Intraosseous lidocaine provides effective analgesia for percutaneous vertebroplasty of osteoporotic fractures

[L'administration intra-osseuse de lidocaïne procure une analgésie efficace pendant la vertébroplastie percutanée de fractures ostéoporotiques]

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Purpose: To assess the safety and efficacy of intraosseous lidocaine (IL), in comparison with *iv* nalbuphine and propacetamol (NP) for analgesia during percutaneous vertebroplasty (PV) in order to avoid general anesthesia in elderly patients.

Methods: Patients (age 68 ± 13 yr, weight 66 ± 6 kg) undergoing PV for osteoporotic fractures were randomized prospectively into two groups: NP (n=50) and IL (n=50). All patients were premedicated (oral hydroxyzine 1 $mg \cdot kg^{-1}$) and had skin infiltration with 5 mL of 1% lidocaine prior to vertebral puncture. Thirty minutes before the procedure, Group NP received, in a blinded manner, 50 mL of *iv* nalbuphine (0.3 $mg \cdot kg^{-1}$) and propacetamol (30 $mg \cdot kg^{-1}$) while Group IL received 50 mL of *iv* saline. During vertebral puncture, Groups NP and IL received, in a blinded manner, 1 $mL \cdot 10\ kg^{-1}$ of intraosseous saline and 1% lidocaine respectively. Pain was assessed during vertebral puncture and cement injection with a four-point verbal rating scale. Additionally, lidocaine plasma kinetics were obtained in 11 IL patients.

Results: Analgesic efficacy was similar in the IL and NP groups (85 *vs* 84%). Group NP had more side effects. Lidocaine peak recorded concentration was 2.6 ± 0.1 $\mu g \cdot mL^{-1}$ i.e., about three times less than the reported toxic limits.

Conclusion: IL is as effective as the association of *iv* NP for analgesia in PV. However, considering that both protocols were insufficient in about 15% of cases, other modalities are needed to further improve analgesia and avoid general anesthesia during vertebroplasty.

Objectif : *Évaluer l'efficacité et la sécurité d'une injection intra-osseuse de lidocaïne (IL) comparée à une sédation iv à base de nalbuphine et de propacétamol (NP) pour l'analgésie des vertébroplasties percutanées (VP) afin d'éviter l'anesthésie générale chez des patients âgés.*

Méthode : *Cent patients devant subir une VP sont prospectivement randomisés en deux groupes : 30 min avant la procédure, le groupe NP reçoit en aveugle 50 mL d'un mélange iv de nalbuphine (0,3 $mg \cdot kg^{-1}$) et de propacétamol (30 $mg \cdot kg^{-1}$) tandis que le groupe IL reçoit 50 mL iv de solution salée. Tous les patients reçoivent une prémédication avec de l'hydroxyzine (1 $mg \cdot kg^{-1}$) et ont une infiltration cutanée avant la ponction vertébrale avec 5 mL de lidocaïne 1 %. Pendant la ponction vertébrale, le groupe NP reçoit à son tour une solution salée alors que le groupe IL reçoit 1 $mL \cdot 10\ kg^{-1}$ de lidocaïne 1 %. La douleur est évaluée pendant l'opération par une échelle verbale à quatre degrés. Un profil cinétique de la lidocaïne plasmatique est réalisé chez les 11 premiers patients.*

Résultats : *Une analgésie efficace est constatée dans les groupes IL et NP dans 85 et 84 % des cas respectivement. Le groupe NP présente plus d'effets secondaires. Le pic plasmatique de lidocaïne circulante est 2,6 ± 0,1 $\mu g \cdot mL^{-1}$ soit trois fois moins que les limites toxiques.*

Conclusion : *La lidocaïne intra-osseuse procure la même analgésie que l'association iv de NP pour les VP. Étant donné que les deux protocoles sont insuffisants dans environ 15 % des cas, d'autres associations sont nécessaires pour améliorer encore l'analgésie et éviter l'anesthésie générale.*

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Accepted for publication September 10, 2001.
Revision accepted November 15, 2001.

PERCUTANEOUS vertebroplasty (PV) is a new technique designed to consolidate pathologic vertebral bodies through the injection of orthopedic cement *(methylmethacrylate)* under fluoroscopic guidance.[1,2] Consolidation provides rapid pain relief to most lytic and painful vertebral body lesions secondary to osteoporosis, hemangiomas and metastatic diseases.[3] The procedure is short (about one hour) but painful during vertebral puncture and cement injection.[2] The duration of each of these painful moments of PV is about five minutes. Different anesthetic techniques have been proposed to control pain during vertebroplasty, but all have important limitations. On the one hand, general anesthesia adds its own risks[4] and prevents clinical assessment of the patient during the procedure. Sedative analgesia with opioids and benzodiazepines, which is currently the main analgesic technique for PV,[2] can be hazardous, specially with the patient in the prone position, as conventional systemic opioid administration entails the potential risk of respiratory depression. The rationale behind the intraosseous injection of a local anesthetic involves a regional blockade of the bone nociceptive fibres, thereby avoiding the major complications of sedation or general anesthesia. In 1947, Orlov performed the first intraosseous anesthesia with lidocaine on a patient's arm after excluding the systemic circulation by a tourniquet.[5] This technique has since been validated by others.[6] However, in the case of intravertebral injection, complete exclusion of the systemic circulation is impossible and consequently, toxicity of the local anesthetic becomes an important concern.

The present study was undertaken to assess both the safety and efficacy of analgesia with intraosseous lidocaine (IL), compared to *iv* nalbuphine associated with propacetamol, for PV of osteoporotic fractures.

Methods

Patient selection

After Institutional Review Board approval and informed consent, 100 ASA physical status I–III patients scheduled to undergo PV for osteoporotic vertebral compression fractures (VCF) were included in this prospective study. The fractures were associated with age-related osteopenia in 85 patients and steroid-induced in the 15 others. Diagnostic criteria for inclusion were: (1) patients suffering from back pain and refractory to a four-week medical treatment (bed rest, analgesics and bracing); (2) physical examination confirming VCF pain which is usually localized to the area of fracture, worsens with weightbearing and improves when the patient lies down; (3) magnetic resonance imaging (MRI) or unenhanced computed tomography scan showing vertebral body collapse and continuity of the posterior vertebral wall. Additionally, an acute VCF can be identified on T1-weighted sagittal sequence of MRI by a low (dark) signal of the vertebral body. The decision to perform a vertebroplasty was made by a multidisciplinary team including a neuroradiologist, a rheumatologist, an orthopedist, a neurosurgeon, and an anesthesiologist. The procedure was discussed with the patients and the potential benefits and risks outlined. The potential complications specified were bleeding at the puncture site, bone infection, diffusion of cement to soft tissues, spinal canal or veins with the risk of neural damage and pulmonary embolism. The thoracic region approach presents an additional risk of pneumothorax. The patients were also informed of the possibility of emergency decompressive surgery in case of important leakage of cement. Patients with coagulation disorders or allergic to any of the drugs used in the study and those with severe renal, hepatic and cardiorespiratory diseases were excluded.

Analgesic protocols and trocar insertion

The patients were randomly allocated to one of the two groups: IL (Group IL, n=50) and *iv* nalbuphine associated with propacetamol (Group NP, n=50). Randomization was done at the department of pharmacology by drawing lots composed of 100 inscriptions (50 of each group) sealed in untitled envelops. The drugs were prepared by the same pharmacologist who was informed only of the patient's weight. With the exception of the first 11 lidocaine patients who had plasma lidocaine measurements, the patient, anesthesiologist and neuroradiologist were blinded to the *iv* and intraosseous solutions used. One hour before the procedure, each patient was premedicated with oral hydroxyzine (1 $mg \cdot kg^{-1}$). On arrival at the radiology unit, a 18-gauge cannula was placed in a peripheral arm vein for fluid and drug infusion. The procedure was performed in a strictly sterile manner. The patients were placed in a prone position with a cushion under the abdomen and breathing room air. Thirty minutes before the injection of cement, group NP received, in a blinded manner, an infusion of 50 mL of nalbuphine (0.3 $mg \cdot kg^{-1}$) associated with propacetamol (30 $mg \cdot kg^{-1}$) over ten minutes while group IL received saline intravenously. The intraosseous injections, concomitant with trocar insertion, were carried out by a senior neuroradiologist (four participated in this study). First, local anesthesia of the trocar insertion tract (from skin to periosteum) was performed with 5 mL of 1% lidocaine using a 21-

gauge needle. Then a 3-mm-diameter, 10-cm long trocar (Escoffier™, Thonon Les Bains, France) was introduced up to the level of the periosteum. A transpedicular route was selected for vertebral body puncture using progressive rotating movements of the trocar. Each progression of the trocar was accompanied by the injection, in a blinded manner, of 1 to 2 mL of a solution containing 1 mL·10 kg^{-1} of either 1% lidocaine (group IL) or saline (group NP) until final placement in the middle of the vertebral body. All patients received the full dose of the solution without flushing considering the small dead space of the trocar shaft (0.5 mL).

Cement injection and monitoring

The trocar was left in place after intraosseous injection of the local anesthetic. Then, the cement mixture (Antibiotic Howmedica, Shannon Co. clair, Republic of Ireland) was prepared with 20 mL of methylmethacrylate powder, 5 mL of liquid methylmethacrylate and 1 g of radiopaque tungsten powder. When the mixture had the viscosity of toothpaste (i.e., about five minutes later), 3 to 10 mL were injected through the trocar using luerlock syringes. The procedure was performed under fluoroscopic guidance with real time imaging during injection of cement to determine the degree of vertebral filling and to detect possible cement leaks. The injection was stopped when the cement reached the posterior vertebral wall or whenever it diffused outside the vertebral body. Cement injection was also stopped immediately if the patients complained of radicular symptoms. Blood pressure, heart rate (HR) and pulse oximetry were monitored throughout the procedure (Eagle 3000™, Marquette medical systems, Milwaukee, USA). Adverse effects and their appropriate management were noted.

Assessment of pain and patient satisfaction

Pain was assessed by means of a four-point verbal rating scale (VRS) adapted from Keele's pain chart[7] [0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain]. The scores were obtained at four different phases: baseline, trocar insertion, trocar in correct position, and finally during cement injection. Repeated measures were performed at each phase and the highest pain score was retained. Analgesic efficacy was defined by a VRS <2. Patients with severe pain during trocar insertion or cement injection received sedation with propofol (0.5 mg·kg^{-1}) in order to prevent unintentional movement. Patient satisfaction was assessed upon leaving the recovery room by a staff nurse, using a satisfaction score (excellent=4, very good=3, good=2, fair=1 or poor=0). The nurse also noted the reasons of dissatisfaction: inadequate pain relief, nausea, vomiting, pruritis, headache, numbness, restlessness, somnolence, blurred vision or any other complaint.

Lidocaine plasma levels

Intraosseous injections of lidocaine were not blinded in the first 11 patients in order to measure lidocaine plasma levels. Following intraosseous injection, venous blood samples of 3 mL were drawn in heparinized tubes at five, ten, 20, 30, 40 and 60 min in each of the 11 patients. Samples were kept vertically, in ice, until centrifugation, and plasma was kept frozen at -70°C until analysis. Plasma lidocaine concentrations were measured using enzyme multiple immunoassay technique (EMIT® Syva Lab Processor 6000 Series, San Jose, CA, USA). Plasma lidocaine levels are expressed as µg·mL^{-1} and the limit of detection was 0.09 µg·mL^{-1}.

Statistical analysis

Age and weight were analyzed by unpaired t tests. Hemodynamic parameters were compared by repeated measures of analysis of variance followed by Tukey *post hoc* test. Analgesic efficacy and patient satisfaction were compared by Chi-square or Fischer's exact test where appropriate. For all comparisons, a P value <0.05 was considered significant.

Results

Clinical outcomes

There were no significant differences between the two treatment groups with respect to age, weight and duration of the procedure (Table I). Analgesic profiles of the IL and NP groups were similar (Table II). Both techniques provided satisfactory pain relief during trocar insertion and cement injection. Severe pain requiring propofol sedation was observed in five IL patients and six in the NP group specially during trocar insertion. Two patients in the IL group had bradycardia (42 and 44 beats·min^{-1}; baseline 75 and 79 beats·min^{-1} respectively) immediately after injection of lidocaine and were managed by 0.5 mg of *iv* atropine in each case. In the NP group, four patients with nausea and one with vomiting required the *iv* injection of metoclopramide 10 mg. After installation in the prone position, two NP patients developed desaturation (SpO_2 90% and 91%; baseline 98% each) for more than two minutes, warranting oxygen administration (6–10 L·min^{-1}) via a face mask. During the injection of cement, slight modifications of mean arterial pressure and HR were observed in the two groups. These changes were transient

TABLE I Demographic and analgesic profiles of the two treatment groups

	IL (n=50)	*NP (n=50)*
Age (yr)	68 ± 12	67 ± 13
Sex: male/female (*n*)	23/27	21/29
Weight (kg)	66 ± 6	66 ± 5
ASA physical status: I/II/III (*n*)	0/21/29	2/22/26
Duration of vertebroplasty (min)	60 ± 15	62 ± 15
Vertebral body concerned: thoracic/lumbar (*n*)	26/24	28/22
Quantity of cement injected (mL)	5 ± 1.5	4 ± 1.3
Propofol used to prevent unintentional movements (mg)	33.3 ± 1.4	32.0 ± 3.0

No statistically significant difference between groups.
IL=intraosseous lidocaine; NP=nalbuphine and propacetamol.

TABLE II Pain assessment during percutaneous vertebroplasty

		Verbal rating scale			
Period	*Group*	*0 (n)*	*1 (n)*	*2 (n)*	*3 (n)*
Baseline	I L	48	2	0	0
	NP	49	1	0	0
Trocar insertion	I L	23	18	5	4
	NP	20	25	2	3
Trocar in place	I L	43	4	3	0
	NP	42	5	3	0
Cement injection	I L	38	5	6	1
	NP	27	13	7	3

Pain was assessed by means of a four-point verbal rating scale: 0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain. No statistically significant difference between groups. IL=intraosseous lidocaine; NP=nalbuphine and propacetamol.

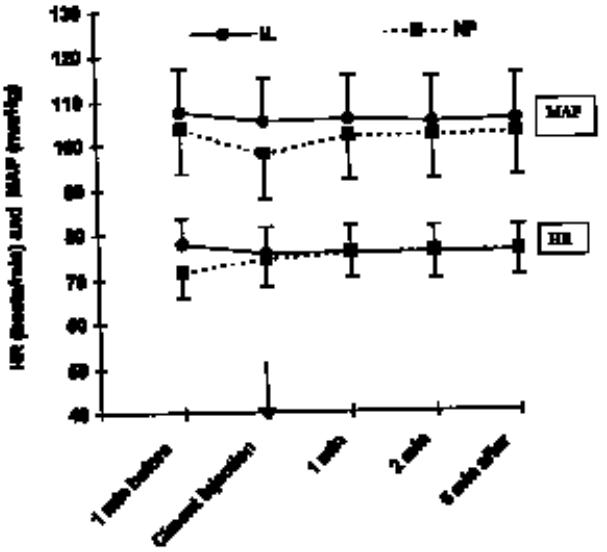

FIGURE 1 Cardiovascular changes during percutaneous vertebroplasty with cement injection into the vertebral body. The changes were not statiscally significant. Data are presented as mean ± SD.

(Figure 1). Overall patient satisfaction rates were 90% and 86% in groups IL and NP respectively (Figure 2). Dissatisfaction with the analgesic techniques were qualified by the terms: painful (one patient in group IL, one in group NP), vomiting (one patient in group NP) and somnolence (two patients in group NP). Discomfort in the prone position was expressed by the remainder of the unsatisfied patients.

Vertebral fracture pain subsided within the first hour after vertebroplasty in 95% of the patients with improved mobility the next day. However, in 5% of the patients, only moderate pain relief was observed within 24 hr. A few incidents associated with vertebroplasty were observed: diffusion of cement to the intervertebral disc (*n*=2), spinal canal (*n*=1) and paravertebral veins (*n*=3). However the patients remained asymptomatic on postoperative follow- up. Recurrent fractures involving the adjacent vertebral bodies (not initially detected) were observed in 12% of patients within three months of vertebroplasty, specially in patients who had persistent pain. A new procedure was performed in these patients without including them in the protocol.

Lidocaine plasma concentrations

Complete data on lidocaine plasma levels were obtained in a subset of 11 patients in the IL group. The mean dose of lidocaine used in these patients was 125 ± 10 mg. This included the 50 mg lidocaine used for skin and periosteal infiltration. Two pharmacokinetic profiles were present (Figure 3). A Tmax for lidocaine concentration (2.0 ± 0.2 $\mu g \cdot mL^{-1}$) was noted at 20 min in seven patients. In the four other patients, the pharmacokinetic profile was similar to an intravascular injection. The Tmax was unknown because at five minutes the plasma lidocaine concentrations of these four patients were already falling and it is likely that the true peak was missed by not measuring the lidocaine concentration earlier. In these patients the recorded lidocaine concentration at five minutes was 2.6 ± 0.1 $\mu g \cdot mL^{-1}$. Pain was mild or absent in the 11 patients. Lidocaine concentrations, obtained at five minutes, in the two patients who developped bradycardia were 2.4 and 2.7 $\mu g \cdot mL^{-1}$ respectively. No other symptoms related to lidocaine toxicity (headache, numbness, restlessness, blurred vision) were observed.

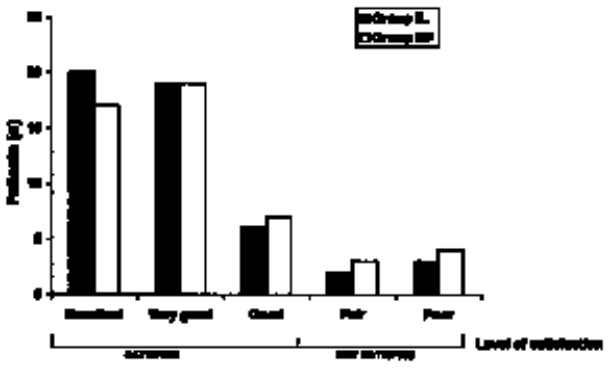

FIGURE 2 Patients' overall satisfaction with the two treatment modalities. No significant difference was observed between the groups. P=0.9 intraosseous lidocaine (IL) *vs* nalbuphine and propacetamol (NP).

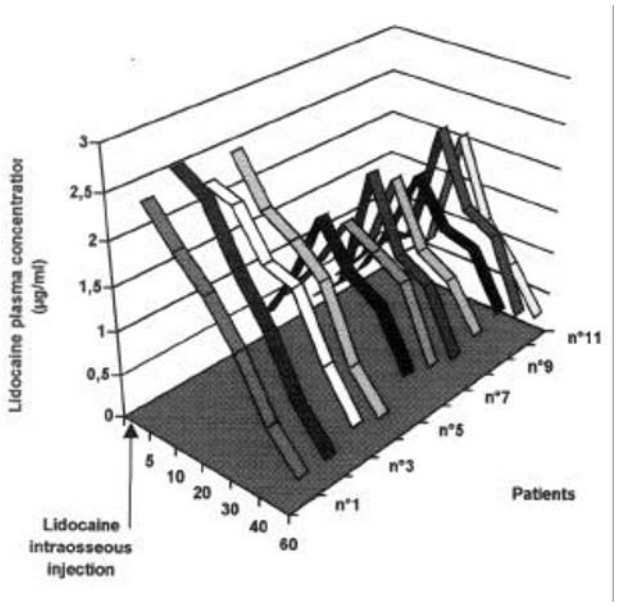

FIGURE 3 Lidocaine plasma concentrations following injection in the osteoporotic vertebral body.

Discussion

Our study indicates that both IL and *iv* association of NP are relevant analgesic alternatives to general anesthesia for patients who undergo PV. The protocols were applied only in patients with well documented osteoporotic vertebral compression fractures without malignancy or any other spinal entities. Patients with severe cardiorespiratory, renal and hepatic disease were intentionally excluded as they required dose adjustments which would have introduced a bias in our study. The underlying pain mechanisms during vertebroplasty have not been clearly elucidated. Sensitization of neural elements by direct pressure[8] or by heat generated during cement polymerization[9] are plausible mechanisms. They produce nociceptive inputs of high intensity and short duration and alternatives to general anesthesia must take this into account.

Our results show that trocar insertion was more painful than cement injection and suggest the need for more effective strategies towards this target. These strategies would imply an understanding of the anatomy of the vertebral body and its interactions with surrounding tissues. Innervation of the vertebral body is provided by the sinu-vertebral nerve, associated with the sympathetic system.[10–12] It is a highly vascularized zone in which the intraosseous vertebral veins form a freely communicating valveless network with paravertebral and extradural plexus veins.[1 3] The rationale of intravertebral injection of lidocaine involves a regional blockade of bone nociceptive inputs. In a recent study, Chandler *et al.*[1 2] reported effective pain relief of osteoporotic vertebral fractures by blockade of the gray ramus communicans nerve, a terminal branch of the sinovertebral nerve, which provides sensory input to the disc and vertebral body. However, these authors injected both lidocaine and triamcinolone to produce the nerve block. It is difficult, therefore to dissociate the analgesic effects of each of these drugs. Our study did not precisely determine the mechanism(s) of pain relief during vertebroplasty.

The highest plasma concentration of lidocaine recorded in this study (2.7 $\mu g \cdot mL^{-1}$) was three-fold below the reported toxic values.[14,15] In a subgroup of four patients who had a pharmacokinetic profile similar to an intravascular injection, the true peak concentrations were unknown because the first plasma levels obtained at five minutes were already falling. It was difficult for us to obtain reliable blood samples earlier because the study design required a slow and progressive (over two minutes) injection of lidocaine. However, pharmacokinetic studies in critically ill patients and during general anesthesia have shown that *iv* injection of 1.5 $mg \cdot kg^{-1}$ or 1 $mg \cdot kg^{-1}$ of lidocaine produces immediate (within 0.5 min) peak plasma concentrations of about 5 $\mu g \cdot mL^{-1}$ without clinical signs of toxicity.[16,17] Thus, even if we consider the intraosseous injection as an *iv* one, the potential risks of such an injection (1 $mg \cdot kg^{-1}$ over two minutes) seems low.

No sympathetic blockade was produced by the intraosseous injection of lidocaine, as demonstrated by the hemodynamic stability in our patients during the

procedure. This is probably because of the low dose of lidocaine used. However, it is important to distinguish between the hemodynamic variations associated with anesthesia and those associated with methylmethacrylate. A transient decrease in blood pressure and HR is generally observed during the injection of cement.[18,19] Hypotension has been attributed to vasodilatation as a result of histamine liberation, or to myocardial depression which are supposed consequences of methylmethacrylate toxicity.[20] More recent studies however, attributed these hemodynamic changes to arterial microemboli which could be visualized by transoesophageal echocardiography.[21] Embolization is proportional to intramedullary pressure[22] and the bone surface involved.[23] Compared with hip arthroplasty, the hemodynamic consequences of methylmethacrylate injection are minimized in PV because of the smaller bone surface involved.

Although small quantities of lidocaine and cement are administered, cautious monitoring of neurologic, hemodynamic and respiratory status of each patient is crucial with regard to potential complications. The choice of lidocaine in this study was motivated essentially by its short half-life,[14] in agreement with the duration of the procedure, and its low intrinsic toxicity compared with other amide local anesthetics. We compared IL anesthesia with *iv* analgesia associating NP. Nalbuphine, an agonist-antagonist semi-synthetic opioid, was chosen rather than conventional opioids, because of its capacity to exhibit a 'ceiling effect' for respiratory depression.[24] However, analgesic efficacy is also limited by this 'ceiling effect'.[25] Therefore, we associated propacetamol to low-dose nalbuphine in order to improve analgesia and reduce side effects. Additionally, propofol sedation was used to prevent unintentional movement in the presence of severe pain. No significant bias in data analysis was introduced as the proportion of severe pain was comparable in the two groups.

Even though perfect analgesia was obtained only in 84% and 85% of patients in groups IL and NP respectively, satisfaction levels were high in the two groups. This paradoxical effect may be explained by the rapid improvement in patient comfort after consolidation of the pathologic vertebral body. Therefore overall satisfaction is probably related to both analgesic medication and PV, suggesting that patient satisfaction score is not a very effective means to evaluate a procedure.

The use of VRS instead of the widely accepted visual analog scale for pain assessment is an important limitation of this study because of the incapacity of the VRS to demonstrate small differences in pain relief. Our choice was motivated by its ease of use intraoperatively, which permitted the assessment of all elderly patients in this particular setting of prone positioning in the radiology suite.

We conclude that IL analgesia is as effective as the *iv* association of NP for PV of osteoporotic fractures. Lidocaine plasma concentrations measured after intraosseous injection in 11 patients suggest lidocaine toxicity should not be a problem with the doses used in this study (max 125 mg). However, considering that both protocols still required the addition of propofol in about 10% of patients, it will be relevant to pursue investigations for more effective analgesic strategies, making general anesthesia unnecessary in these elderly patients.

Acknowledgements

The authors are grateful to Mrs. Valerie Sesay for her linguistic aid; Dr. Brigitte Viaud, Dr.Olivia Delmer, Dr. Jerome Berge, Dr. Jean Pallusiere and the nurse anesthetists of the Department of radiology for their technical assistance.

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