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Pain and associated procedural anxiety in adults undergoing bone marrow aspiration and biopsy

Therapeutic efficacy and feasibility of various analgesics

Anna-Maria Kuivalainen

Academic dissertation

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For my family

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LIST OF ORIGINAL PUBLICATIONS

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

I Kuivalainen AM, Pitkäniemi J, Widenius T, Elonen E, Rosenberg PH. Anxiety and pain during bone marrow aspiration. Scandinavian Journal of Pain 2012; 3: 92-6.

II Kuivalainen AM, Niemi-Murola L, Widenius T, Elonen E, Rosenberg PH. Comparison of articaine and lidocaine for infiltration anaesthesia in patients undergoing bone marrow aspiration and biopsy. European Journal of Pain 2010; 14(2): 160-3.

III Kuivalainen AM, Ebeling F, Rosenberg PH. Warmed and buffered lidocaine for pain relief during bone marrow aspiration and biopsy. A randomized and controlled trial. Scandinavian Journal of Pain 2014; 5: 43-7.

IV Kuivalainen AM, Ebeling F, Rosenberg PH. Premedication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy – a randomized feasibility trial. European Journal of Pain 2013; 17: 1357-64.

V Kuivalainen AM, Poikonen E, Ebeling F, Rosenberg PH. Nitrous oxide analgesia for bone marrow aspiration and biopsy – a randomized, controlled and patient blinded study. *Scandinavian Journal of Pain (in press).*

Permission for reprinting these articles was obtained from their copyright holders. In addition, this thesis presents some unpublished results.

ABBREVIATIONS

BMAB	Bone marrow aspiration and/or biopsy
BMI	Body mass index
CI	Confidence interval
MPQ	McGill Pain Questionnaire
NRS	Numeral Rating Scale
OR	Odds ratio
PASW	Predictive Analytics Software
RCT	Randomized, controlled trial
RSS	Ramsay Sedation Score
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
STAI	State Trait Anxiety Inventory
VRS	Verbal Rating Scale
VAS	Visual Analogue Scale

ABSTRACT

Background: Bone marrow aspiration and/or biopsy (BMAB) is a procedure used to diagnose and follow up various haematological diseases. It is usually performed at either the sternum or the iliac crest. The procedure often causes pain despite local infiltration anaesthesia.

The objective of this study was to evaluate different means of pain relief during BMAB in adult patients. Special attention was paid to pre-procedural anxiety and its effect on pain. The commonly used local anaesthetic lidocaine was compared with articaine, an anaesthetic known for its ability to penetrate bone tissue. The effect of warming and buffering the lidocaine solution, measures expected to improve the anaesthetic action, was examined. Also investigated were sublingual fentanyl and inhaled 50% nitrous oxide (N_2O) in oxygen (O_2) as means of analgesia and sedation during BMAB.

Patients: The patient population comprised 646 adult outpatients from the Department of Haematology, Helsinki University Central Hospital, Finland. Patients were randomized to treatment groups in trials comparing one intervention with another or with placebo. The studies were all patient-blinded. One study was observational and investigated the association between pain and pre-procedural anxiety. Patient recruitment was performed between 2007 and 2014.

Main results: Pre-procedural anxiety intensified pain during BMAB in all trials. Median NRS (Numeral Rating Scale, 0 = no pain, 10 = worst pain imaginable) during infiltration was 3.0 (range 0 – 10, interquartile range (IQR) 3.0), puncture 2.0 (range 0 – 10, IQR 3.0), aspiration 4.0 (range 0 – 10, IQR 4.0), biopsy 4.0 (range 0 – 10, IQR 4.0) and immediately after BMAB 0 (range 0 – 9.0, IQR 1.0). Scores of 8 – 10 comprised 8.1%, 4.7%, 13.9%, and 12.4% of the scores for infiltration, puncture, aspiration and biopsy, respectively. Possible supplemental analgesia or sedation given on patient request in addition to local anaesthesia and study intervention did not lower pain scores during BMAB. Articaine was not found to be superior to lidocaine as a local anaesthetic. Warming and buffering the lidocaine solution diminished pain during infiltration, but did not lower the pain scores during other phases of BMAB.

Sublingual fentanyl (200 µg or 100 µg) did not provide significant pain relief relative to placebo when administered 6 – 64 minutes before BMAB. Dizziness was a frequent side-effect. Inhalation of 50% N_2O in O_2 was no more effective than inhalation of 50% O_2. No significant differences in adverse effects emerged between patients receiving N_2O/O_2 and those receiving 50% O_2. Interestingly, 86% of N_2O patients and 83% of placebo patients would choose the same analgesia method during their next BMAB.

Conclusions: Many patients undergoing BMAB suffer intense pain during the procedure. Pre-procedural anxiety was strongly associated with pain during the various phases of BMAB. The pain from local anaesthetic infiltration with articaine and lidocaine was similar. Buffering and warming the local anaesthetic solution clearly reduced the infiltration pain. However, neither these measures nor the use of sublingual fentanyl or inhalation of N_2O had an impact on the pain caused by aspiration and biopsy.

TIIVISTELMÄ

Tausta: Luuydinnäytteenotto (aspiraatio ja/tai biopsia) on toimenpide, jota tarvitaan erilaisten hematologisten sairauksien diagnostiikassa ja seurannassa. Näyte otetaan yleensä rintalastasta tai lonkkaluun harjanteesta. Toimenpide on usein kivulias paikallispuudutuksesta huolimatta.

Tutkimuksen tarkoituksena oli arvioida erilaisia kivunlievitysmenetelmiä aikuispotilailla, joilta otetaan luuydinnäyte. Erityistä huomiota kiinnitettiin toimenpidettä edeltävään ahdistuneisuuteen ja sen vaikutukseen toimenpidekipuun. Yleisesti käytettyä lidokaiinia verrattiin toiseen paikallispuudutteeseen artikaiiniin, jonka tiedetään läpäisevän hyvin luukudosta. Lidokaiiniliuoksen lämmittämisen ja puskuroinnin arvellaan parantavan puudutteen vaikutusta, joten tätä tutkittiin myös. Lisäksi tutkimuksessa arvioitiin kielen alle annostellun fentanyylitabletin sekä hengitettävän 50% typpioksiduulin (N_2O) ja hapen (O_2) seoksen kipua lievittävää ja rauhoittavaa vaikutusta luuydinnäytteenoton aikana.

Potilaat: Aineisto koostui 646 Helsingin yliopistollisen keskussairaalan hematologian osaston aikuisista avohoidossa olevista potilaista. Potilaat satunnaistettiin ryhmiin niissä tutkimuksissa, joissa yhtä interventiota verrattiin toiseen tai lumeeseen. Näissä tutkimuksissa potilaat sokkoutettiin. Lisäksi yhdessä havainnoivassa tutkimuksessa tutkittiin kivun ja toimenpidettä edeltävän ahdistuneisuuden yhteyttä. Potilasaineisto kerättiin vuosien 2007 – 2014 aikana.

Tulokset: Toimenpidettä edeltävä ahdistuneisuus pahensi kipua luuydinnäytteenoton aikana kaikissa tutkimuksissa. NRS-mediaani (Numeral Rating Scale, 0 = ei kipua, 10 = pahin mahdollinen kuviteltavissa oleva kipu) puudutuksessa oli 3,0 (vaihteluväli 0 – 10, interkvartiilin vaihtelu (IQR) 3,0), pistossa 2,0 (vaihteluväli 0 – 10, IQR 3,0), aspiraatiossa 4,0 (vaihteluväli 0 – 10, IQR 4,0), biopsiassa 4,0 (vaihteluväli 0 – 10, IQR 4,0) ja heti toimenpiteen jälkeen 0 (vaihteluväli 0 – 9,0, IQR 1,0). Korkeimpia pisteitä 8 – 10 antoivat 8,1% potilaista puuduttamisen, 4,7% piston, 13,9% aspiraation ja 12,4% biopsian aikana. Potilaan mahdollinen muu kipu- tai rauhoittava lääkitys puudutuksen ja tutkimuslääkeintervention lisäksi ei vähentänyt kipua luuydinnäytteenoton aikana. Artikaiini ei ollut lidokaiinia parempi paikallispuudutteena. Lidokaiiniliuoksen lämmittäminen ja puskurointi vähensi puudutuksen aiheuttamaa kipua, mutta ei vaikuttanut toimenpiteen muihin kivuliaisiin vaiheisiin.

Kielen alle annosteltu fentanyyli (200 µg tai 100 µg) ei merkittävästi vähentänyt toimenpidekipua lumeeseen verrattuna, kun se annosteltiin 6 – 64 minuuttia ennen toimenpidettä. Huimaus oli yleinen fentanyylin haittavaikutus. Hengitettävä 50% typpioksiduulin ja hapen seos ei ollut tehokkaampi kivunlievityksessä kuin lumekaasuna käytetty 50% happi. Typpioksiduulin ja hapen seosta saaneille potilaille ei kuitenkaan aiheutunut tilastollisesti merkitsevästi enempää haittavaikutuksia kuin lumekaasua saaneille. Peräti 86% typpioksiduulia ja 83% lumetta saaneista olisivat halunneet saman kaasun seuraavaan näytteenottoon.

Johtopäätökset: Monelle potilaalle luuydinnäytteenotto aiheuttaa kovaa kipua. Toimenpidettä edeltävä ahdistuneisuus lisäsi selvästi kipua luuydinnäytteenoton eri vaiheissa. Happaman paikallispuudutteen infiltraation aiheuttama kipu oli samanlainen artikaiinilla ja lidokaiinilla. Liuoksen puskurointi ja lämmitys selvästi vähensivät tätä infiltraatiokipua. Artikaiinilla, puskuroinnilla ja lämmityksellä, kielen alle annostellulla fentanyylillä tai hengitetyllä typpioksiduulilla ei kuitenkaan ollut vaikutusta aspiraatio- tai biopsiakipuun.

1 INTRODUCTION

Many diagnostic and therapeutic medical interventions cause pain that cannot be fully avoided. When a person encounters painful medical procedures repeatedly, the devastating effects of pain on mood and overall wellbeing are pronounced. Cancer sufferers and other chronically ill patients undergo several painful procedures – including bone marrow samplings – during the course of their illness. Performing the procedures may become more difficult when patients suffer from pronounced anxiety, fear and nervousness. Is it acceptable that patients with a severe illness suffer significant pain during diagnostic procedures? Obviously, the answer is no, as adequate pain relief has officially been declared to be a human right (Brennan et al., 2007; Cousins and Lynch, 2011).

Bone marrow aspiration and/or biopsy (BMAB) is performed frequently on the same patients since it is used in the diagnostics and follow-up of various haematological diseases. It involves puncturing the periosteum and the layer of compact bone with a puncture needle and aspiration of the bone marrow liquid with a syringe. Often a biopsy is needed as well. (Riley et al., 2004). Patients receive local anaesthetic infiltration before the puncture, which in adults may be the sole mode of analgesia. Despite local infiltration anaesthesia, puncture, aspiration and biopsy often cause significant pain (Vanhelleputte et al., 2003; Lidén et al., 2009). Furthermore, the infiltration of the acidic local anaesthetic solution (pH 3 – 4) may cause pain and discomfort. In some studies, premedication with oral opioids (Vanhelleputte et al., 2003) or benzodiazepines (Park et al., 2008) has proven useful. Despite these measures, control of pain originating from the bone and bone marrow during BMAB remains a major problem, at least in adults (Hjortholm et al., 2013). Children receive deep monitored sedation or general anaesthesia to control BMAB-related pain.

Anxiety is known to worsen pain during various medical procedures (Perrot et al., 2011; Weisensee et al., 2012) and after major surgery (Ozalp et al., 2003). It has been shown to also intensify pain during BMAB (Lidén et al., 2009). Thus, specifically targeting anxiety may be beneficial in the control of pain during BMAB.

Lidocaine is probably the most often used local anaesthetic during BMAB. The adrenaline-containing solution is very acidic; its pH can be as low as 3 (Tetzlaff, 2000). This often causes tissue irritation and pain during infiltration. Buffering the local anaesthetic solution with sodium bicarbonate has been noted to decrease pain during infiltration (Xia et al., 2002; Ruegg et al., 2009).The rise in pH reduces the dissociation of the lidocaine molecule, which enhances its capability to enter nerve cells and act rapidly on sodium channels (Coventry and Todd, 1989; Quinlan et al., 1992). This may lead to better anaesthesia of the infiltrated tissue area compared with acidic solutions. In addition to buffering, warming the local anaesthetic solution has been shown to reduce pain during infiltration (Hogan et al., 2011).

The effect of local anaesthetics is limited, however. The distribution of the solution in the tissue may sometimes be inadequate and the solution does not always reach the deeper layers of bone tissue. Articaine, an amide-linked local anaesthetic popular in dentistry (Evans et al., 2008), is known to diffuse in bone tissue more effectively than lidocaine (Vree and Gielen, 2005). It may be useful in BMABs as well, as the procedure primarily involves the bone tissue of the sternum or iliac crest.

To manage pain originating from puncture, aspiration and biopsy in adults, supplemental analgesia is often needed. The medication administered should be quickly effective but short-acting, as BMABs are predominantly performed in outpatient clinics that do not have the

resources of long-term monitoring of patients. Furthermore, many patients return to work or other duties soon after the procedure, and thus, the side-effects of the analgesics should be tolerable and temporary.

Fentanyl is a potent opioid that has long been used for rapid pain relief. Due to its considerable first-pass metabolism in the liver, the drug has been administered primarily parenterally in order to achieve suitable bioavailability. It has been administered via transmucosal (oral, nasal), transdermal and intravenous routes (Grape et al., 2010). Recently, a new sublingual formulation of the drug was developed. Sublingual fentanyl is primarily aimed at relieving breakthrough pain in cancer patients. Due to its high degree of liposolubility, fentanyl traverses the oral mucosa rapidly and thus acts fast (Fine and Streisand, 1998). However, the number of studies examining sublingual fentanyl in acute pain settings other than cancer is limited. Sublingual fentanyl might be an effective analgesic given before BMAB, and the pharmacokinetic profile of the drug formulation warrants further investigations.

Nitrous oxide (N_2O) has been used in clinical practice for over 150 years. It is widely used as a safe analgesic during labour pain (Rosen, 2002), and is frequently used during general anaesthesia as a hypnotic and analgesia adjuvant. Due to its low solubility in blood, a steady state between inhaled and alveolar N_2O partial pressures is reached quickly, and its actions are evident within a couple of minutes (Becker and Rosenberg, 2008). Once the patient ceases to inhale, the gas is rapidly eliminated and the possible mild side-effects (dizziness, headache) resolve quickly. Thus, in theory and based on a few small-scale studies (Steedman et al., 2006; Gudgin et al., 2008; Johnson et al., 2008), it might be a suitable analgesic during BMAB.

In these trials, the aim was to control procedural pain during outpatient BMAB with different pharmacological means without having to utilise the intravenous route. Special attention was paid to anxiety prior to the procedure and its influence on pain during BMAB. The occurrence of adverse effects of the methods used was investigated as a secondary outcome.

2 REVIEW OF THE LITERATURE

2.1 Bone marrow aspiration and biopsy

2.1.1 Structure and histology of bone and bone marrow

The periosteum is the outermost layer of bone tissue. It is relatively thin and composed of fibrous connective tissue. It also comprises a network of sensory nerve fibres (Mach et al., 2002). A layer of compact mineralized bone is located beneath it. Compact bone surrounds the marrow cavity, which contains sponge-like bone tissue. Bone marrow is located within the spaces of this spongy bone tissue. Bone marrow comprises haematopoietic cells, fat cells, protein, water and blood vessels. (Ross et al., 2003) Bone marrow is richly innervated by sensory and autonomic nerves. The number of sensory fibres is larger in bone marrow than in the other bone compartments (Mach et al., 2002).

The sensory nerve fibres responsible for pain perception in the periosteum, mineralized bone and bone marrow are primarily of a specific peptide-poor subset of nociceptive C-fibres, which form mesh-like networks within bone tissue together with a subset of myelinated A-fibres (Freeman et al., 2008; Jimenez-Andrade et al., 2010). The distribution of these subsets of nerve fibres is different from that of skin tissue, and they ascend to a different region in the spinal cord than nerve fibres from skin (Jimenez-Andrade et al., 2010), at least in a rat model. However, the bone marrow also receives autonomic innervation, and especially the adrenergic subtype of autonomic nerve fibres participates in the regulation of haematopoietic function (Lucas et al., 2013).

The marrow of most bones in an adult comprises primarily fat cells. However, some bones, such as the sternum, vertebrae, iliac crest, ribs and proximal ends of the femur and humerus, retain their marrow's haematopoietic stem cell activity also during adulthood (Ross et al., 2003; Wang and Berliner, 2007). The marrow of these bones produces the red blood cells, many subtypes of the white blood cells, and platelets that enter the circulation after maturation. However, during some haematological disorders the normal function of the bone marrow is distorted and abnormal cells may emerge. Some bone regions containing haematopoietically active marrow are suitable for bone marrow aspirations and biopsies for examination in these situations, providing the anatomy is suitable for the sampling procedure.

2.1.2 History of bone marrow aspiration and biopsy

Bone marrow sampling for diagnostic purposes has been used for the last 100 years. During this period several kinds of needles and instruments have been introduced into clinical practice (Parapia, 2007). The basic structure and function of the puncture needles for both bone marrow aspirations and biopsies today resemble markedly those in the 1950s. The newest innovation is a powered needle drill (Voigt and Mosier, 2013). The powered technique seems, however, to have gained more attention for use in emergency intraosseal cannulations than for diagnostic punctures. The bone marrow examination is a central and usually indispensable tool in both haematological diagnostics and follow-up, and the benefits of the examination include nowadays also the possibility to use modern applications of molecular biology and immunology.

2.1.3 Indications for bone marrow aspiration and biopsy

Many haematological disorders cannot be specifically diagnosed or excluded in samples of peripheral blood, and thus, examination of bone marrow is needed (Islam, 1997). BMAB is needed in diagnostics of malignant diseases, such as acute or chronic leukaemias, multiple myeloma, lymphomas or metastatic tumors of non-haematological origin (e.g. carcinomas). Other diseases diagnosed or specified with BMAB are myelodysplastic syndromes, myeloproliferative states, some anaemias, cytopenias and amyloidosis. Bone marrow examination may be needed for the diagnosis of some infectious diseases, e.g. tuberculosis. In addition, BMAB is frequently needed during follow-up of these diseases after established diagnosis and treatment such as chemotherapy, modern targeted therapy or stem cell transplantation. (Riley et al., 2004) The procedure is performed on healthy bone marrow donors as well.

2.1.4 Performing bone marrow aspiration and biopsy

Before performing BMAB, the patient should receive information on the indications and technical aspects of the procedure and also on possible adverse effects. The laboratory values, especially haemoglobin value and thrombocyte count, should be checked and attention paid to coagulation parameters, at least in patients on warfarin medication.

The puncture area is inspected and carefully palpated to check the anatomy and possible deviations from the normal in the region and to choose the optimal site. After disinfection of the skin, a local anaesthetic is infiltrated into the skin, subcutaneous tissue and to the proximity of periosteum. Aspiration is performed with single-use, disposable or reusable 16 – 14G needles from either the sternum or the posterior iliac crest. The needle is inserted through the skin, subcutis and periosteum with slow rotating movements through the cortical dense bone. When the resistance gets lighter, the needle tip has reached the marrow cavity. A sample of the liquid bone marrow is then aspirated into a syringe. If a biopsy is needed, it is obtained from the iliac crest. The bone marrow biopsy is performed with a thicker needle, and pressure and rotatory movement are required to get the sample from the marrow (Riley et al., 2004). Once the samples have been taken, a bandage is applied on the puncture wound. The needles used to obtain the samples are presented in *Figure 1*. *Figures 2* and *3* present the aspiration and biopsy, respectively.

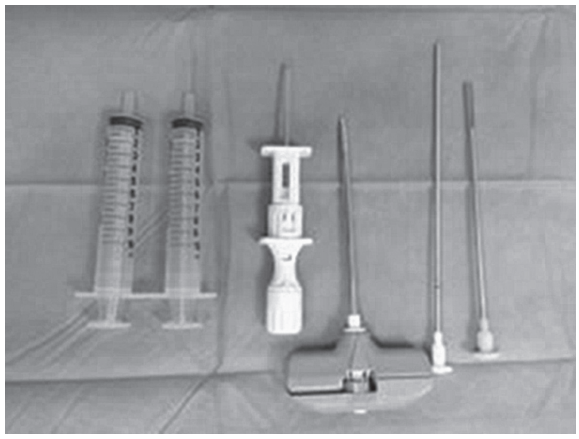

Figure 1. Aspiration and biopsy needles.

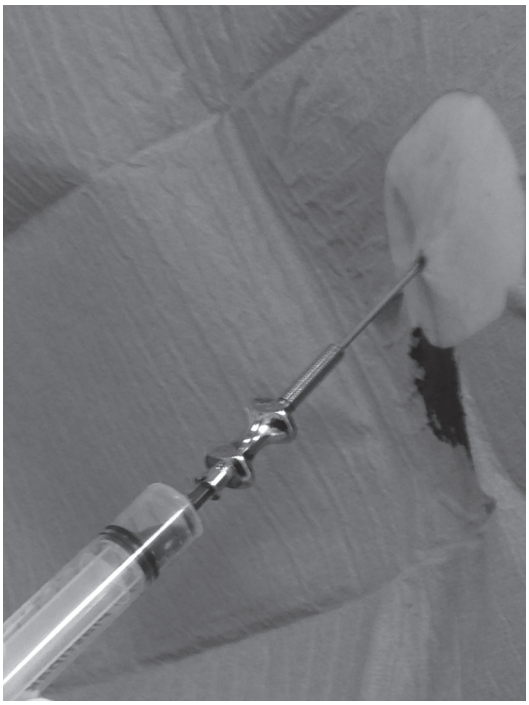

Figure 2. Bone marrow aspiration.

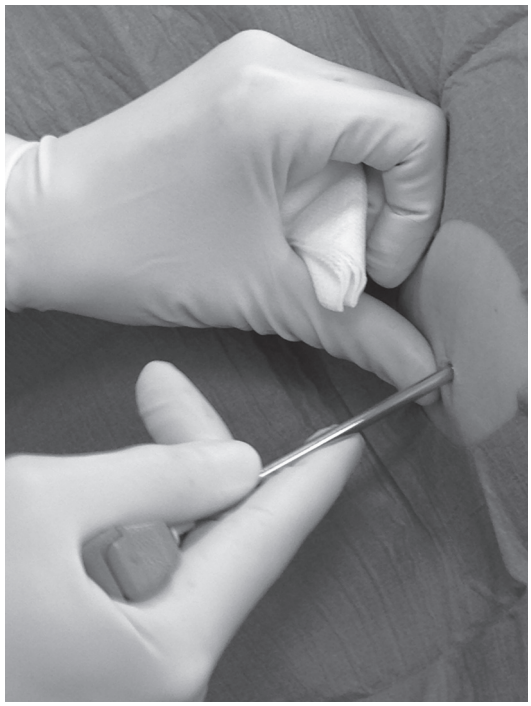

Figure 3. Bone marrow biopsy.

2.1.5 Complications

BMABs are relatively safe procedures with the risk for complications varying between 0.07% and 0.12%. Haemorrhage is the most common complication. (Bain, 2004; 2006; Kuivalainen et al., 2013) The haemorrhage is usually minor (Valebjørg et al., 2014) and may cause small bruises or haematomas. However, there are reports of major haemorrhages to the retroperitoneal space after puncture of the iliac crest (Eikelboom, 2005; Tsai et al., 2008), and haemorrhage-associated nerve damage (Roth and Newman, 2002). Infections of the puncture site may also occur. The sternal puncture may, especially if also the posterior cortex is penetrated, be complicated by cardiac tamponade (Bhootra, 2004) or pneumothorax (Bain, 2003). In addition to acute, procedural pain, BMAB has been reported to cause long-term pain (Bain, 2004). If sedation is used, it seems that it is relatively safe in a selected patient population (Burkle et al., 2004).

Complications can be avoided to a large extent with careful planning of the procedure and cautious palpation and disinfection of the puncture area. However, complications cannot be totally avoided, and thus, patients should be carefully monitored after BMAB, e.g. with questions regarding their condition, possible pain, dizziness or other symptoms. If the patient feels unwell, closer monitoring, such as blood pressure and peripheral oxygen saturation measurements, may be indicated.

2.2 Acute pain

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Anon, 1979). It can be regarded as a useful signal of tissue damage and harm, thus encouraging the avoidance of noxious factors. However, pain causes suffering as well, and when it cannot be avoided, the emotional stress may be devastating.

2.2.1 Pathophysiology of acute pain

Trauma, surgery or other medical procedures as well as numerous diseases cause tissue injury with various mechanical, chemical or thermal stimuli. Direct tissue trauma leads to activation of nociceptive nerve fibres, but it also leads to the release of chemical transmitters, such as cytokines and other inflammatory mediators, neurotransmitters and growth factors, which further activate nociceptive nerves (Carr and Goudas, 1999). These inflammatory mediators are known to increase the firing frequency of the nociceptors, which leads to intensified pain sensation (Momin and McNaughton, 2009). The nociceptive stimuli are transferred in afferent nerve fibres (C and A fibres) to the brain via the spinal cord (Carr and Goudas, 1999). Various factors may affect the transmission; anti- and pronociceptive factors, for instance, may manipulate the stimuli in the spinal cord via the descending pathways (Apkarian et al., 2005). Many psychological factors, such as anxiety, fear, attention and expectations, belong to factors modifying pain sensation (Rainville, 2002). These descending pathways originate from various cortical areas and descend through several routes via, for example the amygdala and hypothalamus to the dorsal horn of spinal cord, where they interact with the nociceptive stimuli originating from the tissue (Apkarian et al., 2005). When the modified impulses finally reach the brain, the stimuli distribute to several sensory cortical areas; the sensation of pain has been generated. Acute pain does not usually last long relative to chronic pain, although the division of the two is not always straightforward; they can be regarded as a continuum rather than two separate states (Carr and Goudas, 1999; Cousins et al., 2000).

2.2.2 Rating scales for assessment of acute pain

Objective tools for assessing pain are non-existent as the sensation of pain is personal, subjective and multidimensional. However, in pain research and various clinical settings, the intensity and sometimes the quality of pain need to be somehow assessed. Various tools are available to measure acute pain intensity and its quality (*Table 1*). The most commonly used tools for measuring intensity are the Numeral Rating Scale (NRS), the Visual Analogue Scale (VAS) and the Verbal Rating Scale (VRS). These have been proven to be valid and reliable (Williamson and Hoggart, 2005). The Red Wedge Scale (RWS), developed from the VAS, may also be used especially after major surgery (Tigerstedt and Tammisto, 1988; Pesonen et al., 2008; 2009). The NRS and VAS scores can be further quantified as mild, moderate and severe pain; the cut-off points for these have varied in different studies. A reduction of 30% – 50% in pain scores has implied a clinically significant change in different studies (Williamson and Hoggart, 2005). These scales have been shown to be somewhat more sensitive than VRS (Breivik et al., 2000). The intensity of pain in children can be measured with the Faces Pain Scale – Revised (Hicks et al., 2001) or the Maunuksela scale (Maunuksela et al., 1987), as the NRS, VAS and VRS may be difficult to use in younger children due to the tests' demands on cognitive capacity. However, in the demented elderly, VRS seems to be the most suitable pain rating scale (Pesonen et al., 2009).

A valuable tool to assess the quality of pain is the McGill Pain Questionnaire (MPQ) (Melzack, 1975; Campbell and Vowles, 2008) and it's short form (SF-MPQ). It is predominantly used with chronic pain sufferers, but is also useful in assessing the quality of acute pain. The questionnaire has been shown to be valid and it is widely used. It has been translated and validated into several languages, including Finnish (Ketovuori and Pöntinen, 1981).

Table 1. Tools to assess pain intensity and its quality.

Scale	Scoring	Use in clinical practice	Features
Numeral Rating Scale (NRS)	0 = no pain 10 = worst pain imaginable. Also 21- and 101-point scales have been used.	Patient indicates the number describing pain intensity.	Illustrates pain intensity. Can be used verbally or graphically.
Visual Analogue Scale (VAS)	100-mm line, where 0 mm indicates no pain and 100 mm the worst pain imaginable.	Patient indicates the point of pain intensity on the line.	Illustrates pain intensity. Can be used horizontally or vertically.
Red Wedge Scale (RWS)	50-cm wedge, where the left edge indicates no pain and the right edge the worst pain imaginable.	Patient indicates the point of pain intensity with a moving vertical pointer on a red-coloured horizontal wedge. The score is the point on the VAS line on the reverse side of the line.	Illustrates pain intensity. Based on VAS. May be more illustrative or simpler to use after major surgery than the traditional VAS.
Verbal Rating Scale (VRS)	Adjectives, such as no pain, mild pain, moderate pain, severe pain. These may be further assigned numbers.	Patient expresses the suitable adjective verbally or in writing.	Illustrates pain intensity. Ordinal variable in which the intervals are not linear.
Faces Pain Scale – Revised (FPS-R)	Comprises 6 images of faces expressing pain of worsening intensity. First face = no pain, last face = excruciating pain.	The child points to the face best representing the pain intensity.	Illustrates pain intensity in children over 4 years. Intervals are close to linear. Can be scaled to numerals 0 – 5 or 0 – 10.
Maunuksela Pain Scale	0 = no pain, 9 = worst possible pain. A scale of 0 – 10 has also been used.	An adult trained observer assesses the intensity of pain. The assessment is based on various findings such as facial expressions and movement of limbs.	Observer-based scale that illustrates pain intensity in children based on assessment of behavioural parameters.
McGill Pain Questionnaire (MPQ)	Comprises 78 sensory, affective and evaluative words, categorized to 20 groups. Words are further scored within groups to obtain the pain rating index (PRI). Includes VRS 0 – 5 as well.	Patient fills out the MPQ with a pen, although verbal administration is possible as well.	Illustrates the sensory and affective quality of pain, and pain intensity is separately illustrated with a 6-point VRS.

2.2.3 Pain associated with medical procedures

Patients undergo various medical procedures, ranging from major surgery to minor outpatient interventions. In 2012, there were 645 038 treatments in Finnish hospitals that included a medical procedure in somatic specialist medical care. Of these treatments, 427 766 were surgical and 109 962 were non-surgical and non-radiological (National Institute for Health and Welfare; http://urn.fi/URN:NBN:fi-fe201312207698). In Finland, approximately 10 000 BMABs are performed annually (Kuivalainen et al., 2013). Many of these procedures are painful, requiring various

means of sedation, pain relief and anaesthesia. The impact of procedural pain on health care costs and well-being is significant.

Acute postoperative pain

Despite the use of multimodal pain relief and various follow-up protocols conducted with acute pain service teams, moderate to severe acute pain after surgery is common. The prevalence of severe pain is estimated to be roughly 10% at rest, while moderate pain is slightly more common, ranging from 30% to 36% (Cousins et al., 2000; Dolin et al., 2002). There is some variation in these proportions of pain intensity, depending on the type and location of the procedure. In another study (Sommer et al., 2008) investigating the prevalence of postoperative pain, 26% of patients reported moderate pain and 15% reported severe pain one hour after the operation at rest. In this study, higher pain ratings were associated with abdominal and spinal/back surgery or surgery of the upper/lower extremities. Furthermore, younger age, female gender, general anaesthesia and major surgery intensified the pain. In a study performed on patients undergoing ambulatory surgery (Gramke et al., 2007), the proportion of patients reporting moderate to severe pain on the day of the operation was 26%, most pain being related to surgery involving the nose, pharynx, abdomen and breasts and to orthopedic operations. These patients are usually discharged on the day of operation and their pain should be treatable at home.

Acute procedural pain

Pain during less invasive medical procedures is also common. During colonoscopy non-sedated patients reported severe pain in 20% and moderate pain in 34% of cases (Hoffman et al., 1998). However, in another study (Takahashi et al., 2005), also performed with non-sedated patients, most patients (71.2%) did not report pain at all during colonoscopy. Interestingly, in this study only 0.7% of participants were willing to undergo the next colonoscopy without sedation, indicating that the procedure causes considerable discomfort. Pain was related to young age, low BMI, first-timers and previous hysterectomy, amongst others.

In a study investigating the prevalence of pain related to liver biopsy, 60% of patients reported moderate or severe pain during the first hour after the biopsy (Eisenberg et al., 2003). In a smaller pilot study (Castéra et al., 1999), 20% of participants reported a VAS score of over 40 mm (on a scale from 0 to 100 mm) during the biopsy.

Pain during dental care is also frequent. In a meta-analysis investigating pain before, during and after root canal treatment, pain prevalence during treatment was 11% – 100% (Pak and White, 2011). However, the proportion of patients suffering severe pain during treatment was low. In another study, pain during root canal treatment was less intense than during other frequently performed dental procedures (Rousseau et al., 2002). In a questionnaire-based study, 42.5% of those having had dental treatment over a 5-year follow-up reported pain during treatment; 19.1% reported that pain was moderate or severe (Maggirias and Locker, 2002).

In summary, many types of procedures and treatments cause pain of at least moderate intensity. While pain may not be fully eliminated, attention should be paid on the methods making the procedural pain tolerable. Furthermore, if the patients need to undergo several painful procedures due to e.g. cancer, the importance of adequate pain relief is highlighted. In cancer patients, pain originating from various procedures is a significant factor in the overall burden of pain (Ripamonti et al., 2014), and thus, should be targeted adequately.

2.3 Anxiety and pain

2.3.1 Mechanisms of the effect of anxiety on pain

Humans make observations during the course of their lives in various situations, encounters and mental states. Through the effect of learning, these observations form memories and eventually affect the expectations that a person has of a specific situation. Over time, these previous experiences and expectations have an impact on the person's pain behaviour (Loeser and Melzack, 1999). The specific mechanism for this has been shown in a study using fMRI imaging (Ploghaus et al., 2001); anxiety and negative expectation of pain modify activation in the hippocampus, specifically the entorhinal cortex. The hippocampal activity further affects the adjacent areas responsible for affective states and intensity coding. However, anxiety affects other brain areas in the descending pathways as well (Apkarian et al., 2005), eventually leading to intensified pain perception. Since variation exists in people's individual histories and expectations and their impact on neural circuitries, the effect of anxiety on pain is also individualistic: some patients may not be fearful at all, e.g. at a dental appointment, whereas others may be terrified.

2.3.2 Measuring acute anxiety

There are numerous tests available that measure the intensity of anxiety in various clinical settings. These are useful in clinical research as well. However, these tests vary with regard to the specific type of anxiety being evaluated. Some tests measure acute, state anxiety, whereas others are validated to measure more chronic anxiety, anxiety disorders or a trait of anxiety. When acute, procedure-related anxiety is evaluated, the tests used should be specifically validated to measure the desired variable.

The intensity of acute, procedural anxiety may be evaluated with various verbal rating scales (e.g. none, mild, moderate, intense) or numeral rating scales (e.g. 0 – 10, where 0 = no anxiety, 10 = worst anxiety imaginable). These scales have been proven to be valid and suitable in busy clinical settings (Benotsch et al., 2000). There are also tests validated to measure dental anxiety specifically (Aartman, 1998; Humphris et al., 2000). The fear of pain questionnaire has been developed to measure general fear related to pain (McNeil and Rainwater, 1998).

The Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger and Vagg, 1984; Spielberger, 2010) is a widely used validated test that has two distinct parts. The state part (STAI-S) measures anxiety as a mental state, i.e. acute anxiety related to acute stressful events. It has been used in various clinical studies investigating the relationship between anxiety and acute pain. The trait part (STAI-T) measures more chronic anxiety, i.e. trait anxiety. Both parts consist of 20 items each. The items in STAI-S have four alternative answers (not at all, somewhat, moderately so, very much so), which are further scored with a scoring key. The range of scores is 20 – 80 for STAI-S, with higher scores indicating a higher intensity of anxiety.

2.3.3 Anxiety and pain during medical procedures

The patient's specific clinical situation has an effect on anxiety: patients about to undergo major surgery are anxious about, for instance, the outcome, postoperative ability to function and how the family will cope, whereas patients having a minor medical intervention, such as a dental procedure, are mainly anxious about aspects of the procedure itself (Oosterink et al., 2008; Powell and Johnston, 2008). However, although the procedure may not be harmful or carry any

high risks of serious adverse effects (e.g. visit to the dentist), the pre-procedural anxiety may nevertheless vary due to differences in personality traits and exposure to conditioning stimuli. Anxiety remains one of the major factors predicting procedural pain.

Anxiety and postoperative pain

Preoperative anxiety has been proposed to have a complex association with postoperative pain through various pathways (Kain et al., 2000). Highly anxious patients suffer more intense postoperative pain and consume more analgesics during the postoperative phase (Ip et al., 2009) than less anxious patients. This has been noted also in the paediatric population (Kain et al., 2006). Since inadequately treated pain during the postoperative period has many adverse effects (Joshi and Ogunnaike, 2005), it is important to treat also the risk factor for pain, pre-procedural anxiety. Risk factors for preoperative anxiety include history of malignancy and smoking, depression and other negative psychological traits, pain, female gender, higher level of education, medium-level surgery and poor physical health (Caumo et al., 2001).

Anxiety and pain during diagnostic procedures

Anxiety is associated with pain during colonoscopy (Ylinen et al., 2009). The association between anxiety and pain could also be seen in a study investigating non-pharmacological anaesthesia adjuncts (Schupp et al., 2005) during radiological procedures. Interestingly, in this study, the state anxiety levels decreased during the procedures, indicating that procedure-related anxiety is at its highest level prior to and at the beginning of a painful procedure. Anxiety is also known to intensify pain during outpatient cystoscopy (Goldfischer et al., 1997) and prostate biopsy (Tekdogan et al., 2008).

Anxiety and dental procedural pain

The connection between anxiety and pain during dental procedures is well established (Maggirias and Locker, 2002; Klages et al., 2004; Weisensee et al., 2012). In addition to anxiety, catastrophizing intensifies dental procedural pain (Sullivan and Neish, 1998). Patient features associated with dental anxiety include depression, generalized anxiety and simple phobias, substance dependence, previous invasive dental treatment (Locker et al., 2001) and previous exposure to traumatic events (de Jongh et al., 2006).

Anxiety and pain during dental procedures can be alleviated or eliminated with, for example, psychological methods (Skaret and Soevdsnes, 2005), oral premedication (Ehrich et al., 1997), inhaled nitrous oxide (Hallonsten et al., 1983), intravenous sedation (Oei-Lim et al., 1998) or even general anaesthesia (Dougherty, 2009).

Anxiety and pain during BMAB

Bone marrow aspirations and biopsies cause pain and anxiety. During the observational phase of a study investigating patients undergoing BMAB, the proportion of patients suffering moderate pain during aspiration was 19.7% and severe pain 15.9% (Vanhelleputte et al., 2003). In another study (Lidén et al., 2009), 56% of patients reported procedural pain of moderate intensity, 32% pain of severe intensity and 3% the worst possible pain. In that study as well as in another observational study (Brunetti et al., 2011), anxiety was strongly associated with procedural pain. In a questionnaire-based study, pain was scored as "bearable" by 59.6% and "unbearable"

by 3.7% of patients (Degen et al., 2010). In that study, pain suffered during previous BMABs predicted pain during subsequent BMABs, and inadequate information regarding BMAB was also seen as a factor intensifying pain. The study did not measure anxiety. Furthermore, many patients had received premedication, although the authors concluded that premedication did not affect pain scores. Other factors reported to be associated with pain during BMAB are female gender, age, pre-existing pain prior to BMAB, patient's socio-economic status, experience of the performing haematologist and procedural factors (such as length of procedure) (Vanhelleputte et al., 2003; Lidén et al., 2009; Talamo et al., 2010). Generally speaking, patients consider pain caused by BMAB to be so intense that they often desire sedation and analgesia in addition to local anaesthetic infiltration (Kuball et al., 2004; McGrath et al., 2013). Furthermore, medical professionals may overlook or underestimate pain and anxiety during BMAB (Kuball et al., 2004; Lidén et al., 2012). There are also reports of inconsistent registration of the level of pain suffered and considerable variation in premedication protocols (Sollazzo et al., 2014).

2.4 Treating pre-procedural anxiety and pain during bone marrow aspiration and biopsy

Studies of varying methodological quality have examined several means of pain relief during BMAB in adults. Trials that were randomized, controlled and investigated pharmacological methods are summarized in *Table 2*. Studies not controlled and/or randomized are reviewed or mentioned in the text only.

2.4.1 Local anaesthetics

Local anaesthetics are agents that cause numbness and analgesia through various mechanisms: after traversing the cell membrane and inhibiting the voltage-gated sodium channel, they antagonize the influx of sodium ions into nerve cells, inhibiting depolarization and propagation of the impulse to the central nervous system. This effect is intensified with blockade of potassium and calcium channels and some G-protein receptors. (McLure and Rubin, 2005) However, many factors, such as pH and the neuronal sheath, influence the kinetics of molecules' influx into nerve cells (Leeson and Strichartz, 2013). Local anaesthetics have several administration routes: infiltration into the skin and subcutaneous tissue (local anaesthesia) or to the proximity of nerves (peripheral nerve blocks, plexus blocks), application to the surgical area, intrathecal or epidural space administration (neuraxial anaesthesia/analgesia) or intravenous administration to a limited region or as continuous systemic infusion. In conjunction with local anaesthesia, adrenaline may be added to the local anaesthetic solution as a vasoconstrictor, which prolongs the effect (Liu et al., 1995) and reduces haemorrhage in the procedure area (Wilmink et al., 1998). Local anaesthetics can be divided into amides, esters, ketones or ethers according to their chemical structure, amides being the most popular in clinical anaesthesiology (McLure and Rubin, 2005).

Table 2. Summary of RCTs examining various pain relief methods during BMAB in adults.

Reference	Patients, *n*	Local anaesthesia	Site of puncture	Intervention	Main results
Ruegg et al. 2009	48	Lidocaine 10 ml (concentration not presented)	Posterior iliac crest	Buffered lidocaine compared with plain lidocaine	Buffering reduces pain during BMAB (P = 0.002)
Vanhelleputte et al. 2003	100	Lidocaine 2% (volume not presented)	Posterior iliac crest and sternum	Peroral tramadol 50 mg compared with placebo	Tramadol reduces pain during aspiration (P = 0.003)
Wolanskyj et al. 2000	25	Lidocaine 1% (volume not presented)	Posterior iliac crest	Peroral lorazepam 2 mg and hydromorphone 2 mg compared with placebo	No difference in pain scores between groups
Chakupurakal et al. 2008	46	Details not presented	Not presented	Intravenous midazolam 2 – 10 mg compared with Entonox (50% mixture of N_2O and O_2), no blinding	Post-procedural recollection of pain was of lower intensity in the midazolam arm (P = 0.01) compared with Entonox.
Milligan et al. 1987	46	Lidocaine 2%, 5 ml	Posterior iliac crest	Peroral lorazepam 4 mg compared with placebo	No differences between groups in pain scores recollected immediately after BMAB. After 24 hours, recollection of pain was 60% lower (P < 0.01) in the lorazepam group.
Park et al. 2008	138	Lidocaine 1%, volume max. 20 ml	Posterior iliac crest	Intravenous lorazepam 1 mg compared with placebo	No difference in pain scores between groups. Lorazepam enhanced willingness to future BMABs (P = 0.044).
Johnson et al. 2008	48	Lidocaine 2% (volume not presented)	Not presented	Inhaled 50% mixture of N_2O/O_2 compared with placebo	N_2O inhalation was an effective analgesic in men, but not in women. Previous painful experiences predicted pain during BMAB (P = 0.015).
Spruyt et al. 2013	97	Details not presented	Not presented	Inhaled methoxyflurane compared with placebo	Patients receiving methoxyflurane had lower pain scores in overall pain (P = 0.011) and aspiration pain (P < 0.001). Minor side-effects were more common in the methoxyflurane group (P 0.028).

Lidocaine

Lidocaine belongs to the amide group of local anaesthetics. It is widely used in local anaesthesia, and the majority of the published studies investigating pain and anxiety during BMAB in adults have used it as a local anaesthetic (*Table 2*). It is fast-acting, and due to a moderate protein binding ability, it is also relatively short-acting (McLure and Rubin, 2005). At room temperature, its pKa is 7.7 – 7.9, which means that in acidic solution the molecule is predominantly in its ionized form. The pH of the commercial lidocaine solutions is usually 5.0 – 6.0, but if adrenaline is added, pH is lowered. The elimination half-life of lidocaine is 45 – 60 minutes. (Tetzlaff, 2000) Lidocaine is metabolized in the liver and further eliminated via the kidneys (McLure and Rubin, 2005). The molecular structure of lidocaine is presented in *Figure 4*.

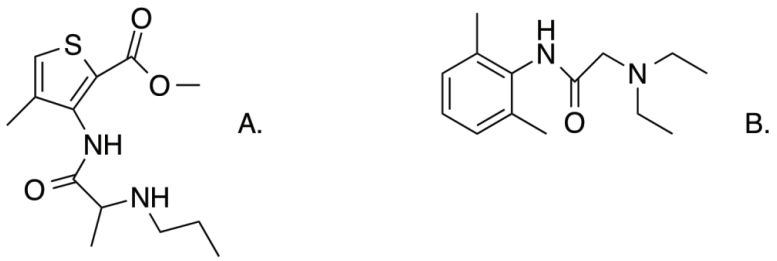

Figure 4. Structural formulas of A. articaine and B. lidocaine.

Articaine

Articaine belongs to the amide group as well, but in addition, the molecule contains an ester group (*Figure 4*). Its pKa is similar to that of lidocaine. The pH of the commercial solutions is around 5.0 (Steele et al., 2009). It has a tiophene ring, which increases the molecule's liposolubility. Thus, articaine is known for its ability to penetrate bone tissue better than lidocaine (Vree and Gielen, 2005; Skjevik et al., 2011). It is fast-acting and quickly hydrolysed by esterases in tissues and plasma, which shortens the elimination time (Vree and Gielen, 2005). Due to its ability to infiltrate bone tissue effectively, it has been widely used in dentistry, where its analgesic capacity has been noted to be at least equal to that of lidocaine (Vähätalo et al., 1993; Malamed et al., 2000). However, in a recent meta-analysis summarizing the relevant studies comparing articaine and licocaine, the analgesic effect of articaine in dentistry was found to be superior to that of lidocaine (Katyal, 2010).

In addition to local anaesthesia, articaine has been used with promising results in spinal anaesthesia (Bachmann et al., 2012), epidural anaesthesia (Noyan et al., 2000; Katircioglu et al., 2008), nerve blocks (Simon et al., 1999) and intravenous regional anaesthesia (Simon et al., 1997). However, no previous studies have investigated its use during BMAB.

Buffering and warming the local anaesthetic

Local anaesthetic solutions are usually acidic (pH 5 – 7), which ensures that the molecules are in their ionized, soluble form. Furthermore, addition of adrenaline to the solution requires even lower pH in order to preserve the drug in its active form. However, these acidic solutions cause pain during infiltration due to tissue irritation. Raising the pH by adding sodium bicarbonate, i.e. buffering, has been shown to cause less pain from skin infiltration before various procedures,

including BMAB (Xia et al., 2002; Ruegg et al., 2009; Kashyap et al., 2011; Welch et al., 2012). Since pH has a major role in regulating the local anaesthetic molecule's ability to traverse the nerve cell membrane (McLure and Rubin, 2005), it is logical that raising the pH of the local anaesthetic solution would have an effect on the analgesic capacity of the solution. In fact, the rise in pH has been shown to enhance the passage of the molecules to the nerve cells and facilitate the onset (Coventry and Todd, 1989; Quinlan et al., 1992; Kashyap et al., 2011) and intensity (Ruegg et al., 2009) of anaesthesia, although contradictory results also exist (Whitcomb et al., 2010).

In a recent meta-analysis, warming the local anaesthetic solution was shown to alleviate pain during infiltration to a clinically significant extent, compared with room temperature solutions (Hogan et al., 2011). In fact, warming and buffering have been demonstrated to have synergistic effects (Mader et al., 1994; Colaric et al., 1998). Thus, combining these two simple methods can lead to marked pain relief during local anaesthetic administration and possibly lead to a better analgesia as well. No earlier studies have evaluated the combined effect of warming and buffering during BMAB.

2.4.2 Opioids

Overview of opioids

Opioids are chemical agents that bind to specific opioid receptors in the central and peripheral nervous system as well as in peripheral tissues (Trescot et al., 2008; Pasternak, 2014), which leads to effective pain relief. Endogenous opioids are responsible for pain relief in placebo analgesia (Riet et al., 1998; Zubieta et al., 2005), among other functions. Opioids can be classified according to their chemical structure. These drugs have distinctive and unique pharmacokinetic and -dynamic profiles (Trescot et al., 2008). Opioids may be administered in various ways: peroral, parenteral (intravenous, intramuscular, transmucosal, transdermal), spinal or epidural. The release of the drug can be further modified (rapid or controlled release), thus meeting the specific needs of the patient. The side-effects of opioids (e.g. dizziness, sedation, respiratory depression, constipation, pruritus, nausea, tolerance) are predominantly dose-dependent (Trescot et al., 2008), although some adverse effects, such as constipation, may occur with smaller doses as well. Furthermore, chronic use of opioids frequently causes addiction, and thus, opioids may be abused (Compton and Volkow, 2006). The indications for use vary from minor conditions (e.g. headache, musculoskeletal pain) to cancer pain management and perioperative treatment of pain. When opioid medication is considered, the indication, the patient's characteristics and the drug's pharmacologic profile determine which preparation is chosen.

Sublingual fentanyl

Fentanyl is a strong opioid belonging to the phenylpiperidine class of opioids (Trescot et al., 2008). It has a relatively rapid onset of action. Due to moderate first-pass metabolism in the liver after oral administration, it has been administered primarily via the parenteral route. Furthermore, it is a highly lipophilic molecule, which makes it ideal for transmucosal administration, i.e. through oral or intranasal mucosa. (Grape et al., 2010) A "lollipop" or lozenge formulation of fentanyl for transmucosal administration has been used for several years for acute breakthrough pain in cancer patients and also during some medical procedures (Fine and Streisand, 1998). A new sublingual formulation of the drug has been developed as well, with better bioavailability. When administered sublingually, the peak fentanyl concentration is reached in 40 – 55 minutes, the first detectable concentrations occurring 8 – 10 minutes after administration. (Lennernäs et

al., 2005). Sublingual fentanyl has been shown to be effective in acute cancer breakthrough pain, the side-effects being similar to other opioids (Lennernäs et al., 2010).

In the paediatric population, oral transmucosal fentanyl in the lollipop formulation was found to be superior to placebo during BMABs or lumbar punctures (Schechter et al., 1995), but nausea and vomiting may restrict its use in this indication. There are no prior studies investigating the usefulness of sublingual fentanyl in adult patients undergoing BMAB.

Other opioids during BMAB

A few studies have investigated the analgesic capacity of the following opioids in adults undergoing BMAB: tramadol (Vanhelleputte et al., 2003), hydromorphone combined with lorazepam (Dunlop et al., 1999; Wolanskyj et al., 2000) and oxycodone combined with paracetamol and lorazepam (Talamo et al., 2010). However, some of these studies are not randomized or even placebo-controlled, which limits their clinical relevance. In conclusion, evidence of effective and feasible opioid premedication in adults prior to BMAB is insufficient and further studies regarding this issue are needed.

2.4.3 Benzodiazepines

Benzodiazepines relieve anxiety and induce sedation. They are $GABA_A$ receptor agonists. Increased $GABA_A$ receptor activity results in an increase in inhibitory activity in the brain, which leads to sedation, anxiolysis and anticonvulsive effects (Lader, 1987). Benzodiazepines also have an impact on the brain's memory function, which leads to anterograde amnesia, at least with midazolam (Bulach et al., 2005). Benzodiazepines can be divided into short-acting (e.g. triazolam) and long-acting (e.g. diazepam), depending on the specific pharmacological profile (Lader, 1987). Benzodiazepines have been extensively used during various medical procedures as sedatives, as anticonvulsants and as anxiolytics in psychiatry. Side-effects, such as tiredness and respiratory depression, may occur with larger doses. With long-term use, tolerance and adverse effects on cognitive function are also frequent (Stewart, 2005). Furthermore, benzodiazepines may be abused (O'Brien, 2005).

Several studies have examined the use of benzodiazepines during BMAB in adults (Milligan et al., 1987; Dunlop et al., 1999; Wolanskyj et al., 2000; Giannoutsos et al., 2004; Chakupurakal et al., 2008; Park et al., 2008); some of these studies have investigated the combined effect of an opioid and benzodiazepine. In summary, most of the studies did not show any benzodiazepine-related reduction in pain scores. These drugs appear to be effective in causing amnesia, and they might increase patients' co-operation. The use of benzodiazepines might be justified, especially in anxious patients, but their long-lasting sedative effect restricts their use in outpatient clinics.

2.4.4 Nitrous oxide

The mixture of nitrous oxide (N_2O) and oxygen (O_2) has been used for over 150 years as a hypnotic and an analgesic during various medical procedures (Masood et al., 2002; Aboumarzouk et al., 2011) and during labour (Rosen, 2002) and as an adjuvant in general anaesthesia. N_2O is a gas at room temperature and normal atmospheric pressure, and it liquefies at -89.5 °C (Trogler, 1999). It has no unpleasant smell or flavour. N_2O has low solubility in blood and adipose tissue, which leads to a short onset of action (within a couple of minutes) after the start of inhalation (Becker and Rosenberg, 2008). Once it reaches the brain, it seems to have many modes of action: activation of antinociceptive descending pathways through endogenous opioid release,

NMDA receptor antagonism, $GABA_A$ agonist release as well as an effect on dopamine and α2 adrenoceptors (Maze and Fujinaga, 2001; Emmanouil and Quock, 2007). Once inhalation of N_2O ceases, the gas redistributes rapidly from the blood to the alveoli and is further exhaled. Such side-effects as headache and dizziness are mild and temporary. Over time or with frequent use, nitrous oxide is known to disturb vitamin B12 metabolism, but this is not the case during short medical procedures (Weimann, 2003). Although administration of N_2O is relatively easy, the adverse effects on health care personnel during extensive exposure to N_2O (Sanders et al., 2008) should be kept in mind and gas scavenging systems should always be used. According to Finnish regulations (Finnish Institute of Occupational Health), the 8-hour time-weighted average N_2O concentration in room air should not exceed 100 ppm.

Inhaled N_2O has been useful in procedural sedation and analgesia in children (Reinoso-Barbero et al., 2011) and during venous cannulations in both children (Hee et al., 2003) and adults (Gerhardt et al., 2001). It has also proven useful during minor procedures in adults (Meskine et al., 2011; Hierons et al., 2012). Furthermore, intraoperative use of N_2O has been shown to reduce the risk for chronic postoperative pain (Chan et al., 2011). Use of N_2O might be beneficial in such minor procedures as BMAB, as reports have been made of prolonged pain after BMAB (Bain, 2004).

Some studies have examined the usefulness of N_2O/O_2 during BMAB (Steedman et al., 2006; Gudgin et al., 2008; Johnson et al., 2008) in the adult population. Only one of these studies was randomized and blinded (Johnson et al., 2008), and the patient populations (48 participants) was relatively small. In that study, N_2O/O_2 was effective in males but not in females. Some studies have been conducted with paediatric population, with varying results (Annequin et al., 2000; Iannalfi et al., 2005). However, in those studies additional medications, such as benzodiazepines, were often used. Additional randomized and placebo-controlled studies are needed before N_2O/O_2 can be regarded as an effective pain-relieving method during BMAB in adult patients.

2.4.5 Other analgesics and sedatives

One study investigated the effects of conscious sedation performed with inhaled methoxyflurane during BMAB (Spruyt et al., 2013), with promising results. After all, methoxyflurane has been shown to increase pain threshold already at subanaesthetic concentrations (Tomi et al., 1993). Deeper sedation with other anaesthetic agents is less often used in adult outpatients undergoing BMAB. However, children usually undergo the BMAB in deep sedation or general anaesthesia (Krauss and Green, 2006). Thus, most studies examining deep sedation during BMAB are conducted with paediatric patient populations. These studies vary with regard to the medication used. There are reports of combinations of opioids and propofol (Holdsworth et al., 2003; Anghelescu et al., 2013), combinations of propofol, midazolam and ketamine (Po et al., 2012) and ketamine alone (Evans et al., 2008). In general, deep sedation or general anaesthesia was found to be effective in reducing procedural pain in children.

Non-pharmacological methods

Pain during BMAB can be alleviated, at least to some extent, by paying attention to the mechanical performance of the procedure. Although traditional needles applied manually are still common, new powered devices for obtaining biopsy samples from the iliac crest have been developed. These devices seem to cause less pain during bone marrow biopsy, and they help to obtain longer

biopsy samples, with no significant rise in complication rates. (Voigt and Mosier, 2013) During aspiration a slow aspiration technique causes less pain than a rapid technique, although rapid aspiration leads to better sample quality (Hasselgren et al., 2014).

Some studies have investigated the efficacy of psychological means of pain relief during BMAB, such as hypnosis (Snow et al., 2012), music therapy (Danhauer et al., 2010; Shabanloei et al., 2010) and art therapy (Favara-Scacco et al., 2001), as well as combined use of psychological methods and pharmacological pain relief and sedation (Lord and Bhuller, 2012). A study comparing magnetic acupressure with sham acupressure (pressure applied to sham acupuncture points) showed no statistically significant difference in median pain scores between the treatment arms (Bao et al., 2011). The authors suggested that the proportion of patients suffering intense pain was higher in the sham group, but due to the small sample size, this effect is probably not clinically significant.

3 AIMS OF THE STUDY

The objective of this study was to assess the efficacy of various analgesic methods on the intensity of pain suffered by adult patients during bone marrow aspiration and/or biopsy and to examine the role of anxiety and other factors in the pain experience. Specific aims were as follows:

1. To measure pain intensity and quality and to assess prevalence and intensity of pre-procedural anxiety and its effect on pain ratings during BMAB. Specific interest was paid to possible differences between the experience of pain during BMAB in first-timers as compared with those having undergone BMAB before (Studies I, II, III, IV, V).
2. To compare analgesic efficacy of articaine and lidocaine infiltration of the tissue layers between the skin and bone during the various phases of BMAB (Study II).
3. To assess the analgesic efficacy of warming and buffering the infiltrated lidocaine solution on pain during BMAB (Study III).
4. To evaluate the analgesic efficacy and side-effects of sublingual fentanyl relative to placebo during BMAB (Study IV).
5. To assess the analgesic efficacy and safety of inhalation of 50% nitrous oxide in oxygen compared with 50% oxygen during BMAB (Study V).

4 PATIENTS AND METHODS

4.1 Patients

This study comprised 646 patients. The participants were outpatients at the Department of Haematology, Helsinki University Central Hospital, undergoing bone marrow aspiration and/or biopsy. Common exclusion criteria in Studies I – V were unstable coronary artery disease, allergy to lidocaine or articaine, BMI over 32 kg/m^2 and inability to communicate in Finnish or Swedish. Inability to give informed consent due to, for example, dementia, other cognitive impairment or poor condition led to exclusion as well. Patients scheduled for BMAB were telephoned before the procedure day and notified of the study protocol (Studies IV – V). Written information was provided on the procedure day. All consecutive patients scheduled to have BMAB on days when the research team was present were considered for inclusion, providing that they did not fulfil the exclusion criteria. The final decision on enrolment was made by the research assistant on these predefined criteria or by one of the researchers. All patients enrolled in the studies gave written informed consent. The patient enrolment took place between 2007 and 2014.

Study I

The study comprised 166 patients; 48 were first-timers for BMAB. All patients were enrolled only once.

Study II

The study comprised 150 patients, of whom 50 received articaine 20 mg/ml, 49 received articaine 40 mg/ml, and 51 patients received lidocaine 20 mg/ml. All solutions contained adrenaline 5 μg/ml. A couple of patients were enrolled two times due to the long study period, and on the second enrolment the patient was allocated to another study group.

Study III

The study comprised 100 patients, half of whom were randomized to receive warmed and buffered lidocaine and the other half served as a control group, receiving room-temperature, unmodified lidocaine. The solutions contained adrenaline 5 μg/ml. The warmed and buffered solution was prepared a couple of minutes before infiltration to ensure adequate preservation. All patients were enrolled only once.

Study IV

The study comprised 160 patients, half of whom were randomized to receive sublingual fentanyl and the other half placebo. The study-specific exclusion criteria were drug abuse or ongoing opioid replacement therapy, predetermined analgesic premedication for the procedure, driving own car or lack of a competent escort. The patient could participate only once.

Study V

In total, 70 patients were randomized to receive either inhaled 50% nitrous oxide in oxygen (35 patients) or 50% oxygen (35 patients). The study-specific exclusion criteria were emphysema or chronic obstructive pulmonary disease (COPD), pneumothorax, Alzheimer's disease or other

cognitive impairment, pregnancy and predetermined analgesic or anxiolytic premedication for the procedure. All patients were enrolled only once.

4.2 Pre-procedural interviews

After giving written informed consent, the participants were interviewed. The interview consisted of the following information:

1. Demographic data, diagnosis or indication for BMAB.
2. Current medications used for pain and anxiety (Studies I, III – V) and for arterial hypertension (Studies IV, V).
3. The grade of pre-procedural anxiety, assessed with STAI-S (Study I), NRS 0 – 10 (Studies III – V), or on the scale 0 – 4, where 0 = no anxiety, 4 = very anxious (Study II).
4. Pre-existing pain and its intensity on the NRS 0 – 10 (Studies I, III – V).
5. Pain during previous BMABs and other minor medical procedures, graded as no pain – slightly painful – very painful (Studies I, III, V).
6. Letter Digit Coding Test (Houx et al., 2002) to obtain the baseline score of the participant's cognitive capacities (Study V). The Finnish version of the test is presented in the Appendix. The test consists of rows of letters, which need to be coupled with specific numbers given in a separate key. The score is the number of correctly combined letter-number pairs finished in a given time.

4.3 Procedure

Some patients received analgesic premedication (intramuscular alfentanil 0.5 – 1 mg) (Studies I, III) or anxiolytic premedication (oral diazepam 5 – 10 mg) (Studies I – IV), given upon patient request 30 – 60 minutes before BMAB. These drugs served also as rescue medication in case of extreme pain or anxiety during BMAB in addition to study drugs (Studies II – V).

With the patient lying down, non-invasive blood pressure was measured (Studies IV, V). In Study IV, the stage of sedation was also evaluated at this point on the Ramsay Sedation Scale (RSS) (Ramsay et al., 1974). The patient then received local anaesthetic infiltration to the procedure area in standardized volumes of 6 ml (sternal manubrium), 8 ml (sternal body) or 10 ml (posterior iliac crest). The local anaesthetic used was lidocaine 20 mg/ml with adrenaline 5 μg/ml (Studies I, IV, V), lidocaine 20 mg/ml or articaine 20 mg/ml or articaine 40 mg/ml, all with adrenaline 5 μg/ml (Study II), warmed lidocaine 20 mg/ml with adrenaline 5 μg/ml buffered with sodium bicarbonate or room-temperature lidocaine 20 mg/ml with adrenaline 5 μg/ml added to 0.9% NaCl (Study III). In all of the studies, one-third of the total volume was infiltrated to the skin, one-third to the subcutaneous tissue and the remaining one-third in the close proximity of the periosteum. After the infiltration, the procedure area was disinfected and draped. The local anaesthetic was left to take effect for at least two minutes before beginning the BMAB.

The performing physician tested the adequacy of local anaesthesia with the puncture needle. If the local anaesthesia was insufficient, another dose (half of the original volume) of the local anaesthetic was infiltrated. The physician then performed the aspiration and, if needed, the biopsy as well. The biopsy was always taken from the posterior iliac crest.

After completion of the BMAB, the puncture area was covered with a bandage and the patient received instructions on how to monitor the puncture site and how to treat post-procedural pain. The patient was discharged after the study interviews if the patient felt well and no signs of bleeding or other complications were present.

4.4 Interventions

Study I

The study was observational, thus, the patients received no study-specific intervention other than the standardized local anaesthesia. All patients received lidocaine 20 mg/ml with adrenaline 5 µg/ml (Lidocain c. Adrenalin, Orion Pharma, Espoo, Finland).

Study II

Patients were randomized to receive either articaine 20 mg/ml, articaine 40 mg/ml (Ultracain, Sanofi-Aventis, France) or lidocaine 20 mg/ml (Lidocain, Orion Pharma, Espoo, Finland). Adrenaline (Adrenalin, Leiras Takeda Pharmaceuticals, Helsinki, Finland) was added to all of the solutions to yield a concentration of 5 µg/ml.

Study III

Patients were randomized to receive either warmed and buffered lidocaine or room-temperature, unmodified lidocaine. Warmed and buffered lidocaine solution was made from 8 ml of lidocaine 20 mg/ml with adrenaline 5 µg/ml (Lidocain c. Adrenalin, Orion Pharma, Espoo, Finland) and 2 ml of sodium bicarbonate 75 mg/ml (Natriumbicarbonate Braun 75 mg/ml, B. Braun, Melsungen, Germany). Before mixing these two solutions, they were warmed in separate syringes to 32˚C under a heating lamp. After warming, these were mixed in one syringe. The solution for the control group was made from 8 ml of lidocaine 20 mg/ml with adrenaline 5 µg/ml (Lidocain c. Adrenalin, Orion Pharma, Espoo, Finland) added to 2 ml of NaCl 0.9% solution. This solution was kept at room temperature. In conclusion, in both groups the total volume of local anaesthetic solution was 10 ml with the same lidocaine concentration, but with different temperature and pH (7.3 in the warmed and buffered solution, 3.7 in the control solution).

Study IV

All study participants received lidocaine 20 mg/ml with adrenaline 5 µg/ml (Lidocain c. Adrenalin, Orion Pharma, Espoo, Finland). Patients randomized to the fentanyl group (80 participants) received sublingual fentanyl 200 µg (Abstral®, ProStrakan Ltd, Galashiels, Scotland, UK), but if the patient was in poor health, weighed less than 50 kg or was over 70 years old, the dose given was 100 µg. Patients randomized to the placebo group (80 participants) received a similar, rapidly dissolving tablet without any pharmacologically active ingredients. The patient received the tablet 10 – 30 min before the procedure was assumed to begin.

Study V

Patients randomized to the N_2O/O_2 group (35 participants) were given a double mask (Medicvent AB, Umeå, Sweden), which was connected to a single-use filter and a valve that triggered gas flow only during sufficiently deep inhalation. When the patient breathed through the mask, 50% N_2O/O_2 (Livopan®, the Linde Group, Germany) was administered during inhalation. The exhaled

gas was led from the mask via plastic hoses to a device (Excidio®, the Linde Group, Germany) breaking N_2O down to nitrogen and oxygen, thus reducing N_2O pollution.

Patients randomized to placebo (35 patients) received 50% oxygen through a mask attached to a ventilation bag (Laerdal silicone resuscitator, Stavanger, Norway) further connected to a rotameter providing fresh gas flow of 10 l/min.

The patients were advised to start inhalation 2 – 3 minutes before the beginning of local anaesthetic infiltration. The local anaesthetic was lidocaine 20 mg/ml with adrenaline 5 μg/ml (Lidocain c. Adrenalin, Orion Pharma, Espoo, Finland). Patients were advised to breathe continuously through the mask throughout the procedure to ensure adequate analgesia, but they were allowed to have pauses as well. In this case, the patient was advised to restart inhalation 2 – 3 minutes before the next painful phase of BMAB. After the BMAB was complete, the patient ceased the inhalation.

4.5 Tests for pain and post-procedural interviews

The research assistant interviewed the patient 30 – 60 minutes after the procedure. It was assumed that the peak effect of the study medication had worn off (Studies IV-V) by this time. The participant answered questions regarding general condition, possible side-effects of the study drugs and pain felt after the BMAB. In Study IV, the patient's peripheral oxygen saturation was monitored as well. The respiration rate was monitored in Studies IV and V. The Numeral Rating Scale (NRS, 0 – 10) was used in all studies to measure procedural pain intensity. In Studies II – IV, the patient scored the pain felt during the phases of the procedure (local anaesthetic infiltration, puncture, aspiration, biopsy) when the BMAB was still ongoing. In Studies I and V, the pain scores were obtained after the procedure, during the post-procedural interview. In addition, in Study I, the patients were asked to describe the pain using the Finnish pain vocabulary (Ketovuori and Pöntinen, 1981).

During the telephone interview on the following day the patients answered questions regarding their general condition, post-procedural pain and possible pain medication taken as well as possible complications affecting the puncture site. In Study II, the patient was telephoned also two weeks after the procedure and the same questions were repeated. Either the research assistant or another member of the research group performed these interviews.

4.6 Blinding and randomization

Study I was observational and did not include any randomization or blinding. In Studies II – V, randomization was performed with sealed envelopes. In Study II, one of the non-blinded researchers prepared the used local anaesthetic solutions in a room separate from the procedure room. This researcher did not participate in patient enrolment or interviews, and thus, the study was kept double-blind. The performing physician was kept blind as well.

In Study III, the non-blinded research assistant prepared the local anaesthetic solution after the patient was enrolled and interviewed, that is, just before the beginning of the BMAB. This study was only patient-blinded.

In Study IV, a nurse assisting the performing physician and not otherwise involved in the study opened the envelope and gave the sublingual tablet (fentanyl or placebo) to the participant according to the instructions on the envelope. Thus, Study IV was double-blinded, as the patient, the performing physician and the research assistant performing the interviews were kept blinded regarding the drug administered.

In Study V, a member of the research group opened the randomization envelope in the procedure room and made the preparations for the allocated gas, just before the patient entered the room. The patient and the research assistant performing the interviews were kept blinded to the gas used. Regardless of the study group, the non-blinded researcher gave the patients the same instructions on how to use the mask. Due to visible differences in gas administration equipment between the two study arms, it was not possible to keep the assisting personnel or the performing physician blinded. However, they handled the patient similarly regardless of the gas used.

After the BMAB, patients were not asked about which randomization group they thought they had been assigned.

4.7 Statistics

The sample size in every trial was based on a power calculation. The normality of the variables was assessed with the Shapiro-Wilk test. The NRS scores as well as variables measuring anxiety were not normally distributed. Thus, in all studies, the majority of the analyses were conducted with non-parametric tests. In Studies I and III – V, the differences in pain scores between study groups were analysed with ordinal regression analysis. Factors assumed to have a confounding effect (e.g. age, gender, pain or anxiolytic medication) were included in the analysis. In Study II, the pain and anxiety scores between the three groups were analysed with the Kruskal-Wallis test. ANOVA was used when appropriate. The Mann-Whitney U test was used in unadjusted comparisons (Studies I, II) and the X^2 –test in comparison of proportions between groups (Study I).

Logistic regression analysis was used in Studies IV and V to assess the side-effects of the study drugs used. These analyses were adjusted for factors assumed to have a confounding effect. In Study V, logistic regression analysis was used also to assess whether differences were present in cognition test results between the groups. SPSS versions 16.0, 17.0 and 22.0, and PASW version 18.0 (IBM, New York, NY, USA) were used in the analyses. A P-value < 0.05 was considered to be statistically significant. The results are presented as mean, median, standard deviation (SD), percentage, interquartile range (IQR), odds ratio (OR) and its confidence intervals (CI).

4.8 Ethics

In every trial, participants gave written informed consent before randomization. Patients unable to speak and understand Finnish or Swedish were excluded, as were patients diagnosed with dementia or another cognitive impairment (e.g. mental disability) preventing full understanding of the trial. The hospital ethics committee of the Helsinki and Uusimaa Hospital District approved all trials. In addition, the former Finnish National Agency for Medicines (present-day Finnish Medicines Agency, Fimea) approved Study II and Fimea was also notified of Studies IV and V.

5 RESULTS

The basic characteristics of the participants in Studies I – V are presented in *Table 3*.

Table 3. Demographic data of participants.

[a]Other diagnoses include miscellaneous states such as thrombocytosis, thrombocytopenia, infections, hypersedimentation or diagnosis unknown.

	Study I	Study II	Study III	Study IV	Study V
Gender (male/female)	100/66	78/72	61/39	94/66	37/33
Age (years), mean (SD), *range*	53 (15), *17 - 87*	54 (14), *18 - 82*	56 (15), *19 - 89*	59 (14), *19 - 89*	59 (12), *17-80*
Height (cm), mean (SD), *range*	172 (10), *149 - 197*	172 (11), *153 - 204*	174 (10), *145 - 190*	172 (9.0), *153 - 193*	172 (8.0), *150 - 186*
Weight (kg), mean (SD), *range*	76.5 (16), *42 - 130*	76.0 (17), *46 - 125*	77 (14), *40 - 111*	75 (14), *43 - 115*	78 (15), *52 - 130*
Site of aspiration, *n*					
- Sternal manubrium	36	62	21	31	8
- Sternal body	27	11	28	27	8
- Iliac crest	100	77	51	102	54
Diagnoses, *n*					
- Lymphoma	32	19	16	26	11
- Leukaemia	59	80	44	47	19
- Myeloma	9	5	10	17	7
- Myelodysplastic syndrome	5	8	1	7	3
- Other malignancy	5	7	3	14	2
- Anaemia	9	4	2	4	6
- Healthy donor	9	5	3	4	0
- Other[a]	41	22	21	41	22
Performed by, *n*					
- Doctors in training	36	40	40	88	41
- Specialists	130	110	60	72	29

5.1 Factors associated with pain during the bone marrow aspiration and biopsy

Anxiety was a predictor of procedural pain in all trials. In Study I, high anxiety scores were associated with pain during local anaesthetic infiltration, puncture and aspiration, whereas in Study V it was associated with aspiration pain only. In conclusion, anxiety can be regarded as one of the most important factors predicting procedural pain during BMAB.

Being a first-timer had an effect on pain scores in Studies I, II and V, but the effect was ambiguous: it was related to both increased and decreased pain scores. Age was found to affect pain ratings in some studies (Studies I, III, IV); higher age was associated with lower pain scores. Women suffered more pain during local anaesthetic infiltration than men in Study V, but during other BMAB phases the pain scores were similar. When all trials were combined, the experience of the performing haematologist (specialist vs. specializing physician) had no clear effect on pain

scores. Pain and anxiety during previous BMABs or other minor medical procedures predicted pain during the present BMAB as (Studies I and III).

Patients using pain or anxiolytic medication (regular or temporary) did not have lower pain scores during BMAB (Studies I, III, IV, V). There were 16/ 11/ 20/ 13 patients on regular and 15/ 11/ 19/ 6 patients on temporary pain medication, and 14/ 10/ 17/ 4 patients on regular and 8/ 4/ 9 / 2 patients on temporary anxiolytic medication in Studies I/ III/ IV/ V, respectively. In some studies (Studies I, III), premedication with intramuscular alfentanil was allowed upon patient request, with no significant pain-alleviating effect during bone marrow sampling, despite alleviating pain during local anaesthetic infiltration (Study III). Premedication with diazepam had varying effects: in Study I, no effect was found, whereas in Study III aspiration pain was slightly lower. However, due to the small number of patients receiving premedication with diazepam, no conclusions can be drawn about its effectiveness.

In Study I, patients described the quality of pain felt during BMAB with words belonging mostly to the sensory class (mainly words indicating punctate, incisive or constrictive pressure). However, aspiration pain was described also with affective words, indicating a different quality of pain than in the other BMAB phases.

5.2 Anxiety during bone marrow aspiration and biopsy

5.2.1 Anxiety scores

The median score of pre-procedural anxiety was relatively low in all trials: 38 (range 20 – 71, IQR 15) measured with STAI-S in Study I, 1 (range 0 – 4, IQR 4, where 0 = no anxiety, 4 = very anxious) in Study II, 3.0 (range 0 – 10, IQR 4) measured with NRS in Study III, 3.0 (range 0 – 10, IQR 4) measured with NRS in Study IV and 3.5 (range 0 – 10, IQR 5) measured with NRS in Study V. However, in every trial, some patients were extremely anxious.

5.2.2 Factors influencing anxiety

Factors related to higher levels of anxiety are presented in *Table 4*. Female gender was the only variable associated with high pre-procedural anxiety in all trials. In Study II, also younger age and being a BMAB first-timer intensified anxiety, but this association was not evident in the other studies. Pain, anxiety and nausea during previous BMABs were associated with higher anxiety scores, as were pain and anxiety during other previous minor medical procedures (Study I).

Table 4. Factors related to intensified pre-procedural anxiety. NS = non-significant.

Variable	Statistical significance				
	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Gender	P = 0.022	P < 0.001	P < 0.001	P = 0.023	P = 0.02
Age	NS	P = 0.002	NS	NS	NS
First-timers	NS	P = 0.008	NS	NS	NS
Painful previous BMABs	P < 0.001	-	P < 0.001	-	NS
Anxiolytic medication	P = 0.019	-	NS	NS	NS

5.3 Articaine infiltration anaesthesia

Patients receiving articaine 20 mg/ml or 40 mg/ml, all with adrenaline 5 µ/ml, had similar pain scores as patients receiving lidocaine 20 mg/ml with adrenaline 5 µ/ml, and no statistically significant differences were detected. *Figure 5* presents the distribution of the pain scores. Biopsy pain seemed to be slightly lower in patients receiving articaine, but this difference did not reach statistical significance.

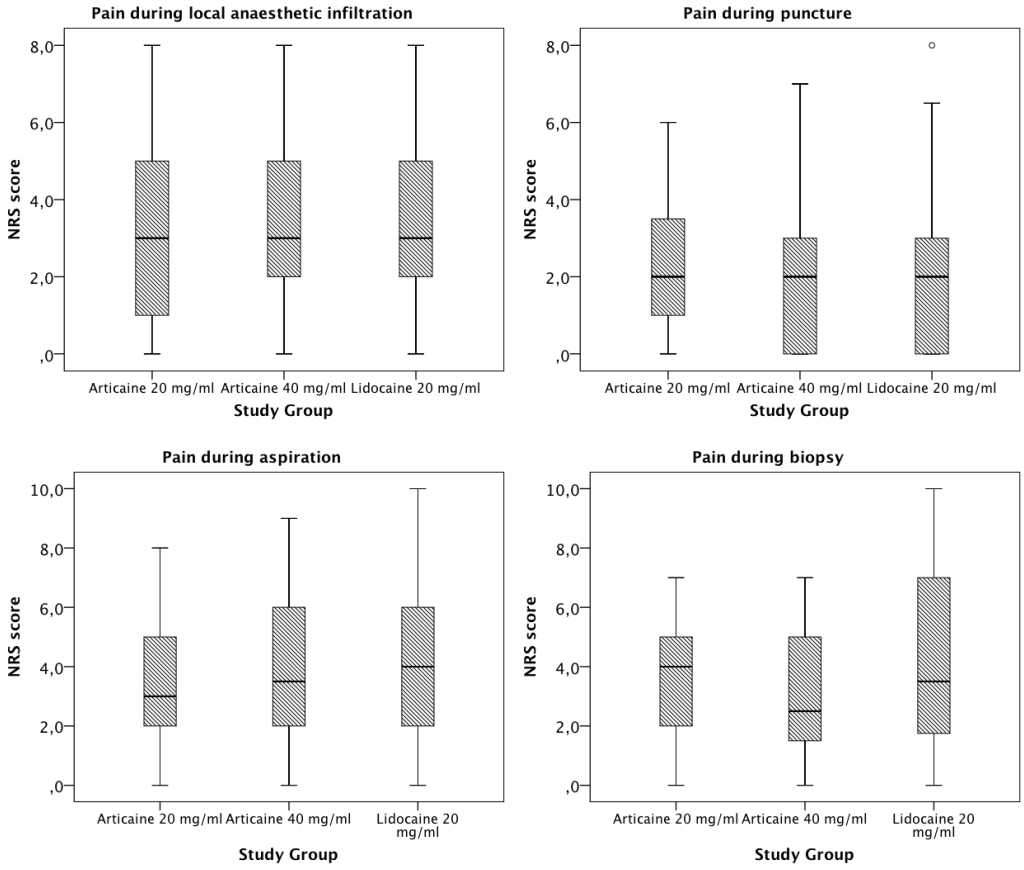

Figure 5. Pain scores presented as boxplots (Study II).

5.4 Warming and buffering lidocaine solution

Pain during local anaesthetic infiltration was significantly less intense in patients receiving warmed and buffered lidocaine compared with unmodified solution (OR 0.29, 95% CI [0.13; 0.62], P = 0.002, NRS median 2.0 vs. 4.0). However, no statistically significant differences emerged in pain scores during other phases of BMAB in the adjusted analysis. In the unadjusted analysis, patients receiving warmed and buffered lidocaine suffered more pain during aspiration (OR 2.10, 95% CI [1.05; 4.22], P = 0.036, NRS median 5.0 vs. 3.5). *Figure 6* shows the pain scores during BMAB as boxplots.

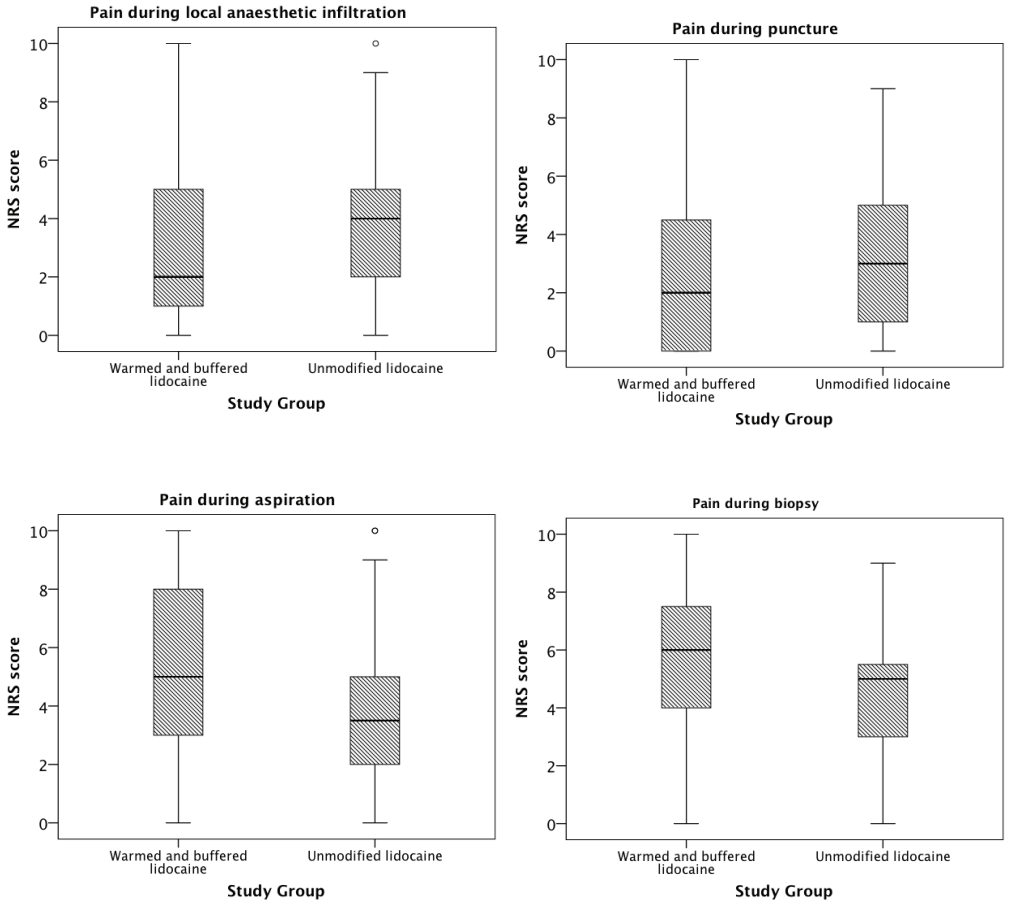

Figure 6. Pain scores presented as boxplots (Study III).

5.5 Sublingual fentanyl

Sublingual fentanyl proved to be ineffective in relieving pain during BMAB. The pain scores were similar in both groups (*Figure 7*), and no statistically significant differences in pain scores emerged. However, patients receiving sublingual fentanyl suffered significantly more dizziness than patients receiving placebo ($P < 0.0001$, OR 7.24, 95% CI [2.69; 19.46]). Patients who vomited after the procedure ($n = 4$) had all received sublingual fentanyl. Nevertheless, fentanyl did not cause excessive sedation, as all patients remained within the awake levels of the sedation scale RSS. Furthermore, no significant drops occurred in the peripheral oxygen saturation values.

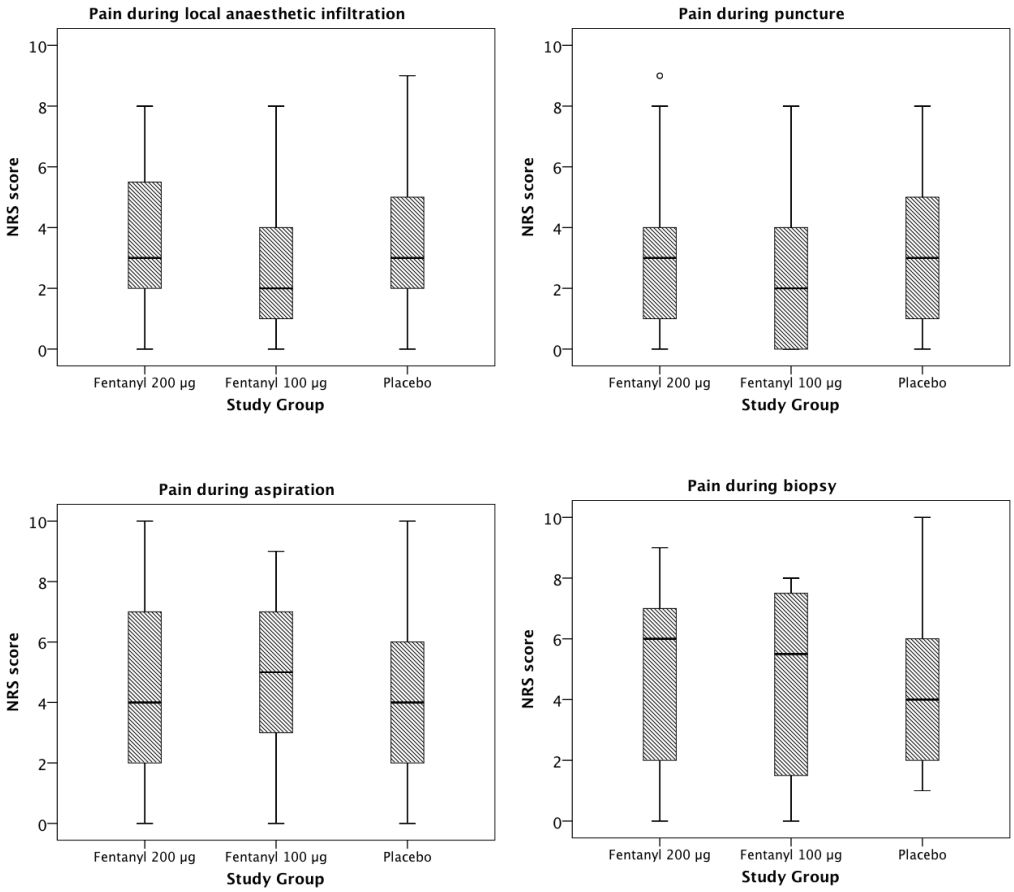

Figure 7. Distribution of pain scores presented as boxplots (Study IV).

5.6 Nitrous oxide

Patients who inhaled 50% N_2O in oxygen had similar pain scores during BMAB as patients inhaling 50% oxygen. *Figure 8* shows the distribution of pain scores. Four patients (3 from the placebo group) needed an additional local anaesthetic infiltration. Nitrous oxide was relatively well tolerated; only one patient felt slightly nauseous after receiving nitrous oxide, 7 patients had transient dizziness (5 patients had received nitrous oxide, 2 patients placebo) and 3 patients (all from the placebo group) had headache. Nitrous oxide did not have adverse effects on cognitive function measured with the Letter Digit Coding Test. When patients were asked whether they would like to receive the same analgesia during the next BMAB, 30/35 patients (86%) in the N_2O/O_2 group and 29/35 patients (83%) in the placebo group answered yes.

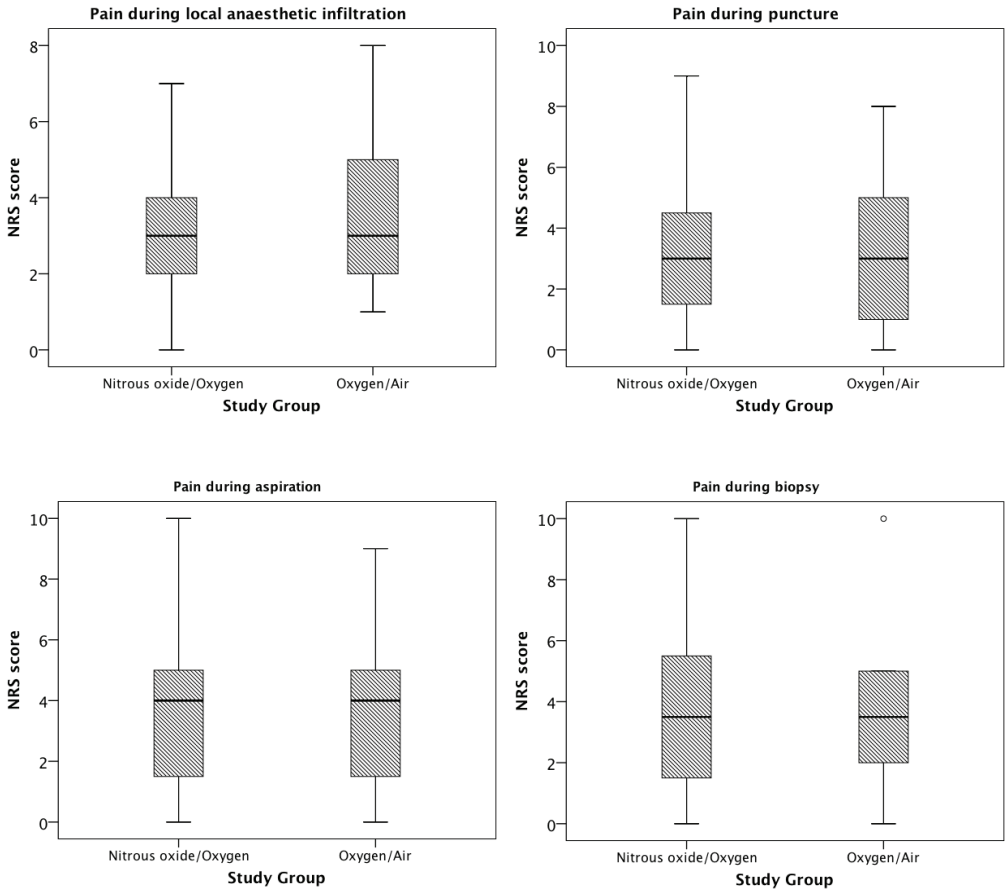

Figure 8. Pain scores presented as boxplots (Study V).

5.7 Telephone interviews

During the telephone interview performed on the following day by the research assistant or another member of the study group some patients reported local reactions, such as haematoma or minor bleeding, redness or edema, at the puncture site. There were no reports of serious complications caused by the procedure, although two patients (Studies IV and V) reported experiencing a sensory and motor block of the lower extremity, presumably due to abnormal distribution of the local anaesthetic to lumbar plexus nerves, and another patient (Study IV) developed an infection of the puncture area and needed treatment with intravenous antibiotics.

The median pain score at this telephone interview on the day following the procedure was 0 (range 0 – 7, IQR 1) when all trials were combined. Some participants (14.8%) had taken pain medication at home (mostly paracetamol or ibuprofen).

Study II included a second telephone interview 2 weeks after the BMAB. At this point, most patients (92.6%) were pain-free and reported good general condition.

6 DISCUSSION

These studies showed that although the majority of patients undergoing BMAB suffered only minor or moderate procedural pain, some patients (4.7% – 13.9%) suffered intense or excruciating pain (NRS 8 – 10). Premedication with sublingual fentanyl or inhaled nitrous oxide during the procedure were not helpful in reducing the pain, nor was intramuscular alfentanil or oral diazepam, given at the request of some participants. Patient's own medication for pain or anxiety also did not ease pre-procedural anxiety or BMAB-related pain. The use of articaine for infiltration analgesia instead of the regularly used lidocaine or warming and buffering the lidocaine solution did not ease procedural pain, although warming and buffering did reduce pain during local anaesthetic infiltration. A clear finding was that pre-procedural anxiety is a major risk factor predicting procedural pain.

Anxiety and pain during BMAB

Studies I – V showed a clear association between pre-procedural state anxiety and pain during BMAB. The association between anxiety and pain during BMAB has been noted in other studies as well (Lidén et al., 2009; Tanasale et al., 2013). In these studies, in addition to pre-procedural state anxiety, anxiety about needle insertion (Lidén et al., 2009) and outcome of the examination (Lidén et al., 2009; Tanasale et al., 2013) were associated with pain during BMAB. Anxiety is established to intensify pain during other medical procedures as well (Maggirias and Locker, 2002; Ylinen et al., 2009) and following surgery (Ozalp et al., 2003).

Patients with painful memories from previous BMABs or from other minor procedures were found to suffer more intense anxiety and pain during the present BMAB than other patients. This finding is in line with results from other studies with patients undergoing BMAB (Degen et al., 2010) or with dental patients (Maggirias and Locker, 2002). Furthermore, in another study conducted with dental patients, pre-procedural anxiety predicted post-procedural recall of pain intensity and its unpleasantness (Gedney et al., 2003). Thus, previous painful and adverse memories intensify pre-procedural anxiety and procedural pain and, through the intensified anxiety level, may also affect post-procedural recollection of pain. Nevertheless, this may aid in identifying patients more prone to pain: adequate premedication and other pain-relieving methods could be aimed specifically at patients reporting high levels of anxiety and painful memories of previous BMABs. However, it is noteworthy that patients who had taken pain or anxiolytic medication at home did not suffer less pain during BMAB than the others. Moreover, in Study I, anxiolytic medication was related to an increased level of anxiety. Thus, regular need for pain and/or anxiolytic medication might itself be regarded as a risk factor for pain during BMAB.

Female gender was associated with higher scores of anxiety relative to males in all trials. This association has already been noted in surgical patients during the preoperative phase (Karanci and Dirik, 2003; Yilmaz et al., 2012), in patients undergoing gastrointestinal endoscopy (Eberhardt et al., 2006) and in dental patients, especially younger females (Holtzman et al., 1997). However, procedural pain scores during BMAB did not differ between the genders, expect in Study V, where pain caused by local anaesthetic infiltration was more intense in women than in men.

Increasing age was associated with lower scores of anxiety (Study II) and procedural pain (Studies I, III, IV). In other studies examining pain during BMAB, a similar inverse correlation

between age and pain has been noted (Vanhelleputte et al., 2003; Lidén et al., 2009; Talamo et al., 2010; Tanasale et al., 2013). Although there is evidence of decreased inhibitory pain modulation (Edwards et al., 2003) and altered pain thresholds (Lautenbacher et al., 2005) in older patients, acute, procedural pain appears to be better tolerated in the elderly population during several medical procedures (Li et al., 2001; Takahashi et al., 2005). Increasing age may have positive effects on life experiences and stress tolerance, which facilitate acceptance of painful stimuli.

Articaine infiltration anaesthesia for BMAB

Study II failed to show any significant differences in pain scores between patients receiving articaine and lidocaine infiltration. However, the use of articaine has been found to lead to anaesthetic success more often than lidocaine in dentistry (Katyal, 2010). Nevertheless, since many trials are conducted with 4% articaine and 2% lidocaine, the higher amount of local anaesthetic molecules in the articaine solution may in part contribute to the better quality results with articaine (Becker and Reed, 2012). In Study II, the comparison with 2% lidocaine (20 mg/ml) was made using two articaine concentrations, 2% (20 mg/ml) and 4% (40 mg/ml). Although the differences were non-significant, the proportion of patients suffering moderate or intense pain (NRS ≥ 4) was slightly lower in patients receiving articaine 20 mg/ml than lidocaine 20 mg/ml during aspiration. The difference was even greater during puncture and biopsy, when articaine 40 mg/ml was compared with lidocaine 20 mg/ml.

The two-minute latency period between infiltration of the local anaesthetic and beginning of the procedure is relatively short. Since the pKa of both articaine and lidocaine is higher than the pH 7.4 of subcutaneous tissue in healthy subjects, the molecules are predominantly in their water-soluble, ionized form after the infiltration, which delays the onset of anaesthesia (Becker and Reed, 2012). However, in the case of articaine, lipophilicity may increase when an intramolecular hydrogen bond forms (Skjevik et al., 2011). Although the bone-penetrating capacity of articaine has been shown to be superior to lidocaine (Vree and Gielen, 2005), the beneficial effect may not be evident if the molecules have insufficient time to diffuse and infiltrate the entire thickness of the bone tissue. At least in dentistry, the onset of satisfactory anaesthesia in a tooth may take several minutes for both articaine and lidocaine (Corbett et al., 2008).

Warmed and buffered lidocaine for infiltration

The skin and periosteum have nociceptors that react to, for instance, temperature, chemical composition changes of surrounding tissue medium and pressure. Excessive stimulation eventually leads to sensation of pain. (Koltzenburg, 2000) As the local anaesthetic solutions containing adrenaline are manufactured to be acidic in order to preserve the adrenaline, the infiltration of the solution causes irritation of these nociceptors, which leads to sensation of pain. If the solution is taken directly from the refrigerator, the cold injectate further intensifies pain. In Study III, pain during local anaesthetic infiltration was significantly less intense when the lidocaine solution was warmed to 32°C and buffered to a pH of 7.3 (NRS median 2.0 vs. 4.0). The warmed and buffered solution was prepared just prior to its use. Buffered solutions may be stable for weeks if adequately preserved, but addition of adrenaline shortens the preservation time (Davies, 2003).

A recent meta-analysis revealed that buffering the local anaesthetic solution leads to less intense infiltration pain (Hanna et al., 2009). This effect has been noted during BMAB as well (Ruegg et al., 2009). The study by Ruegg et al. showed that pain during all BMAB phases was

less intense when buffered solution was used. However, Study III failed to show any clinically or statistically significant difference in pain scores other than those during infiltration.

Warmed local anaesthetics have been shown to cause less pain than room-temperature solutions (Hogan et al., 2011) and the pain during infiltration is of similar intensity as that of buffered lidocaine (Brogan et al., 1995).

In conclusion, the evidence for significantly lowered pain intensity during infiltration of buffered and warmed solution is clear, and thus, warming and buffering should be routinely carried out prior to local anaesthetic administration. Furthermore, buffering and warming the solution is not difficult or time-consuming. Studies I – V showed that pain during local anaesthetic infiltration is intense (NRS 8 – 10) in surprisingly many patients (8.1%), indicating that more attention should be paid to techniques for reducing this pain.

Overall efficacy of local anaesthesia for BMAB

Besides the periosteum, the bone marrow is richly innervated by sensory nerves (Mach et al., 2002; Jimenez-Andrade et al., 2010), and the pain originating from these nerves may be impossible to eliminate by a subcutaneous infiltration of a local anaesthetic, particularly if it is allowed to diffuse for only a couple of minutes. Intraosseous infiltration of the local anaesthetic solution is possible during specific dental procedures (Bigby et al., 2006). However, for BMAB, it is probably not conceivable, as local anaesthetics may cause cell damage (Werdehausen et al., 2012) and distort cell morphology (Nicolson et al., 1976). This probably would hinder proper diagnostics of bone marrow tissue. Furthermore, due to the dense vasculature of the bone marrow, the local anaesthetic may be absorbed to the systemic circulation, increasing the risk of side-effects. In conclusion, although local anaesthetic infiltration is relatively effective in relieving pain originating from skin, subcutaneous tissue and the periosteum, the pain originating from the deeper bone tissue may require additional methods of pain relief, at least in patients having intense pre-procedural anxiety.

Premedication with sublingual fentanyl

Study IV did not show any reductions in the pain scores of patients receiving sublingual fentanyl compared with placebo. Another significant finding from this study was that sublingual fentanyl caused dizziness significantly more often than placebo. Nausea and vomiting were also more common in patients receiving fentanyl. This limits the use of the drug in outpatient settings, as the side-effects should be tolerable, allowing discharge home soon after the procedure.

As the sublingual formulation of fentanyl is relatively new, no earlier studies have yet investigated its use for BMAB or other medical procedures. Oral transmucosal fentanyl, the older fentanyl "lollipop" formulation, has been noted to be effective in treating pain during BMAB in a paediatric population (Schechter et al., 1995), although nausea was common. Its feasibility as a premedication for medical procedures other than BMAB has been examined in, for instance, patients undergoing retinal photocoagulation (Hillier et al., 2009), gynaecological brachytherapy (Proud, 2007) and general surgery (Macaluso et al., 1996). Furthermore, it has proved to be beneficial as a first-line treatment of pain caused by battlefield injuries (Wedmore et al., 2012) and in treatment of migraine attacks (Landy, 2004). In general, oral transmucosal fentanyl has been shown to be effective in reducing acute pain of non-cancer origin, and in most cases, the side-effects have been tolerable. However, some of these studies have lacked a control group, randomization or blinding.

In conclusion, sublingual fentanyl in doses of 100 μg and 200 μg was not sufficient as a premedication for BMAB, as the pain-relieving effect did not reach statistical nor clinical significance and side-effects were common. If the dose was increased to levels used for cancer breakthrough pain (300 – 800 μg) (Nalamachu et al., 2012), the respiratory and emetic side-effects would probably be unacceptable in an outpatient population. Nevertheless, in selected patients, such as those having intense pre-procedural anxiety or painful memories from previous BMABs, it might be justified to consider premedication with moderate doses of sublingual fentanyl. Sublingual administration would in any case be more pleasant than intramuscular or intravenous administration. Future studies should aim at identifying patients who would profit from premedication with sublingual fentanyl. Its effectiveness in this patient population should also be determined.

Nitrous oxide during BMAB

Study V showed that in an unselected outpatient population undergoing BMAB inhalation of the mixture of 50% nitrous oxide in oxygen (N_2O/O_2) was no more effective than inhalation of placebo (50% O_2) in alleviating procedural pain. The evidence from previous studies performed with adult patients undergoing BMAB has been inconsistent, and moreover, some of the studies showing positive results have been either small, non-randomized or not blinded (Steedman et al., 2006; Gudgin et al., 2008). The only randomized, placebo-controlled study of a relatively small sample size (Johnson et al., 2008) showed that inhaled nitrous oxide is effective in relieving BMAB pain in men, but not in women.

Although adequate analgesia was not achieved with nitrous oxide in Study V, the gas administration proved to be safe, with gas causing no more adverse effects than placebo. Nitrous oxide had no measurable effect on cognitive function assessed 30 minutes after BMAB, indicating that patients can be discharged soon after completion of the procedure provided that they feel well and have no related complications such as extensive bleeding.

Nitrous oxide is a greenhouse gas (Ishizawa, 2011) that has been shown to cause occupational health risks for medical personnel (Sanders et al., 2008). Thus, if nitrous oxide is administered, measures should be taken to ensure that the gas is used properly (e.g. with the use of demand valves), that medical personnel is not exposed to harmful concentrations of the gas (gas scavenging systems or devices destroying the exhaled nitrous oxide, such as Excidio®) and that the patient and medical personnel are adequately guided on how to use the gas administration system.

In conclusion, the overall evidence of the usefulness of inhaled nitrous oxide during BMAB is deficient and more randomized controlled trials are needed before it can be recommended as a routine analgesic and sedative during BMAB in adult populations. In addition, not all patients need pain medication other than a local anaesthetic, so it is advisable to adequately select the patients most prone to pain for administration of inhaled nitrous oxide.

Physicians, nurses and other medical professionals should remember that BMAB is a source of intense, even excruciating pain and anxiety for many patients. The suffering of patients should not be underestimated.

Limitations of the study

Although the association between pain and anxiety was clear, there might have been confounding factors that were left unadjusted. For example, the indication for the procedure varied among

participants; some were healthy bone marrow donors, whereas others had a suspected or diagnosed malignant disease. This probably had an effect on the intensity of pre-procedural anxiety and further on the procedural pain. Possible chronic anxiety or other psychiatric states might have affected the state of pre-procedural anxiety as well.

In Studies I and III – V, the level of experience of the performing physician was adjusted. Level of experience had an effect on pain only in Study IV: puncture pain was slightly lower during BMABs performed by doctors in training compared with specialists. However, contradictory results also exist (Vanhelleputte et al., 2003). The studies were not specifically powered to investigate the difference between doctors in training and specialists, which might explain our finding that the level of experience of the performing doctor did not have a significant effect on pain during all phases of BMAB.

The patients were asked to score the procedural pain during ongoing BMAB (Studies II – IV) or during the post-procedural interview (Studies I, V). The time of the interview itself might have affected the pain scores. In Study I, the pain scores were obtained after the procedure because they were derived from a special pain vocabulary, the learning of which demanded some time and consideration from the patient. In Study V, obtaining the scores during ongoing BMAB would have disturbed the continuous inhalation of the study gas. However, in the post-procedural interview the relief felt after the completed procedure might have reduced the pain scores in Studies I and V. Furthermore, in some cases the patients might have had problems in differentiating between the BMAB phases after the completed procedure, which could have caused further bias in the pain scores.

The success of blinding was not controlled by asking the patients about the group to which they thought they were assigned. In Study III, the performing physician probably felt the difference between syringes containing warmed or room-temperature local anaesthetic. Furthermore, Study III was only patient-blinded. In Studies IV and V, patients might have been able to guess the group into which they were randomized due to possible adverse effects of the study drug. In Study V, the personnel in the procedure room were able to recognize the study group from the difference in the masks in the N_2O/O_2 and placebo groups.

Some factors limit the interpretation of the results of Study IV. As the time latency from receiving the study drug to the beginning of BMAB varied, it is possible that some patients did not fully achieve the pharmacological effects of fentanyl. Furthermore, some patients might have swallowed the drug. The pharmacokinetic profile of sublingual administration is compromised if the drug is swallowed, possibly leading to suboptimal analgesia.

Study V was performed in an unselected group of patients undergoing BMAB. Therefore, the research population was heterogeneous with regard to pain sensitivity and grade of anxiety, and many patients had both low pain scores and low anxiety scores regardless of the study group. Thus, the beneficial effect of nitrous oxide compared with placebo may have been lost due to inclusion of patients not benefiting from supplemental analgesia in the first place. The gas administration demanded very close patient contact by the investigating staff, including instructions on how to hold the mask and how to breathe, and measurement of blood pressure. One cannot exclude that the exceptional nursing attention and attendance of an anaesthesiologist may have influenced the patient's satisfaction with the procedure despite the pain. This assumption is supported by the fact that over 80% of the patients in both study groups would have desired the same gas treatment during their next BMAB.

7 CONCLUSIONS

Based on these studies, the following conclusions can be drawn:

1. The intensity of pain during BMAB is associated with acute pre-procedural state anxiety; a high level of anxiety is related to a higher score of pain. Female gender is associated with higher anxiety scores. Patients with a history of painful or anxiety-provoking BMABs suffer more pain during the subsequent BMABs. Age seems to have an inverse correlation with pain. Pain during BMAB was mostly described with sensory words, although during aspiration affective words were also used.
2. Articaine was as effective as lidocaine as a local anaesthetic for BMAB.
3. Warming and buffering the lidocaine solution that contained adrenaline diminished the intensity of pain during infiltration significantly compared with room-temperature, unmodified lidocaine with adrenaline. However, pain during the subsequent BMAB phases did not differ between patients receiving warmed and buffered lidocaine and those receiving unmodified lidocaine.
4. Sublingual fentanyl administered before BMAB was not effective in reducing pain, as the pain scores were similar in the fentanyl and placebo groups. Adverse effects (dizziness and nausea) were significantly more common in patients receiving fentanyl.
5. Patients receiving inhaled 50% nitrous oxide in oxygen did not have lower pain scores than patients inhaling placebo gas. Nevertheless, nitrous oxide was safe and did not cause serious side-effects or adverse effects on cognition.

8 FUTURE IMPLICATIONS

Pain and anxiety associated with BMAB continue to be significant problems for many patients because nociceptive pain from the richly innervated bone marrow seems to be difficult to eliminate with conscious sedation and analgesia. Patients who are likely to suffer intense pain during BMAB should be recognized in advance, and analgesics and sedatives should be aimed specifically at these patients. Risk factors for pain during BMAB are anxiety, young age and pain and anxiety during previous BMABs. Future studies should concentrate on these patients specifically. The clinical feasibility and effectiveness of analgesics and sedatives, such as inhaled nitrous oxide and benzodiazepines, should be evaluated in randomized, controlled studies performed with patients recognized to be at risk of suffering intense pain during BMAB. Deep conscious sedation and analgesia with, for example, propofol and remifentanil might be useful for those patients most prone to pain. Buffered local anaesthetics should always be used, as buffering markedly reduces pain during infiltration.

Attention directed to the mechanical performance of the procedure could be beneficial as well, as evidence suggests that the powered bone marrow biopsy system causes less pain than conventional puncture methods.

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11 APPENDIX: Letter Digit Coding Test (Finnish version)

W	B	T	P	V	D	G	C	J
1	2	3	4	5	6	7	8	9

Harjoitus:

T	W	C	G	J	V	B	D	P	V	P	T	D	C	B

Testiosa:

P	D	V	B	T	D	P	W	B	J	D	T	C	V	G

J	P	W	C	B	V	J	D	P	C	G	W	T	B	V

T	G	V	B	P	W	C	V	D	J	W	J	G	D	C

G	T	J	C	W	C	G	D	J	P	B	V	T	C	B

W	P	G	V	B	J	C	P	T	C	G	W	J	D	V

J	P	G	D	G	B	J	C	W	V	T	B	D	T	W

T	V	G	W	D	P	V	D	B	J	G	T	J	B	P

W	C	T	V	P	B	J	G	W	D	V	C	T	P	G