>
<th>Study Number</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (cases) at beginning of the study</td>
<td>32</td>
<td>82 (84)</td>
<td>40</td>
<td>88</td>
</tr>
<tr>
<td>Number of patients (cases) analyzed</td>
<td>28</td>
<td>76 (78)</td>
<td>29</td>
<td>79</td>
</tr>
<tr>
<td>Number of patients excluded from the study</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Loss of follow up</td>
<td>-</td>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>No pain at a level of ≥ 3 on the NRS</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Re-operation due to bleeding</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>
Table 7. Patients’ clinical and demographic data in the original Studies I–IV. Data are mean (standard deviation).

<table>
<thead>
<tr>
<th>Original study</th>
<th>N = included in analyses</th>
<th>Age, years</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Sex, Female / male</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>28</td>
<td>25 (9)</td>
<td>159 (9)</td>
<td>71 (14)</td>
<td>16 / 12</td>
</tr>
<tr>
<td>II</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination group</td>
<td>20</td>
<td>24 (2)</td>
<td>170 (8)</td>
<td>69 (9)</td>
<td>12 / 8</td>
</tr>
<tr>
<td>KTP group</td>
<td>20</td>
<td>24 (2)</td>
<td>172 (9)</td>
<td>65 (12)</td>
<td>10 / 10</td>
</tr>
<tr>
<td>APAP group</td>
<td>18</td>
<td>25 (3)</td>
<td>170 (8)</td>
<td>68 (9)</td>
<td>11 / 7</td>
</tr>
<tr>
<td>Placebo group</td>
<td>20</td>
<td>24 (2)</td>
<td>166 (10)</td>
<td>64 (16)</td>
<td>13 / 7</td>
</tr>
<tr>
<td>III</td>
<td>29</td>
<td>30 (7)</td>
<td>171 (8.6)</td>
<td>74 (9.6)</td>
<td>19 / 10</td>
</tr>
<tr>
<td>IV</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial I</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Mo</td>
<td>17</td>
<td>23 (2)</td>
<td>167 (58)</td>
<td>67 (9)</td>
<td>14 / 3</td>
</tr>
<tr>
<td>IM morphine</td>
<td>14</td>
<td>25 (6)</td>
<td>169 (8)</td>
<td>63 (15)</td>
<td>9 / 5</td>
</tr>
<tr>
<td>Trial II</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Mo</td>
<td>25</td>
<td>25 (4)</td>
<td>169 (7)</td>
<td>64 (11)</td>
<td>18 / 7</td>
</tr>
<tr>
<td>IM morphine</td>
<td>23</td>
<td>24 (4)</td>
<td>172 (9)</td>
<td>68 (15)</td>
<td>14 / 9</td>
</tr>
</tbody>
</table>

5.2 Pain on the day of operation

5.2.1 Pain scores at rest and on swallowing

Pain at rest and swallowing were the main outcome measures in all four studies. In Study I, AUC pain at rest and on swallowing during the first 10 postoperative hours were significantly greater on the blunt/cold dissection side compared to the HS side.

In Study III pain scores were similar when comparing to the morphine and NaCl sides at all times during the two-weeks follow-up after TE.

In Study IV, the pain scores at rest and on swallowing were similar compared to the active control IM group at all times on the operation day when morphine was infiltrated into non-inflamed tissue after the third molar extraction (Trial I). At the same time, the AUC pain scores on swallowing at between 2–6 hours were significantly higher in the active control IM group when morphine was infiltrated into inflamed tissue after the third molar extraction (Trial II), demonstrating the minimal analgesic effect of SM morphine.
5.2.2 Pain intensity difference scores, time to onset and use of rescue analgesics (Study II and IV)

In Study II, the pain intensity difference scores and the summations of them at rest and on swallowing (PIDR, PIDS, SPIDR and SPIDS) were significantly greater in the active treatment groups than in the placebo group at each time point through the first 10 hours after third molar extraction. In the combination group, the PIDR score was greater than in the other groups during the first 1.5 hours after the medication was taken. Distinguishable pain relief at rest (PIDR ≥ 1) and on swallowing (PIDS ≥ 1) occurred significantly faster in the combination group compared to the other groups. In the combination group, the time before taking rescue medication was significantly greater than the APAP or placebo groups, and in the APAP group it was significantly greater compared to the placebo group. There was no difference in the time before taking rescue medication between the KTP group and the combination group.

In Study IV, the time for the first analgesic intake was similar between groups.

5.3 Pain in the late postoperative phase (Studies I, III and IV)

In Studies I and III, the pain scores remained high during the first week in all treatment groups after TE. During the first postoperative week AUC pain scores at rest (Figure 7a and Original Publication I, Figure 2a), on swallowing (Figures 5, 7b and Original Publication I, Figure 2b) and the day's average (Figure 8b), worst (Figure 6), and worst otalgia (Figure 8a and Original Publication I, Figure 3) were similar between the treatment sides.

In Study I, the second postoperative week’s pain levels, expressed as AUC at rest (Original Publication I, Figure 2a), on swallowing (Figure 5 and Original Publication I, Figure 2b) and the day's, average and worst (Figure 6), were significantly lower on the blunt/cold dissection side than on the HS side. The second postoperative week’s otalgia levels (Original Publication I, Figure 3), expressed as AUC were also lower on the blunt/cold dissection side than on the HS side.

In Study III pain levels at rest (Figure 7a), on swallowing (Figure 7b) and the day's average (Figure 8b), and worst otalgia (Figure 8a) were similar in the both treatment groups during the second postoperative week.
Fig. 5. In Study I, postoperative pain in the morning and evening on swallowing after tonsillectomy on the Harmonic scalpel side (●) and the blunt dissection side (□). AUC pain scores on swallowing were higher on the Harmonic scalpel side compared to the blunt dissection side in the second postoperative week. Numerical rating scale (NRS) pain scores are expressed as median with interquartile range.

Fig. 6. In Study I, after tonsillectomy the postoperative day's worst pain in the morning and evening on the Harmonic scalpel side (●) and the blunt dissection side (□). AUC day's worst pain scores were higher on the Harmonic scalpel side compared to the blunt dissection side in the second postoperative week. Numerical rating scale (NRS) pain scores are expressed as median scores with interquartile range.
In Study III, postoperative pain in the morning and evening at rest (a) and on swallowing (b) on the morphine (■) and on the NaCl (□) side after tonsillectomy. Significant differences compared to the 1st postoperative day’s evening rate are highlighted with an asterisk (*). No statistically significant differences between the sides were noted. Numerical rating scale (NRS) pain scores are expressed as median scores with interquartile range.

In Studies I and III, postoperative pain levels at rest and on swallowing were significantly reduced between POD6 - POD9 (Table 8).

In the third molar extraction study (IV), the first postoperative week’s pain scores on swallowing (Original Publication IV Figures 3a and 3b), at rest (Original Publication IV Figures 2a and 2b), the day’s worst (Figure 9b) and average (Figure 9a), and least were moderate and descending after third molar extraction. There were no differences between the groups at any observation points.
Fig. 8. In Study III, postoperative day’s worst otalgia (a) and day’s average (b) pain in the evening on the morphine side (●), and on the NaCl side (○) after tonsillectomy. Significant differences compared to the 1st postoperative day’s evening rates are highlighted with an asterisk (*). No statistically significant differences between the sides were noted. Numerical rating scale (NRS) pain scores are expressed as median scores and interquartile range.
Fig. 9. In Study IV, the day’s average (a) and worst (b) postoperative pain after third molar extraction. Numerical rating scale (NRS) pain scores are expressed as mean scores with 95%CI, OD (operation day).
Table 8. The time of pain reduction after tonsillectomy in Studies I and III. The postoperative day (POD) when pain was significantly reduced compared with the POD1 evening scores. Wilcoxon Signed Rank Test.

<table>
<thead>
<tr>
<th>Duration of Pain</th>
<th>Study I</th>
<th></th>
<th>Study III</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Harmonic</td>
<td>Blunt Dissection</td>
<td>Peripheral</td>
<td>NaCl</td>
</tr>
<tr>
<td>Evening pain at rest</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Evening pain on swallowing</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Evening worst level of otalgia</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Day’s least</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Day’s average</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Day’s worst</td>
<td>9</td>
<td>7</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

5.4 Consumption of analgesics

In Study I, all patients received IV and IM oxycodone in the recovery room or on the ward during their stay overnight during the early postoperative phase. The median oxycodone consumption was 18 mg (interquartile range, 14–24).

In Study III, all patients received IV fentanyl during their 6-hour stay in the recovery room or on the ward. Median fentanyl consumption was 75 μg (interquartile range, 50–100). In Studies I and III, codeine consumption was statistically significantly reduced compared to the POD1 values from POD7 (Table 9). In Studies I and III, mean POD that patients did not take the codeine combination was comparable (7.3 and 7.8, respectively). Almost half of the patients did not need to take the codeine combination on the POD8. Interestingly, codeine consumption was comparable at all time-points between Studies I and III (Table 9).

In Study IV postoperative total codeine consumption after third molar extraction was lower than in the TE studies. Only 41% of the patients needed codeine on the operation day and 24% on POD2 (Table 10).
Table 9. Codeine consumption after tonsillectomy during the 1.–14. postoperative days (PODs) in Studies I and III. Codeine consumption is expressed as median scores with interquartile range. Each POD consumption is compared to the POD1 value (Wilcoxon Signed Rank Test. N, the number of patients who used the codeine). The Panacod ® (paracetamol 500 mg + codeine 30 mg) was converted into a comparable dosage of codeine (as 30 mg codeine).

<table>
<thead>
<tr>
<th>POD</th>
<th>Study I</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Codeine mg N p-value</td>
<td>Codeine mg N p-value</td>
</tr>
<tr>
<td>1</td>
<td>90 (37.5–120) 25</td>
<td>120 (60–165) 28</td>
</tr>
<tr>
<td>2</td>
<td>120 (60–180) 23 0.1</td>
<td>120 (90–165) 26 0.74</td>
</tr>
<tr>
<td>3</td>
<td>60 (30–120) 22 0.9</td>
<td>105 (7.5–150) 21 0.131</td>
</tr>
<tr>
<td>4</td>
<td>90 (37.5–142.5) 22 0.9</td>
<td>120 (0–180) 20 0.472</td>
</tr>
<tr>
<td>5</td>
<td>60 (0–120) 20 0.3</td>
<td>120 (15–165) 18 0.551</td>
</tr>
<tr>
<td>6</td>
<td>60 (0–112.5) 19 0.1</td>
<td>90 (0–165) 20 0.253</td>
</tr>
<tr>
<td>7</td>
<td>30 (0–82.5) 18 0.002</td>
<td>90 (0–135) 18 0.021</td>
</tr>
<tr>
<td>8</td>
<td>0 (0–82.5) 13 0.003</td>
<td>60 (0–120) 14 0.006</td>
</tr>
<tr>
<td>9</td>
<td>0 (0–30) 10 0.001</td>
<td>0 (0–90) 14 0.001</td>
</tr>
<tr>
<td>10</td>
<td>0 (0–30) 8 0.001</td>
<td>0 (0–60) 11 0.001</td>
</tr>
<tr>
<td>11</td>
<td>0 (0–0) 4 0.001</td>
<td>0 (0–0) 8 0.001</td>
</tr>
<tr>
<td>12</td>
<td>0 (0–0) 4 0.001</td>
<td>0 (0–0) 4 0.001</td>
</tr>
<tr>
<td>13</td>
<td>0 (0–0) 3 0.001</td>
<td>0 (0–0) 3 0.001</td>
</tr>
<tr>
<td>14</td>
<td>0 (0–0) 1 0.001</td>
<td>0 (0–0) 0 0.001</td>
</tr>
</tbody>
</table>

In Studies I and III, APAP (Study I) and KTP (Study III) consumption was greater during POD1 after TE. APAP (Study I) consumption was significantly reduced from the POD8 compared with POD1 consumption. KTP (Study III) consumption was also significantly reduced on POD9 compared with POD1 consumption. In Study I, 25% patients still used APAP and in Study III, 35% patients used KTP for pain treatment at POD14 (Table 11).
Table 11. Non-opioid analgesic (paracetamol = APAP or ketoprofen = KTP) consumption after tonsillectomy in Studies I and III. In Study I, other non-opioid analgesics were converted into a comparable dose of 500 mg of APAP (50 mg KTP, 400 mg ibuprofen, or 1 tab Panacod®). In Study III, other non-opioid analgesics were converted into a comparable dose of 50 mg KTP (500 mg APAP, 400 mg IBP or 1 tablet of Panacod®). Consumption for each POD is compared to the POD1 value (Wilcoxon Signed Rank Test). N, the number of patients who used the analgesics; POD, postoperative day. Values are expressed as median with interquartile range.

<table>
<thead>
<tr>
<th>POD</th>
<th>Study I</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APAP Marker</td>
<td>KTP Marker</td>
</tr>
<tr>
<td>1</td>
<td>2750 (1625–3500)</td>
<td>550 (412–600)</td>
</tr>
<tr>
<td>2</td>
<td>3750 (2125–4000)</td>
<td>500 (500–600)</td>
</tr>
<tr>
<td>3</td>
<td>3000 (2000–4000)</td>
<td>550 (450–600)</td>
</tr>
<tr>
<td>4</td>
<td>3000 (2500–4000)</td>
<td>550 (450–600)</td>
</tr>
<tr>
<td>5</td>
<td>3000 (2000–4000)</td>
<td>550 (500–600)</td>
</tr>
<tr>
<td>6</td>
<td>2500 (1562.5–3000)</td>
<td>550 (450–600)</td>
</tr>
<tr>
<td>7</td>
<td>2000 (1500–3000)</td>
<td>500 (350–594)</td>
</tr>
<tr>
<td>8</td>
<td>1500 (1000–2500)</td>
<td>400 (325–538)</td>
</tr>
<tr>
<td>9</td>
<td>1000 (500–1500)</td>
<td>300 (250–475)</td>
</tr>
<tr>
<td>10</td>
<td>1000 (0–1500)</td>
<td>250 (150–350)</td>
</tr>
<tr>
<td>11</td>
<td>500 (0–1500)</td>
<td>200 (25–300)</td>
</tr>
<tr>
<td>12</td>
<td>0 (0–1000)</td>
<td>100 (0–100)</td>
</tr>
<tr>
<td>13</td>
<td>0 (0–500)</td>
<td>0 (0–150)</td>
</tr>
<tr>
<td>14</td>
<td>0 (0–500)</td>
<td>0 (0–100)</td>
</tr>
</tbody>
</table>

In Study II, the total amount of supplemental IBP was comparable between the groups (Table 12). In Study IV, NSAID consumption was comparable between the groups (Original Publication IV, Table 2).

Table 12. Postoperative Ibuprofen consumption (mg) after third molar extraction in Study II. There was no difference between the groups. N, the number of patients that used analgesics after third molar extraction; POD, postoperative day. Ibuprofen consumption is expressed as median with interquartile range. Duncan multiple comparisons test.

<table>
<thead>
<tr>
<th>Study II (n = 78)</th>
<th>Combination group</th>
<th>Ketoprofen group</th>
<th>Paracetamol group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD 1 (63)</td>
<td>800 (400–1500)</td>
<td>800 (400–1600)</td>
<td>1600 (600–2000)</td>
<td>800 (400–1500)</td>
</tr>
<tr>
<td>POD 2 (52)</td>
<td>800 (0–1600)</td>
<td>800 (0–1200)</td>
<td>800 (200–2000)</td>
<td>400 (0–1500)</td>
</tr>
<tr>
<td>POD 3 (49)</td>
<td>400 (0–1600)</td>
<td>800 (0–1200)</td>
<td>400 (0–1600)</td>
<td>400 (0–1100)</td>
</tr>
</tbody>
</table>

Patients were asked to assess the duration of pain and their restrictions due to pain for two weeks after third molar extraction. The median number of restrictions on
everyday activity, pain duration at rest and swallowing were 4, 3, and 2 respectively. However, the median of days absent from work varied from one days (patients were mainly university students). Overall, pain and analgesic consumption after third molar extraction were lower than after TE.

5.5 Side effects

In Study I, four patients reported postoperative bleeding after TE. Only two patients needed a re-operation. One was bleeding from the blunt/cold dissection side on the day of the operation and the other from the HS side on POD4. These two patients were excluded from the final analysis as re-operation caused a major irregularity in normal pain medicine consumption. The rate of return to the theatre and early PTH were 6.25% and 10% respectively.

In Studies II and IV, 78 and 66 percent of the patients respectively, reported bleeding on the POD1 and 32 and 25 percent on the POD2, respectively. There was no difference between groups in either study.

In Study II, sedation levels were similar between the treatment and placebo groups.

In Study IV, sedation scores were significantly higher in the peripheral group in the first hour after surgery in Trial I. Moreover, sedation scores were significantly higher in the peripheral morphine groups compared to the IM groups if Trial I and II data are analyzed completely 1 and 2 hours after surgery (Table 13).

A few ADEs occurred in both groups during the study period. PONV was the most common ADE. In all studies, PONV was not different between the groups. In Studies I, III and IV, around 30 percent of patients experienced PONV events on the operation day. After third molar extraction in Study II, however, the PONV frequency was 18 percent. In Study II, pain rescue medication included only IBP, while in Study IV patients were instructed to take the codeine combination for severe pain, and almost 40 percent of the patients needed to take this on the day of the operation. There was also a strong correlation between codeine consumption and PONV, while there was a trend towards more nausea when a higher dose was taken. A negative correlation seemed to exist between cigarette smoking and PONV on the operation day (Table 14).
Table 13. Sedation assessment after surgery by rating the intensity frequencies on a four-point scale (none, mild, moderate, severe). Data analyzed between operation groups in Studies II and IV. (Pearson Chi-Square test).

<table>
<thead>
<tr>
<th>Original study</th>
<th>Sedation after medication</th>
<th>Sedation 1 h after medication</th>
<th>Sedation 2 h after medication</th>
<th>Sedation 3 h after medication</th>
<th>Sedation 4 h after medication</th>
<th>Sedation 6 h after medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study II Combination</td>
<td>6 / 9 / 3 / 2</td>
<td>4 / 8 / 5 / 2</td>
<td>4 / 5 / 6 / 2</td>
<td>5 / 4 / 7 / 2</td>
<td>5 / 5 / 5 / 3</td>
<td>7 / 6 / 1 / 4</td>
</tr>
<tr>
<td>Study II Ketoprofen</td>
<td>7 / 7 / 5 / 0</td>
<td>7 / 6 / 4 / 1</td>
<td>10 / 4 / 2 / 3</td>
<td>9 / 3 / 5 / 1</td>
<td>9 / 5 / 1 / 3</td>
<td>9 / 3 / 2 / 5</td>
</tr>
<tr>
<td>Study II Placebo</td>
<td>5 / 12 / 2 / 1</td>
<td>4 / 6 / 8 / 1</td>
<td>5 / 7 / 5 / 3</td>
<td>7 / 7 / 3 / 2</td>
<td>5 / 4 / 7 / 2</td>
<td>7 / 6 / 5 / 0</td>
</tr>
<tr>
<td>Study IV Trial I Peripheral Mo</td>
<td>11 / 3 / 3 / 0</td>
<td>4 / 11 / 2 / 0</td>
<td>5 / 8 / 4 / 0</td>
<td>5 / 6 / 5 / 1</td>
<td>9 / 5 / 3 / 0</td>
<td>7 / 7 / 2 / 1</td>
</tr>
<tr>
<td>IM morphine</td>
<td>12 / 2 / 0 / 0</td>
<td>11 / 2 / 1 / 0</td>
<td>9 / 4 / 1 / 0</td>
<td>8 / 3 / 2 / 1</td>
<td>9 / 3 / 1 / 1</td>
<td>9 / 2 / 2 / 1</td>
</tr>
<tr>
<td>Study IV Trial II Peripheral Mo</td>
<td>16 / 6 / 2 / 0</td>
<td>13 / 10 / 1 / 1</td>
<td>10 / 6 / 8 / 1</td>
<td>9 / 6 / 8 / 2</td>
<td>9 / 8 / 7 / 1</td>
<td>9 / 11 / 5 / 0</td>
</tr>
<tr>
<td>IM morphine</td>
<td>16 / 4 / 3 / 0</td>
<td>16 / 7 / 0 / 0</td>
<td>14 / 7 / 1 / 1</td>
<td>12 / 7 / 4 / 0</td>
<td>8 / 12 / 2 / 1</td>
<td>13 / 8 / 2 / 0</td>
</tr>
</tbody>
</table>

1 Significant higher sedation levels for the peripheral morphine group compared to the IM group.

In Study III, the mean maximum loss of weight was two kg during the two-week period.

Table 14. In Study IV correlation between postoperative nausea and vomiting (PONV) with codeine consumption and potentially influencing factors (smoking). OD, operation day; POD, postoperative day, Kendall’s correlation test.

<table>
<thead>
<tr>
<th>PONV Correlation Coefficient / P values</th>
<th>OD Consumption</th>
<th>1 POD Consumption</th>
<th>2 POD Consumption</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>0.23 / 0.024</td>
<td></td>
<td></td>
<td>-0.2 / 0.037</td>
</tr>
<tr>
<td>1 POD</td>
<td>0.25 / 0.019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 POD</td>
<td>0.29 / 0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In Studies II and IV, operation side oedema and trismus scores were mainly similar after surgery until POD2. In Trial I of Study IV, however, oedema was significantly greater in the peripheral morphine group than in the IM morphine group at POD1, while other related symptoms such as trismus were similar between the groups. The clinical significance of these findings is therefore debatable.
6 Discussion

6.1 Postoperative pain management after tonsillectomy

Our study population was homogenous, consisting of healthy young adult patients only. Therefore our studies focused on adult TE management. Pain after TE has been shown to be more intense in adults compared to children (Kamarauskas et al. 2013). In addition, measuring pain accurately in children is often difficult because small children may not be able to verbalize, and a faces pain scale may be confusing for children.

Operation technique has the potential role of determining the quality, intensity and duration of postoperative pain. Therefore, Study I focused on the HS technique effect and addressing the question of whether HS TE could be associated with less pain than the blunt/cold dissection TE.

The main finding was that the use of the HS technique for adult TE results in lower NRS scores immediately after surgery compared to the blunt/cold dissection technique. However, this beneficial effect had disappeared in the period soon after surgery. The intensity of pain remained high in patients operated with HS, especially during the second week after surgery. These findings are not in dissonance with the impression from the 16 other studies summarized in the literature review; in essence, that HS does not seem to provide consistent benefit regarding pain scores after TE (Table 3). The clinical applicability of results is ambivalent and controversial. Study I as well as Walker and colleague’s study (Walker & Syed 2001) were among the first published studies that investigated the use of HS for TE.

Today we can draw the same conclusion as we concluded fifteen years ago (Study I), that “the problem of postoperative pain in TE probably cannot be solved with present-day operative techniques”. None of the recent TE techniques has been demonstrated to have consistent meaningful perioperative or postoperative benefits over the traditional blunt/cold dissection technique, and the optimum instrumentation technique for TE is still controversial.

A recent histological evaluation study suggested that thermal damage around the operation site mucosa was minor, and there was no difference between laser, radiofrequency, HS, and blunt/cold dissection techniques. It was speculated that patient discomfort and pain are more dependent on the anatomical location of the palatal tonsil and indirectly through ongoing irritation of the uncovered wound,
rather than on the quality of the wound injury resulting from TE techniques (Slouka et al. 2016). A meta-analysis showed that pain after new TE techniques was not different compared to the blunt/cold dissection TE technique. Some evidence was found, however, that appears to favor the vessel sealing system (Alexiou et al. 2011). No overall consensus favoring one technique over another has been reached (Alexiou et al. 2011, Sayin & Cingi 2012).

As a part of multimodal pain management in Study III, we wanted to determine whether peripheral morphine is beneficial in improving postoperative pain. To the best of our knowledge, the effect of peripheral morphine after TE was evaluated for the first time ever in Study III. The main finding here was that morphine injected in the peritonsillar tissue provides no effect on pain scores in comparison with IM morphine injection. Thus, we can confirm that the peripheral application of morphine did not offer any clinical advantage for TE pain management.

The postoperative analgesic effect of peripherally applied opioids has been investigated for different surgical procedures with conflicting clinical benefits. There are no clinically available opioid agonist analgesics which selectively activate peripheral opioid receptors. Therefore, in many clinical trials, locally administered, low doses of morphine were used more often (Nielsen et al. 2015).

A previous study found that the peripheral administration of pethidine to the peritonsillar fossa (Elhakim et al. 1997) provided considerable postoperative pain relief after TE in the first 24 hours in infants and children, while Nikandish and colleagues observed no significant pain relief in older children (Nikandish et al. 2008). The major difference between our study and these prior studies is that the previous studies combined a local anaesthetic with an opioid, while ours did not.

In Study I, the median maximal NRS pain score was six on POD1 after TE. This was in accordance with findings from the recent cohort studies that TE is associated with equal or even higher pain intensities than some major surgeries, such as open cholecystectomy or hip joint replacement (Gerbershagen et al. 2013, Guntinas-Lichius et al. 2014).

In the TE Studies (I, III), pain, consumption of APAP/NSAID and codeine remained high during the first week after TE. Over 25 percent (25% in Study I and 34% in Study III) of patients still required APAP/NSAID on a daily basis at the end of the second week after TE. This is in accordance with recent studies that followed up pain for at least two weeks. Sarny and colleagues showed that over 75% of patients had higher pain scores on POD4-POD7 (Sarny et al. 2012). It has been reported that pain continued at a high level for the first week after TE in adult patients (Kamarauskas et al. 2013) and children (Hamunen & Kontinen 2005).
Overall, these earlier studies and our Studies I and III suggest that patients undergoing TE still suffer severe pain and receive inadequate pain relief.

A return to regular diet was the initial concern after TE in connection with severity of pain. In Study III, the mean maximum amount of weight loss was 2 kg during the two-week period, which may be described as a drawback caused by deficient pain management. A delay in the returning to a regular diet has also been noted in other comparison trials of TE techniques (Oko et al. 2005, Ericsson & Hultcrantz 2007, Khan et al. 2012, Pajic-Penavic et al. 2013).

In Study I, PTH was rated between 13–26% as moderate during the first seven POD follow-ups. This is in accordance with a previous study by Sarny and colleagues, who reported an incidence of haemorrhage of 21% after TE. They observed that a high level of pain was clearly associated with an increased risk of haemorrhage (Sarny et al. 2012).

In the TE studies (I, III), a codeine combination was used as a rescue drug in patients with moderate and severe pain (if pain NRS scores at rest were over five). Codeine consumption remained high for at least the first week after TE. The proportion of patients using codeine was over 80%, 70% and 60% on the second, fifth and seventh PODs, respectively, in both TE studies. Codeine consumption decreased significantly on the seventh POD in both studies. This is consistent with previous observations of pain endured at a high level for one week after TE in adults during the reepithelization of the wound. (Kamarauskas et al. 2013, Sarny et al. 2012).

Another rising concern is the side effects of codeine after TE because codeine strongly influences the variability of cytochrome P450 activity. In Studies I and III, codeine consumption ranged between the minimum and maximum of instructed doses (0–180 mg) during the first postoperative week. These large dose differences may be partly due to a genetic variation in pain sensitivity, analgesic effects and metabolism (Ciszkowski et al. 2009, Cajanus et al. 2016). Codeine has commonly been used for severe pain in adults after TE. Use in children after TE is controversial due to genetic variation (Benyamin et al. 2008, Ciszkowski et al. 2009, Weaver 2013, Kuehn 2013, Sadhasivam & Chidambaran 2012). Codeine is a pro-drug that is metabolized through the Cytochromes 2D6 enzyme to morphine; therefore, codeine potency depends upon this enzyme function. Because of genetic polymorphism (ultra-rapid metabolizers), some individuals could convert much more codeine to morphine.

Overall, we did not register any serious drug related side effects during Studies I and III after TE even though APAP, NSAID, and codeine consumption was
remarkably high. This may be a result of the fact that the patients in the present studies were healthy young adults. The side effect profile may have been different if more vulnerable patients had been recruited. As the FDA warning implies, codeine’s CNS- and respiratory depression risks can cause more death after tonsil surgery than previously believed (Goldman et al. 2013). On the other hand, other opioids agonists may be even less safe than codeine in the TE patient population, which includes a high prevalence of children with obstructive sleep apnoea (Weaver 2013).

6.2 Postoperative pain management after third molar extraction

As a multimodal approach, a combination of APAP and KTP, and peripheral opioid effect were evaluated after third molar extraction in Studies II and IV. In contemporary surgery, one of the most common postoperative pain management approaches is the use of APAP and a NSAID to enhance pain relief and to reduce opioid requirements after third molar extraction. A diversity of combinations is currently employed in clinical practice, and well-documented studies are needed to support clinical practice (Dahl et al. 2014). This was the purpose of Study II in which an APAP and KTP combination was associated with higher SPIDR and SPIIDS at 1.5 hours and shorter onset of pain relief compared with other groups. ADEs remained the same between groups receiving APAP or KTP alone or a placebo. These findings agree with those in later studies that a combination of IBP and APAP work additively for analgesic effects with no additional ADEs (Derry et al. 2013, Moore et al. 2011, Mehlisch et al. 2010a, Mehlisch et al. 2010b, Daniels et al. 2011, Bailey et al. 2014, Alexander et al. 2014). Hence, we concluded that the combination of KTP and APAP provides enhancement for acute pain management and an alternative to a combination of NSAID and opioid formulations after third-molar extraction.

APAP analgesic potency is limited, but its use may reduce postoperative morphine consumption (Peduto et al. 1998). In Study II, the time to rescue medication was longer in the APAP group than in the placebo group. In line with our observation, a meta-analysis by Doleman and colleagues showed that APAP administration reduced pain scores at up to 2 hours. In addition, 24-hour opioid consumption and the incidence of vomiting postoperatively were reduced (Doleman et al. 2015).

In Study IV, peripheral morphine was associated with lower pain scores on swallowing if administrated into inflamed tissue, but not into non-inflamed tissue.
Our results are consistent with previous studies demonstrating that the peripheral morphine effect was more prominent when morphine was injected in inflamed tissue before third molar extraction (Kaczmarzyk & Stypulkowska 2005, Likar et al. 2001).

In clinical use, peripheral opioids can produce some analgesia if applied to inflamed tissue (Kaneko et al. 2014). Peripheral tissue inflammation induces peripheral opioid receptors’ up-regulation at peripheral sensor neurons, but this response is not sufficient for timely up-regulation after surgery (Stein & Küchler 2013). If the sensitivity of the peripheral opioid receptors depends on the degree of inflammation, this may impair the peripheral morphine effects. This may provide a relevant explanation for why we could not show any benefit in a local administration of morphine in Trial I in Study IV (no inflammation), or in Study III.

Although the present study demonstrated a peripheral morphine analgesic effect more prominent on swallowing if administered into inflamed tissue compared to the same IM dose, the clinical relevance of this effect is indeterminate after third molar extraction.

In Study IV, patients were allowed to take codeine for severe pain. Forty-five, 43, and 25 percent of patients used codeine on the operation day and on the POD1 and POD2, respectively. Thirty-one percent of the patients experienced PONV. There was a significant correlation between codeine use and PONV in the first three PODs. These findings are in line with previous studies that postoperative opioid use increases postoperative side effects (Oderda et al. 2007, Minkowitz et al. 2014). There seemed to be a negative correlation between cigarette smoking and PONV on the operation day in Study IV. Nonsmoking status has been reported to be one of the predictive factors associated with an increased risk for PONV (Koivuranta et al. 1997, Apfel et al. 2012).

Sedation scores in Trial I in Study IV (no inflammation) remained higher in those patients who received peripherally administered morphine in the early postoperative period. As a conclusion, one could assume that the peripheral application of morphine may not offer substantial clinical advantage for third molar extraction pain management.

### 6.3 Methodological considerations

Many previous studies used pain assessment at rest, but we also used a dynamic assessment (e.g. otalgia, when drinking water). Postoperative pain intensity in the
TE Studies (I, III) was compared between the bilateral operation sides and was sensitive to demonstrate the efficacy of different surgical techniques and single-shot treatments. This model eliminated the effect of individual differences (e.g. sex, age, race, anxiety, genetic factors and pain tolerance) during the pain assessments as our patients acted as their own control. This design may, however, be associated with a difficulty in assessing from which side the pain is emanating, problems with cross contamination and issues with blinding (Grainger & Saravanappa 2008). Blinding is extremely important when outcome measures involve some subjectivity, such as an assessment of pain. Assessing the impact of verbal suggestions on the placebo response is of great importance for clinical trials as patient expectations can influence trial outcomes (Carlino et al. 2011). The expectations induced by verbal suggestions may elicit a placebo response. For example, thoracic surgery patients in the postoperative phase requested less analgesic treatment than controls when they mistakenly believed that an IV infusion contained analgesic (Pollo et al. 2001). In this model, the primary outcome is pain scores. Hence, patient analgesic consumption and time to use rescue medication are not comparable.

In Study III, it was possible to analyse data from forty patients from the operation day, and these results showed that the pain scores did not differ between sides at any time during the operation day. Patient data after discharge from hospital were lost for eleven patients, as they did not return their pain diary for the final analysis. To increase the reliability of the long-term data analyzed, we excluded these 11 patients from analyses (due to missing follow-up pain diary) even though we could have included them when analyzing the operative day scores. However, even when those patients were included in the analyses, the results remain the same (data not shown). Our results regarding the 14 days’ postoperative period may be biased due to differences in participating and non-participating patients.

Local anaesthetics with epinephrine may have had an impact on peripheral morphine absorption. Therefore, the efficacy of perioperative pain intervention could be difficult to observe. This could be one of the reasons, why we failed to observe an analgesic effect for the peripheral opioid during the first two hours after surgery in Trial II of Study IV.

In all four studies, the postoperative care observer and the patients did not know the treatment sides or medication. In Study I, a double blind randomization process needed to be more precise as the surgeons obviously knew the operation side. This is a weakness of studies comparing operative techniques. A surgeon who was not involved in the operation, however, performed the postoperative clinical examination and follow-up.
In Study II, the study coordinator instructed the patients after surgery as to how to self-administer the study drugs. The active drug and placebo were given in sealed envelopes and included written advice. We believe that the randomization procedure was successful in all Studies (I–IV) and thereby reduced the risk of a serious imbalance in known and unknown factors influencing the outcome. It is possible, however, that the differences in the number of subjects (because Trials I and II were randomized together) may have affected the results of the trials in Study IV. In Study IV, the patients’ preoperative fear of the blockade/operation was at the same level between the groups. It has been shown that a high preoperative pain expectation, pain catastrophizing and long-term fear are risk factors for postoperative pain management and can influence pain sensation and level after surgery (Sommer et al. 2010). In Studies I, II, and III, fear and pain catastrophizing were not assessed before the operation. The proportion of female participants was high in Studies I–IV, and the patient population was mostly young adults. Gerbershagen and colleagues demonstrated that younger age, preoperative chronic pain intensity, and female sex are associated with higher postoperative pain intensities and that these associations are consistent over a large number of different types of surgeries (Gerbershagen et al. 2014). In Studies I and III, the gender imbalance could not have caused bias as the patients acted as their own control. The applicability of the results in the male population might be limited however.

6.4 Clinical implications

Opioid-sparing drugs and locally acting drugs are important components of multimodal analgesia, and they enable a reduction in both systemic opioid consumption as well as ORADEs. A multimodal analgesia approach has the potential to enhance analgesia while simplifying dosing, increasing compliance and limiting safety risks. The safety and efficacy of pain treatment could increase by using a combination of pharmacologically different analgesics. NSAID and APAP are currently considered to be an integral part of postoperative pain management. Bedwell and colleagues found that IBP with APAP combination was safe and effective compared to codeine with APAP combination after TE in children (Bedwell et al. 2014).

We have convincing evidence that combining two analgesics can provide additional levels of analgesia in third molar extraction with acute pain and that the drug-specific effects are essentially additive (Seymour et al. 1996, Breivik et al. 1999, Merry et al. 2010, Ong et al. 2010, Derry et al. 2011, Moore & Hersh 2013,
Atkinson et al. 2015). The analgesic efficacy of the APAP/NSAID combination has been demonstrated in different population and surgical procedures, including both soft tissue and orthopedic (Hiller et al. 2006), elective TE (Mather & Peutrell 1995, Hiller et al. 2004) and gynecological (Montgomery et al. 1996, Bakhsha et al. 2016) procedures.

Postoperative pain management ought to be designed for different surgical procedures and for each patient’s individual needs. Pain management is still an unresolved challenge for postoperative TE care. A high level and duration of pain increased postoperative complications such as disrupted food intake, and decreased patient’s satisfaction. Third molar extraction was associated with a high level of pain in the early postoperative period. Both these small procedures affect the patient quality of life.

We observed no effect on pain severity after local infiltration of morphine at the end of TE. The effect may have been noticeable if we had used morphine-6-glucuronide (a peripherally restricted opioid) (Dahan et al. 2008). We found, however, that peripheral opioids produce pain relief if applied to inflamed tissue. Our observation is consistent with experimental studies, but clinical application requires further studies with, for example, an agent that targets peripheral receptors exclusively.
7 Conclusions

1. Tonsillectomy using the Harmonic Scalpel was found to decrease pain at rest and on swallowing on the first operation day. However, otalgia, pharyngeal pain at rest and on swallowing were increased during the second postoperative week with HS compared to the blunt/cold dissection technique.

2. The combination of paracetamol and ketoprofen acquired a rapid onset of analgesia compared to either drug given alone after the third molar extraction; meanwhile the incidence of adverse drug events remained similar.

3. The peripheral administration of morphine to the tonsillar fossa at the end of tonsillectomy did not decrease early and long-term postoperative pain severity on the injected side compared to a placebo.

4. The peripheral administration of morphine into inflamed tissue before third molar extraction resulted in significantly lower pain scores at swallowing compared to an administration into non-inflamed tissue.
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