



Short Communication

Comparison of articaine and lidocaine for infiltration anaesthesia in patients undergoing bone marrow aspiration and biopsy

Anna-Maria Kuivalainen^{a,*}, Leila Niemi-Murola^b, Tom Widenius^c, Erkki Elonen^c, Per H. Rosenberg^b^a Department of Anaesthesiology and Intensive Care Medicine, University of Helsinki, Post-box 20, FIN-00014 Helsinki, Finland^b Department of Anaesthesiology and Intensive Care Medicine, Helsinki University Hospital, Finland^c Department of Haematology, Helsinki University Hospital, Finland

ARTICLE INFO

Article history:

Received 17 February 2009

Received in revised form 17 April 2009

Accepted 28 April 2009

Available online 26 May 2009

Keywords:

Bone marrow aspiration

Local anaesthesia

Articaine

Lidocaine

Pain relief

Anxiety

ABSTRACT

Infiltration anaesthesia with articaine, a local anaesthetic able to penetrate bone, may relieve procedural pain better than lidocaine in bone marrow aspiration and biopsy. This randomised, double-blind study comprised 150 patients with suspected or known haematologic disease. Either articaine 20 mg/ml (50 patients), articaine 40 mg/ml (49 patients) or lidocaine 20 mg/ml (51 patients), all with adrenaline 5 µg/ml, was infiltrated in volume of 6 ml (sternal manubrium), 8 ml (sternal body) or 10 ml (iliac crest) 2 min before puncture. Numerical rating scale score (median, range) at injection of local anaesthetic was 3.0 (0–10), at bone puncture 2.0 (0–8), at aspiration 3.5 (0–10) and at biopsy (48 patients) 3.0 (0–10). Pre-procedural anxiety, rated on a verbal scale, correlated significantly with experienced pain ($P < 0.01$). Very anxious patients had fewer previous bone marrow examinations ($P < 0.01$) and they experienced more pain during aspiration ($P < 0.05$). In the post-interview 42 patients reported appearance of pain (median 2.0, range 1–7) after 6.2 h, on average, and 15 patients needed oral analgesics. No parameter differed significantly between the groups.

In conclusion, the quality of infiltration anaesthesia for bone marrow punctures and aspiration with articaine and lidocaine was similarly poor. Several patients experienced strong pain which correlated with the degree of anxiety.

© 2009 European Federation of International Association for the Study of Pain Chapters. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Bone marrow aspiration and/or biopsy (BMAB) are often associated with considerable discomfort and pain (Williams and Nelson, 1995; Vanhelleputte et al., 2003; Giannoutsos et al., 2004). Patients having malignant haematologic disorders undergo several times BMABs and adequate pain relief may have a major impact on their quality of life. There are reports of prolonged pain after a painful BMAB (Bain, 2004, 2005).

Lidocaine is commonly used for infiltration anaesthesia in BMAB (Giannoutsos et al., 2004; Park et al., 2008). Articaine, an amide-type local anaesthetic favoured by dentists because of its rapid onset and ability to penetrate bone (Vree and Gielen, 2005), may provide better analgesia for bone penetrating procedures than other currently used local anaesthetic. Articaine blocks isolated nerves better than lidocaine (Potočnik et al., 2006), and in dentistry, the nerve blocking effect of articaine has been similar (Ram and Amir, 2006; Rosenberg et al., 2007; Sherman et al., 2008) or better (Evans et al., 2008) than that of lidocaine. The pur-

pose of this double-blind and randomised study was to compare articaine and lidocaine for relief of pain and discomfort in adult patients undergoing BMAB.

2. Patients and methods

This study was approved by the hospital ethics committee and Finnish National Agency for Medicines. The study included 150 adult out-patients with suspected or known haematologic disease undergoing BMAB (Table 1). Based on the study on maxillary infiltrations of articaine 40 mg/ml with adrenaline and lidocaine 20 mg/ml with adrenaline (Evans et al., 2008) we calculated that for a significant difference ($\alpha = 0.05$, power 80%) at least 35 patients are needed per group.

2.1. Local anaesthetics

Patients were randomized to three different groups: lidocaine 20 mg/ml (Lidocain[®], Orion Pharma, Finland), articaine 20 mg/ml (Ultracain[®], Sanofi-Aventis comp., France) and articaine 40 mg/ml. Adrenaline 5 µg/ml was added to the local anaesthetic solutions before use. The physician performing the aspiration and / or biopsy was blinded to the solution used.

* Corresponding author. Tel.: +358 50 4087629; fax: +358 9 47174017.

E-mail address: anna-maria.kuivalainen@helsinki.fi (A.-M. Kuivalainen).

Table 1
Demographic data of the patients.

	Lidocaine 20 mg/ml (n = 51)	Articaine 20 mg/ml (n = 50)	Articaine 40 mg/ml (n = 49)
Gender (M/F)	27/24	29/21	22/27
Age (years) (mean, range)	54 (18–76)	55 (20–82)	53 (21–80)
Length (cm) (mean, SD)	173.2 (10.9)	172.7 (10.0)	169.3 (10.9)
Weight (kg) (mean, SD)	77.4 (17.4)	76.0 (16.3)	75.0 (16.6)
Site of aspiration (no. of patients)			
–Manubrium sterni	23	18	21
–Corpus sterni	6	2	3
–Crista iliaca	22	30	25
Diagnoses (no. of patients)			
–Non-Hodgkin lymphoma	4	6	9
–Myeloma	4	0	1
–Leukemia	28	29	23
–Myelodysplastic syndrome	2	3	3
–Healthy donor	4	1	0
–Other	9	9	13
Performed by			
–Doctors in training (no. of patients)	12	14	14
–Specialists (no. of patients)	39	36	35

2.2. Local anaesthetic infiltration and punctures

Before the procedure, the skin, the subcutaneous tissue and the periosteum of the bone were anaesthetized by infiltrating anaesthetic solution with a 21 G needle using a third of the scheduled volume into each compartment. The volume of the solution was 6 ml for bone marrow aspiration at the sternal manubrium, 8 ml for aspiration of the sternal body and 10 ml for aspiration and/or biopsy of the iliac crest. Two minutes after infiltration of the local anaesthetic drug, a 14–16 G bone marrow aspiration needle was inserted into the marrow. If the patient was also scheduled for biopsy, this was always performed as the last step. The bone marrow biopsy was taken from the iliac crest, near the site of the preceding aspiration, using an 8 G needle (Angiotech, T-lock™, Gainesville, FL, USA). If anaesthesia was not adequate for the insertion of the aspiration needle, half the initially used amount was administered for the second infiltration.

2.3. Tests for anxiety and pain

Before the bone marrow procedure the anxiety level of the patient was evaluated on a verbal scale 0–4, where 0 = no anxiety, 4 = very anxious. Emotions such as nervousness, fear, tension and stress were not separated in the pre-procedural examination and, thus, they were covered under the “anxiety” score. The patients received sedative premedication (diazepam orally) by request.

During the procedure the effectiveness of anaesthesia was evaluated at predetermined times using the numeral rating scale (NRS) (0 = no pain, 10 = worst pain imaginable). The analgesic effect was evaluated during application of the local anaesthetic, during puncture, during bone marrow aspiration, during bone marrow biopsy and immediately after the procedure. Also the grade of subjective unpleasantness during puncture and aspiration was registered on the scale 0–4 (0 = no feeling at all, 4 = very unpleasant experience).

2.4. Post-intervention interviews

Thirty minutes after the bone marrow aspiration and/or biopsy the patients were interviewed. The interviewer was blinded to the used local anaesthetic solution. The patients' present general condition and the pain score were recorded. They were also asked if the pain during injection was stronger or milder than expected.

After 24 h the patient was interviewed by telephone by a blinded member of the study group. Structured questions about

general condition, haematomas or bleeding at the puncture site, the grade of pain and the need for medicines were asked. The patient was also asked to compare the painfulness of the procedure to that of the previous bone marrow samplings. The patient was once more contacted after 2 weeks and again the general condition, and grade and location of the possible pain were evaluated.

2.5. Statistics

The demographic data was analyzed using ANOVA and non-parametric data with non-parametric tests including Kruskal–Wallis and Mann–Whitney U. Spearman Rank correlation was used with parametric data.

3. Results

Patient characteristics were comparable between the three local anaesthetic groups (Table 1). Twenty-nine patients (19.3%) were first-timers. Eight patients took part in the study twice and one patient three times. Forty of the procedures were performed by doctors in training, the rest by specialists.

3.1. Anxiety

Prior to the procedure, the patients expressed varying level of anxiety on the scale 0–4 (median 1.00, mean 1.28, SD 1.43, range 0–4) without difference between the groups. Sixty-eight patients (45.3%) were not anxious at all (score 0), while 16 patients (10.7%) were very anxious (score 4). Six patients received diazepam 5–10 mg orally prior to the procedure. In comparison with those patients having had previous experience from the procedure, the level of anxiety was higher ($P < 0.01$) in patients having their first BMAB.

3.2. Pain experience

The median pain score on the NRS at the injection of the local anaesthetic was 3 (mean 3.5, range 0–10), the first-timers reporting higher scores than the others ($P < 0.05$). In eight patients (four patients in the lidocaine 20 mg/ml group and four patients in the articaine 20 mg/ml group), a second local anaesthetic infiltration was made because of inadequate anaesthesia as tested by pricking with the bone marrow aspiration needle.

Table 2
Number of patients with pain score ≥ 4 , or < 4 , on the Numerical Rating Scale (NRS, 0 = no pain, 10 = worst imaginable pain) at different steps of bone marrow aspiration or biopsy. There were no statistically significant differences between the groups.

	Lidocaine 20 mg/ml (N = 51)		Articaine 20 mg/ml (N = 50)		Articaine 40 mg/ml (N = 49)		Tot. (150 patients)	
	NRS < 4	NRS ≥ 4	NRS < 4	NRS ≥ 4	NRS < 4	NRS ≥ 4	NRS < 4	NRS ≥ 4
Puncture, no. of patients	39 (76.5%)	12 (23.5%)	38 (76.0%)	12 (24.0%)	43 (87.8%)	6 (12.2%)	120 (80.0%)	30 (20.0%)
Aspiration, no. of patients	22 (43.1%)	29 (56.9%)	28 (56.0%)	22 (44.0%)	26 (53.1%)	23 (46.9%)	76 (50.7%)	74 (49.3%)
Biopsy, no. of patients	6 (50.0%)	6 (50.0%)	9 (45.0%)	11 (55.0%)	10 (62.5%)	6 (37.5%)	25 (52.1%)	23 (47.9%)

The median NRS pain score at the insertion of the aspiration needle was 2 (mean 2.1, range 0–8), and at aspiration 3.5 (mean 3.9, range 0–10). The bone marrow biopsy was performed to 48 patients and the median NRS score at these biopsies was 3.0 (mean 3.5, range 0–10). Thirty patients (20.0%) reported 4, or higher pain scores on the NRS during the puncture with the aspiration needle (Table 2), with no significant difference between the groups. A still larger proportion of the patients (49.3% and 47.9%, respectively) found the BMAB to be painful (NRS score ≥ 4).

In the articaine 40 mg/ml group there was a smaller proportion of patients who experienced a considerable degree of pain (NRS score ≥ 4) at the puncture with the aspiration needle and at the biopsy in comparison with the other two groups (Table 2), but this, as well the pain experiences associated with the other procedural steps in the three local anaesthetic groups were not statistically significantly different.

3.3. Post-intervention interviews

In the 24-h telephone interview, 12 patients (8.0%) reported that there was a small haematoma at the puncture site and two patients reported the occurrence of a small haemorrhage at the puncture site. Median NRS of all patients at this time was 0.0 (mean 0.65, range 0–7). After the bone marrow examination 42 patients started to feel pain at the puncture site in 6.2 h, on average, with a median NRS score of 2.0 (mean 2.9, range 1–7). Fifteen of these patients needed pain-medication within 24 h from the procedure, mostly oral paracetamol or ibuprofen. Seventy-three patients (48.7%) reported that the injection of the anaesthetic solution had been less painful than expected. Ninety-five patients (63.3%) told that the procedure had been less painful and after-pain experience had been less uncomfortable in 62 patients (41.3%) than expected. Sixteen patients (10.6%) thought that the procedure was more painful and 15 patients (10.0%) experienced more pain afterwards than they had expected. There were no significant differences between the local anaesthetic groups, but both the pain during the aspiration procedure ($P < 0.05$) and the post-procedural recollection of pain ($P < 0.01$) correlated significantly with pre-procedural anxiety. After 2 weeks, 143 patients (95.3%) reported good general condition, median NRS was 0.0 (mean 0.15, range 0–7.5) and 139 patients (92.6%) scored 0.

4. Discussion

There was no significant difference in the effect between the three local anaesthetic solutions. At each stage of the performance of the bone marrow sampling, starting from the initial local anaesthetic infiltration, there were several patients reporting strong pain (NRS score ≥ 4) in each group, including also a few patients in each group with very strong or excruciating pain (NRS score 8–10).

The pain intensity during bone marrow aspiration correlated with the degree of pre-procedural anxiety, as recently shown also by Lidén and co-workers (2009), which again was inversely related to how many times the patient had already experienced a BMAB, i.e., the first-timers were more anxious and reported high pain scores.

The rapid onset of action and the good bone penetrating ability of articaine, which seems to benefit dental patients (Vree and Gielen, 2005), could not be demonstrated in our BMAB patients. In the case of the bone penetrating puncture with the aspiration needle there was a possible analgesic efficacy trend in favour of the stronger articaine solution, i.e., only 12.2% of the patients reported pain score ≥ 4 in the articaine 40 mg/ml group while the corresponding percentage was approximately the double in the other groups (NS). Furthermore, none of the patients receiving articaine 40 mg/ml needed another local anaesthetic infiltration, while this was needed in four patients in each of the other groups. It cannot be excluded that allowing the local anaesthetic to act longer than 2 min before penetrating the bone, could have improved the anaesthetic effect.

The pain and discomfort which originate from stretching and disruption of the innervated bone marrow (Calvo and Forteza-Vila, 1969; Mach et al., 2002) during the aspiration may be impossible to eliminate only by local anaesthetic infiltration of the puncture site. Relatively thick needles (14–16 G) are considered best suited for the aspiration of large bone marrow blood volumes. On the other hand, the biopsy needles are usually about twice thicker than the aspiration needles, 8 G in our department. Although there was a slightly lower proportion of patients in the articaine 40 mg/ml group that reported strong pain (≥ 4 on the NRS) during biopsy compared to the other groups, conclusions cannot be made because of the variable time latency from local anaesthetic infiltration to the biopsy and due to the small number of biopsy patients.

The need for additional analgesics in BMAB has been stressed repeatedly (Vanhelleputte et al., 2003; Steedman et al., 2006). Vanhelleputte and colleagues, who applied lidocaine 20 mg/ml for local anaesthesia, were able to reduce the pain during bone marrow aspiration significantly by premedicating the patient with oral tramadol (Vanhelleputte et al., 2003). In their study, interestingly, pre-procedural educational information about the procedure or previous experience from the procedure did not seem to reduce the pain. This contrasts our findings of less pain in the non-premedicated patients with previous experience of the procedure.

Anxiety is related to higher pain perception both in experimental conditions in volunteers (Keogh et al., 2006) and in patients undergoing surgery for breast cancer (Özalp et al., 2003). This logical concept was clearly seen in our study, too, where those patients who had their first bone marrow examination were very anxious and found the procedure more painful than the more experienced ones.

4.1. Limitations

BMABs performed by senior haematologists are usually less painful than those performed by trainees (Vanhelleputte et al., 2003). Since only 40 of the bone marrow examination procedures in our study were performed by non-specialist haematologists (not randomized), no detailed subgroup analysis regarding a possible relationship between the doctors' procedural experience and patients' pain and anxiety was made. The local anaesthetic infiltration and the latency until the start of the bone marrow puncture were standardized and timed using a stopwatch by a research assistant, which means that the experience (specialist vs. trainee) should not have

any significant confounding impact at least on the quality of infiltration anaesthesia and on bone puncture-related pain results.

Rating the degree of anxiety on a verbal zero-to-four point scale was probably too simplified because we did not score separately all emotional and somatic signs and symptoms associated with anxiety, as recommended e.g., by Spielberger and Vagg (1984). However, despite this simplification we were probably successful in rating the general emotional state of the patients immediately before BMAB.

5. Conclusions

Infiltration of articaine 20 mg/ml, articaine 40 mg/ml and lidocaine 20 mg/ml (all with adrenaline) produced similarly inadequate anaesthesia for BMAB. The infiltration of the potent local anaesthetics at the site of the puncture was also often very painful. A high level of overall anxiety correlated with the degree of pain experienced during bone marrow aspiration.

References

- Bain BJ. Bone marrow biopsy morbidity and mortality: 2002 data. *Clin Lab Haematol* 2004;26(5):315–8.
- Bain BJ. Bone marrow biopsy morbidity: review of 2003. *J Clin Pathol* 2005;58(4):406–8.
- Calvo W, Forteza-Vila J. On the development of bone marrow innervation in new born rats as studied with silver impregnation and electron microscopy. *Am J Anat* 1969;126(3):355–71.
- Evans G, Nusstein J, Drum M, Reader A, Beck M. A prospective, randomized, double-blind comparison of articaine and lidocaine for maxillary infiltrations. *J Endod* 2008;34(4):389–93.
- Giannoutsos I, Grech H, Maboreke T, Morgenstern G. Performing bone marrow biopsies with or without sedation: a comparison. *Clin Lab Haematol* 2004;26(3):201–4.
- Keogh E, Barlow C, Mounce C, Bond FW. Assessing the relationship between cold pressor pain responses and dimensions of the anxiety sensitivity profile in healthy men and women. *Cognitive Behav Ther* 2006;35(4):198–206.
- Lidén Y, Landgren O, Arnér S, Sjölund KF, Johansson E. Procedure-related pain among adult patients with hematologic malignancies. *Acta Anaesthesiol Scand* 2009;53(3):354–63.
- Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, et al. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 2002;113(1):155–66.
- Özalp G, Sarioglu R, Tuncel G, Aslan K, Kadiogullari N. Preoperative emotional states in patients with breast cancer and postoperative pain. *Acta Anaesthesiol Scand* 2003;47(1):26–9.
- Park SH, Bang SM, Nam E, Cho EK, Shin DB, Lee JH, et al. A randomized double-blind placebo-controlled study of low-dose intravenous Lorazepam to reduce procedural pain during bone marrow aspiration and biopsy. *Pain Med* 2008;9(2):249–52.
- Potočník I, Tomšič M, Sketelj J, Bajrović FF. Articaine is more effective than lidocaine or mepivacaine in rat sensory nerve conduction block in vitro. *J Dent Res* 2006;85(2):162–6.
- Ram D, Amir E. Comparison of articaine 4% and lidocaine 2% in paediatric dental patients. *Int J Paediatr Dent* 2006;16(4):252–6.
- Rosenberg PA, Amin KG, Zibari Y, Lin LM. Comparison of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine when used as a supplemental anesthetic. *J Endod* 2007;33(4):403–5.
- Sherman MG, Flax M, Namerow K, Murray PE. Anesthetic efficacy of the Gow–Gates injection and maxillary infiltration with articaine and lidocaine for irreversible pulpitis. *J Endod* 2008;34(6):656–9.
- Spielberger CD, Vagg PR. Psychometric properties of the STAI: a reply to Ramanaiah, Franzen, and Schill. *J Pers Assess* 1984;48(1):95–7.
- Steedman B, Watson J, Ali S, Shields ML, Patmore RD, Allsup DJ. Inhaled nitrous oxide (Entonox) as a short acting sedative during bone marrow examination. *Clin Lab Haematol* 2006;28(5):321–4.
- Vanhelleputte P, Nijs K, Delforge M, Evers G, Vanderschueren S. Pain during bone marrow aspiration: prevalence and prevention. *J Pain Symptom Manage* 2003;26(3):860–6.
- Vree TB, Gielen MJ. Clinical pharmacology and the use of articaine for local and regional anaesthesia. *Best Pract Res Clin Anaesthesiol* 2005;19(2):293–308.
- Williams WJ, Nelson DA. Examination of the marrow. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, editors. *Williams Hematology*. 5th ed. New York: McGraw-Hill; 1995. p. 15–22.