

## 72-hour epidural infusion of 0.125% levobupivacaine following total knee replacement: a prospective, randomized, controlled, multicenter evaluation

Andrea Casati<sup>1†</sup>, Randall Ostroff<sup>2</sup>, Cesar Casimiro<sup>3</sup>, Aniko Faluhelyi<sup>4</sup>, Juan Medina<sup>5</sup>, Guido Fanelli<sup>1</sup>, and the Chiropolis Study Group<sup>6</sup>

<sup>1</sup>Dept. of Anaesthesiology, University Hospital, Parma, Italy; <sup>2</sup>Abbott Laboratories, Abbott Park, IL, USA; <sup>3</sup>Abbott Laboratories, Madrid, Spain; <sup>4</sup>Dept of Anaesthesiology, Semmelweis Egyetem Ortoped Klinika, Budapest, Hungary; <sup>5</sup> Dept of Anaesthesiology, Hospital de Conxo, Madrid, Spain; <sup>6</sup>Participating clinicians as co-authors are presented in Appendix A

**Abstract.** *Background and aim of the work:* To evaluate the efficacy in terms of pain relief and degree of motor impairment of a continuous epidural infusion of 0.125% levobupivacaine in patients undergoing total knee replacement surgery. *Methods:* 186 patients receiving effective epidural analgesia with 0.125% levobupivacaine during the first 24 hours after surgery were randomly allocated to receive postoperative analgesia for the following 48 hours consisting in either a continued epidural infusion of 0.125% levobupivacaine (Levobupivacaine group, n = 96), or IV PCA morphine only (Morphine PCA group, n = 90). An independent observer recorded the average amount of morphine required per hour following randomisation, pain intensity, degree of motor blockade and occurrence of side effects. *Results:* Median (range) hourly morphine consumption during the study period was 0.21 (0.00-4.65) mg/hr in the Levobupivacaine group and 0.43 (0.04-4.65) mg/hr in the Morphine PCA group (P = 0.005). The quality of pain relief was adequate (VAS < 30 mm) in both groups, but patients in the Levobupivacaine group showed lower VAS values during motion than patients in the Morphine PCA group (P = 0.001). No differences in the proportion of patients with clinically relevant motor block (Bromage's score  $\geq 1$ ) were reported between the two groups. *Conclusions:* Continuing the epidural infusion of a concentration of levobupivacaine as low as 0.125% improves pain relief with a 50% reduction of hourly morphine consumption after total knee replacement even during the second and third postoperative days, and does not result in a gross impairment of motor function. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Postoperative analgesia, epidural, local anesthetic, levobupivacaine, analgesic, morphine, intravenous infusion, patient-controlled

### Introduction

Levobupivacaine is the pure S(-) enantiomer of bupivacaine, and has been demonstrated to be less cardiotoxic than the racemic mixture (1-4). Initial clinical studies reported that epidural levobupivacaine produces reliable regional anaesthesia in surgical patients, with an onset of sensory and motor blocks nearly equivalent to those produced by racemic bupivacaine (5-7). Postoperative epidural infusion of concentra-

tions of levobupivacaine as low as 0.125% improves pain relief during the first postoperative day (7-9); however, little information is available in the literature concerning its efficacy when prolonging the infusion up to 72 hours after surgery. The aim of this prospective, randomised, open-label, controlled, multicentre investigation was to evaluate the efficacy in terms of pain relief and degree of motor impairment of a continuous epidural infusion of 0.125% levobupivacaine during the second and third postoperative days in pa-

tients undergoing total knee replacement surgery and having an effective epidural analgesia during the first postoperative day.

## Methods

Thirteen Hospitals participated in the study in three different countries (Hungary, Italy, and Spain). The Ethics Committee of each participating institution approved the study protocol, and written informed consent was obtained from all studied patients.

Eligible patients for the study included those with ASA physical status I-III and arthrosis knee diagnoses, who were undergoing primary total knee replacement, and received a continuous epidural infusion of 0.125% levobupivacaine for the first 24 hours after surgery for their postoperative pain control. The same operative technique and the same surgical approach was used in all hospitals. Patients with a contraindication to epidural catheter placement, allergies to any drugs that were to be administered during the study, or who required treatment with any analgesic other than that used in the study or PCA morphine during the randomised treatment period were excluded.

As routine in participating Institutions, antithrombotic prophylaxis was given to all patients using subcutaneous low molecular weight heparin once a day, starting from the evening before surgery. Pre-operative medication was obtained with midazolam 0.03 mg/kg. All studied patients had an epidural catheter placed before surgery at the L2-L3 or L3-L4 interspace using a midline approach and a loss of resistance technique; then surgical anaesthesia was provided at the discretion of each investigator according to their Centre standard of care. At the end of surgery all patients received a 10 ml loading dose of 0.125% levobupivacaine followed by a continuous infusion of the same solution (Chirocaine 0.125%, Abbott Laboratories, Abbott Park, IL, USA). The infusion rate was initially set at 10 ml/h. If the patient did not complain of pain after 4 hours of infusion, the infusion rate was progressively adjusted downward in 2 ml steps every 4 hours in order to provide adequate pain relief ( $VAS \leq 30$  mm) using the minimum infusion rate. If the patient complained of pain, the infu-

sion rate was titrated in 2 ml increments to a maximum infusion rate of 16 ml/h. No other pain medication such as opioids or nonsteroidal anti-inflammatory drugs were given to the patient during the first 24 hours after surgery, and if adequate pain relief ( $VAS \leq 30$  mm) was not achieved despite the use of the maximum allowed infusion rate with no signs of effective sensory block (loss of pinprick sensation at the corresponding dermatomes), the case was considered as a technical failure, and the patient was withdrawn from the study.

There were no difference between the two groups about postoperative hospital stay. After a 24-hour period of effective epidural analgesia, patients were randomly allocated using a sealed envelope technique to one of two groups. Patients in the Levobupivacaine group ( $n = 96$ ) continued the epidural infusion of 0.125% levobupivacaine at the final infusion rate from the first 24 hours of infusion. Patients in the Morphine PCA group ( $n = 90$ ) had their epidural catheter removed, and analgesia was provided by IV PCA morphine alone. For rescue analgesia and to better objectivate analgesic efficacy of epidural infusion, patients of Levobupivacaine group also had a patient-controlled (PCA) morphine infusion. This constituted the beginning of the Randomised Treatment Period, which was continued for other 48 hours. The PCA pump (Abbott Gemstar, Abbott APM, Abbott Life-Care 4, Abbott Laboratories, Abbott Park IL., USA; or Braun Perfuser, B-Braun, Germany) was set to deliver 1 mg doses with a 6-minute lockout period and a maximum allowed dose of 24 mg/4 h.

An independent observer that was not directly involved in patient care recorded the average hourly amount of morphine required to maintain an adequate pain relief following randomisation, as well as pain intensity, and degree of motor blockade. The degree of pain was measured during motion using a 100 mm visual analogue scale (VAS). The degree of motor block was evaluated according to routinely used Bromage's scale (0 = able to elevate lower limb with extended knee; 1 = able to flex the knee against gravity; 2 = able to move the foot only; 3 = no movement at all). The presence of a Bromage's score  $\geq 1$  during the study period was considered as clinically relevant motor blockade. Patients were assessed at 6-hour intervals

throughout the treatment period. The occurrence of any adverse event requiring unplanned therapy during the study period, including the incidence of postoperative nausea/vomiting (PONV), was also recorded.

The calculation of the required sample size was based on results from previous investigations (7, 8, 10). The primary endpoint was the detection of a difference in mean hourly consumption of morphine of 0.6 mg/h or larger, with an effect size with a standard deviation ratio of 0.5: 64 patients per group were required accepting a two-tailed  $\alpha$  error of 5% and a  $\beta$  error of 20% (11). Secondary endpoints were the evaluation of the quality of pain relief and recovery of motor function: 84 patients per group were required to detect a 10 mm difference in the degree of pain measured with the VAS with an effect size with a standard deviation ratio of 0.5, and accepting a two-tailed  $\alpha$  error of 5% and a  $\beta$  error of 10% (11); moreover 82 patients per group were required to detect a difference in the proportion of patients with a clinically relevant motor block (Bromage's score  $\geq 1$ ) from less than 0.05 in patients of Morphine group PCA to 0.2 in patients of Levobupivacaine group accepting a two-tailed  $\alpha$  error of 5% and a  $\beta$  error of 10% (11). Considering a 10% reduction of power because of dropouts and protocol violations we planned to enrol at least 90 patients per group.

### Statistical analysis

Statistical analysis was performed using a SAS statistical software package (SAS 8.2, SAS Institute, Cary, NC, USA). A centre effect was first excluded, and then normal distribution of considered data was evaluated using the Kolgomorov-Smirnov test. Treatment comparison of the mean morphine PCA use per hour was performed using a non-parametric two-way ANOVA on ranks with treatment and centre effects. The Tukey's and Sheffe's tests were used for post hoc analysis. The Bonferroni's correction was also used as indicated for multiple testing. The number of PCA attempts per hour was compared using Wilcoxon rank-sum test. The degree of pain was evaluated using a non-parametric two-way ANOVA on ranks for repeated measures with Tukey's and Sheffe's tests for post hoc analysis. Categorical variables were compared

using the contingency table analysis and the Fisher's exact test. The primary analysis population for the efficacy analyses was the intent-to-treat population, which included all randomised patients. A P value  $\leq 0.05$  was considered as statistically significant.

### Results

A total of 186 patients were included in the 13 participating hospitals; 12 patients (6%) discontinued the drug before completing the study for the reasons given in Table 1. The majority of patients (174/186, 94%) had their surgical procedure performed with an epidural block alone, while 12 patients (12/186, 6%) also had general anaesthesia integrated with the epidural block to complete surgery. All surgical procedures were performed using a thigh tourniquet. No differences in anthropometric parameters (male dominance is random in both groups), duration of surgery, and levobupivacaine infusion rate at the end of the pre-randomisation period were reported between the two studied groups (Table 2).

Average hourly morphine consumption during the study period was lower in the Levobupivacaine group compared with the Morphine PCA group (Figure 1). When considering the degree of pain recorded during motion throughout the study in the two groups, even though the average pain levels were acceptably low in both groups (targeted VAS  $\leq 30$  mm), patients in the Levobupivacaine group consistently reported lower levels of VAS compared to patients in the Morphine PCA group (Figure 2).

No differences in haemodynamic parameters and peripheral oxygen saturation values were observed between the two groups during the study period, with no differences in the incidence of hypotension. Interest-

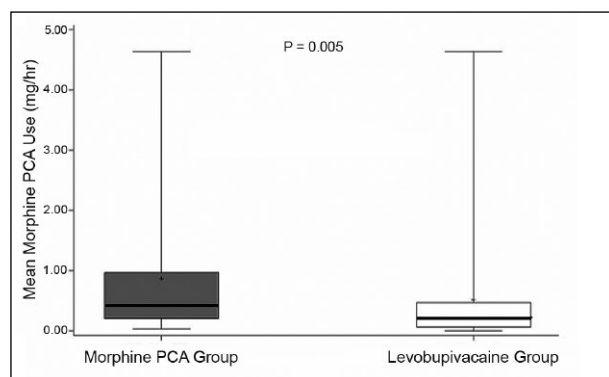
**Table 1.** Patients discontinuing the study in the two groups

	Morphine PCA Group (n = 96)	Levobupivacaine Group (n = 90)
Adverse event	0	1
Technical failure	1	3
Protocol violation	1	2
Withdrew consent	3	1

**Table 2** - Anthropometric characteristics of the studied patients

	Morphine PCA Group (n = 90)	Levobupivacaine Group (n = 96)	P value
Gender (Males/Females)	68/22	73/23	0.99
Age (yrs)	70±8.6	69±8.5	0.60
Weight (kg/m <sup>2</sup> )	79±13	77±15	0.44
Height (cm)	162±8.3	162±8.2	0.76
Body Mass Index (kg)	30.1±4.9	29.5±5.2	0.76
Duration of surgery (h)	1.9 ± 0.7	1.8±0.5	0.30
Levobupivacaine infusion rate at the end of Pre-Randomisation Period (ml/h)	11±3	10±3	0.53

Data are presented as number or mean ± standard deviation



**Figure 1.** Hourly morphine consumption during the study period in patients receiving epidural infusion of 0.125% levobupivacaine with PCA morphine for rescue analgesia (Levobupivacaine group, n = 96) and those receiving PCA morphine only (Morphine PCA group, n = 90).

[Values are presented as median (the line across each box plot) and interquartile range (25% quartiles fall below each median line, and 75% quartiles above median markers within each box plot). Lines extending above and below each box plot represent the range of hourly morphine consumption.]

ingly, despite the infusion of local anaesthetic through the epidural catheter, no differences in the proportion of patients with clinically relevant motor block (Bromage's score  $\geq 1$ ) were reported between the two groups (Figure 3). No differences in side effects were reported between the two groups (Table 3).

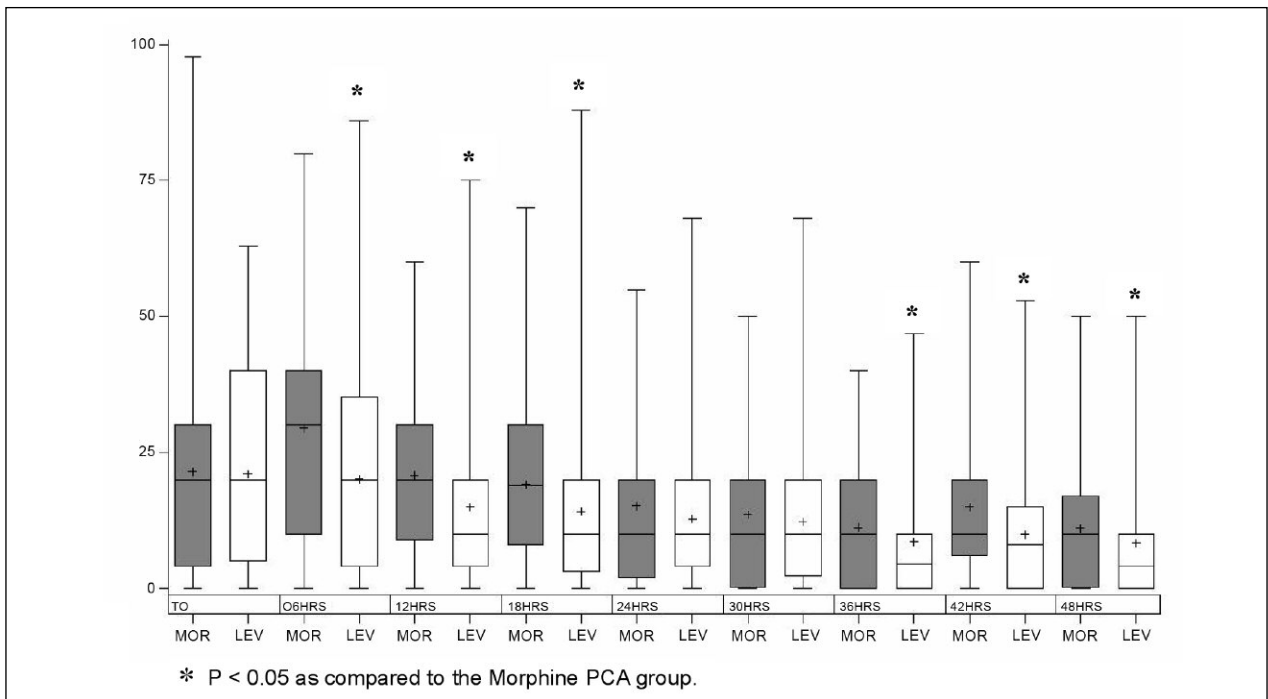
## Discussion

This prospective, randomised, controlled, multi-centre study evaluated clinical the efficacy of epidural

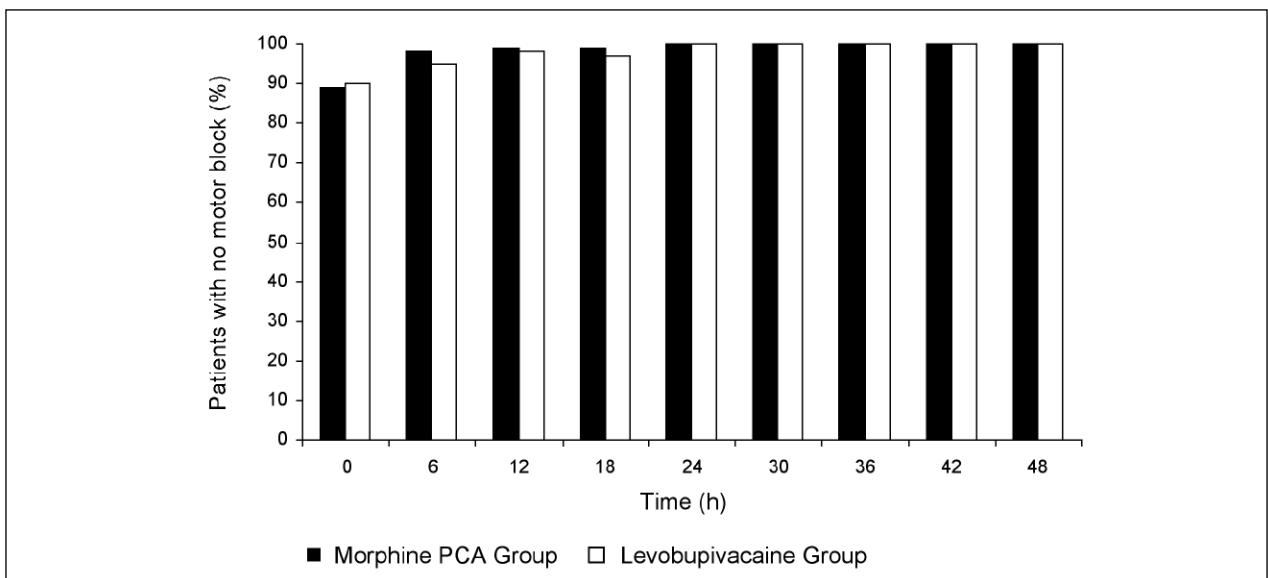
infusion of 0.125% levobupivacaine for up to 72 hours after total knee replacement, and showed that prolonging epidural infusion after the first postoperative day resulted in a 50% reduction of hourly morphine consumption, with better postoperative analgesia and no clinically relevant effects on recovery of motor function when compared to intravenous patient controlled morphine analgesia.

Murdoch et al (8) evaluated the clinical use of 0.0625%, 0.125%, and 0.25% concentrations of levobupivacaine epidurally infused for 24 hours after hip or knee joint replacement, and reported that the 0.25% concentration provided better pain relief, but was also associated with unacceptable motor blockade (Bromage 2-3) in up to 50% of patients. Reducing the concentration of levobupivacaine resulted in less motor block, but also in worse pain control and increased morphine consumption. In the present investigation epidural infusion of 0.125% levobupivacaine from 24 to 72 hours after surgery improved pain control even if all patients had adequate pain relief (VAS  $\leq 30$  mm), and yet was not associated with a clinically different motor blockade when compared to patients receiving no local anaesthetic at all.

Unfortunately, in the present investigation motor block was evaluated using only a "rude" scoring system such as the Bromage's scale; since one of the outcomes of the study was the evaluation of recovery of motor function a more detailed motor testing could have allowed to better evaluate actual motor strength of the limbs in the two groups. However the difficulties in achieving a good standard in motor block evaluation among the different participating centres prevented us



**Figure 2.** Pain intensity recorded during movement at Day 1 and Day 2 in patients receiving epidural infusion of 0.125% levobupivacaine with PCA morphine for rescue analgesia (Levobupivacaine group n = 96 [LEV]) and those receiving PCA morphine only (Morphine PCA group n = 90 [MOR]).  
 [Values are presented as median (the line across each box plot) and interquartile range (25% quartiles fall below each median line, and 75% quartiles above median markers within each box plot). Lines extending above and below each box plot represent the range of hourly morphine consumption.]



**Figure 3 -** Proportion of patients with complete recovery of motor function (modified Bromage’s score = 0) during Day 1 and Day 2 in patients receiving epidural infusion of 0.125% levobupivacaine with PCA morphine for rescue analgesia (Levobupivacaine group, n = 96) and those receiving PCA morphine only (Morphine PCA group, n = 90)

**Table 3** - Incidence of significant adverse events

	Morphine PCA Group (n = 90)	Levobupivacaine Group (n = 96)	P value 0.213
Acute myocardial infarction	0	1	
Unstable angina	0	1	
Atrial fibrillation	1	0	
Tachycardia	0	3	
Hypotension	7	9	
Constipation	3	0	
Nausea	2	6	
Vomiting	4	9	
Bladder Distension	1	0	
Pruritus	0	1	

Data are presented as number (%)

from applying a more sensitive motor evaluation. For this reason we considered as clinically relevant motor block in the statistical analysis the presence of even the minimum degree of motor impairment (Bromage's score  $\leq 1$ ). For the same reason we accepted a  $\beta$ -error as low as 10% in the power calculation for this outcome.

Nevertheless, even if the evaluation system we used was not very sensitive, it is known that epidural anaesthetics frequently cause motor block, especially when administered at a lumbar level (12); in agreement with findings reported by Murdoch et al (8) using such a low concentration of levobupivacaine minimized the effects on motor recovery, which is important to accelerate patient mobilization and improve postoperative rehabilitation. This concept deviates somewhat from findings reported by Dervede et al (13), who evaluated epidural infusion of 15 mg/hr of levobupivacaine for 48 hours after abdominal surgery using three different concentrations (0.15%, 0.5%, and 0.75%), and reported no differences in motor blockade among these three different concentrations. However, in their study the authors did not change the total dose of epidural levobupivacaine. Moreover, thoracic epidural analgesia is associated with less motor block than lumbar epidural block.

Senard et al (14) reported adequate pain relief with no motor block using levobupivacaine with a concentration as low as 0.1%; however, according to their study design, patients also received a large epidural infusion of morphine (1 mg/hr), which may

explain the differences if compared to the results reported by Murdoch et al (8).

The average hourly consumption of morphine observed in the present study was lower than that reported by other investigators (15-17), and was generally less than 1 mg/hr. Milligan et al (17) reported an average hourly consumption of morphine of around 1.5 mg/hr during the first 24 hours after total hip arthroplasty. However, it must be considered that Milligan et al assessed patients only during the first postoperative day, which is associated with the highest degree of pain after major joint replacement surgery; on the contrary, in the present investigation we considered the second and third postoperative days. This explains the relatively smaller hourly consumption of morphine observed. Despite the low hourly consumption of morphine, maintaining epidural infusion on the second and third postoperative days resulted in a further 50% reduction of hourly morphine consumption, and this was also associated to a 50% reduction of the intensity of pain reported by studied patients receiving epidural analgesia if compared to those receiving only systemic morphine analgesia.

Another major pitfall of this study is that patients of the control group did not receive an epidural infusion of placebo, potentially introducing an observer bias. It is well known that epidural analgesia not only improves pain relief after surgery both at rest and during movement (18, 19), but also reduces maximal blood catecholamine and cortisol, improves the forced

vital capacity (FVC), reduces the incidence of renal failure, and overall cardiac morbidity (19, 20). These advantages counterbalance the potential risk for epidural catheter related complications, which are also acceptable low in patients receiving standard antithrombotic prophylaxis, if recommendations on catheter administration are followed (21, 22). Nonetheless, our Ethical Committees judged ethically unacceptable giving the patients an even minimum risk of epidural catheter-related complications without the advantages of epidural analgesia. For this reason the control group had the catheter removed, and the study was designed with an open-label design, rather than a double blinded one.

In conclusion, the results of this prospective, randomised, controlled, multicentre investigation showed that prolonging epidural infusion of a concentration of levobupivacaine as low as 0.125% improves postoperative analgesia with a 50% reduction of hourly morphine consumption even on the second and third postoperative day after total knee replacement surgery, without relevant effects on motor function.

## Acknowledgements

This study was supported by a grant from Abbott (Chicago, USA) [study name: M03-584].

## References

- Forster RH, Markham A. Levobupivacaine: A review of its pharmacology and use as a local anaesthetic. *Drugs* 2000; 59: 551-79.
- Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *Anesth Analg* 1998; 86: 797-804.
- Bardsley H, Gristwood R, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. *Br J Clin Pharmacol* 1998; 46: 245-9.
- Kawano T, Oshita S, Takahashi A, et al. Molecular mechanisms of the inhibitory effects of bupivacaine, levobupivacaine, and ropivacaine on sarcolemmal adenosine triphosphate-sensitive potassium channels in the cardiovascular system. *Anesthesiology* 2004; 101: 390-8.
- Bader AM, Tsen LC, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine vs. bupivacaine for Cesarean delivery. *Anesthesiology* 1999; 90: 1596-601.
- Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. *Br J Anaesth* 1998; 81: 899-901.
- Casati A, Santorsola R, Aldegheri G, et al. Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic bupivacaine and ropivacaine. *J Clin Anesth* 2003; 15: 126-31.
- Murdoch JA, Dickson UK, Wilson PA, Berman JS, Gad-Elrab RR, Scott NB. The efficacy and safety of three concentrations of levobupivacaine administered as a continuous epidural infusion in patients undergoing orthopedic surgery. *Anesth Analg* 2002; 94: 438-44.
- Casati A, Borghi B, Fanelli G, et al. Interscalene brachial plexus anesthesia and analgesia for open shoulder surgery: a randomized, double-blinded comparison between levobupivacaine and ropivacaine. *Anesth Analg* 2003; 96: 253-9.
- Casati A, Vinciguerra F, Cappelleri G, et al. Levobupivacaine 0.2% or 0.125% for continuous sciatic nerve block: a prospective, randomized, double-blind comparison with 0.2% ropivacaine. *Anesth Analg* 2004; 99: 919-23.
- Browner WS, Black D, Newman B, Hulley SB. Estimating sample size and power. In: Hulley SB, Cummings SR, Eds. *Designing clinical research - an epidemiologic approach*. Baltimore: Williams & Wilkins, 1988; 139-50.
- Sveticic G, Gentilini A, Eichenberger U, et al. Combinations of bupivacaine, fentanyl, and clonidine for lumbar epidural postoperative analgesia. A novel optimisation procedure. *Anesthesiology* 2004; 101: 1381-93.
- Dernedde M, Stadler M, Bardiau F, Boogaerts J. Comparison of different concentrations of levobupivacaine for postoperative epidural analgesia. *Acta Anaesthesiol Scand* 2003; 47: 884-90.
- Senard M, Kaba A, Jacquemin MJ, et al. Epidural levobupivacaine 0.1% or ropivacaine 0.1% combined with morphine provides comparable analgesia after abdominal surgery. *Anesth Analg* 2004; 98: 389-94.
- Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; 91: 8-15.
- Chelly JE, Greger J, Gebhard R, et al. Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. *J Arthroplasty* 2001; 16: 436-45.
- Milligan KR, Convery PN, Weir P, Quinn P, Connolly D. The efficacy and safety of epidural infusions of levobupivacaine with and without clonidine for postoperative pain relief in patients undergoing total hip replacement. *Anesth Analg* 2000; 91: 393-7.
- Rathmell JP, Wu CL, Sinatra RS, et al. Acute post-surgical pain management: a critical appraisal of current practice, December 2-4, 2005. *Reg Anesth Pain Med* 2006; 31(Suppl 1): 1-42.

19. Guay J. The benefits of adding epidural analgesia to general anesthesia: a metaanalysis. *J Anesth* 2006; 20: 335-40.
20. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; 93: 853-8.
21. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med* 2003; 28: 172-97.
22. O'Rourke MR, Rosenquist RW. Applying the ASRA guidelines to the use of low-molecular-weight heparin thromboprophylaxis in major orthopedic surgery. *J Arthroplasty* 2004; 19: 919-22.

Accepted: 19th March 2008

Correspondence: Prof. Guido Fanelli

Department of Anaesthesiology

University Hospital of Parma

Via Gramsci 14 - 43100 Parma, Italy

Tel. +39 0521 702 161

Fax +39 0521 984 735

E-mail: guido.fanelli@unipr.it; www.actabiomedica.it

**Appendix A:** All physicians participating at the Chiropolis Study group are co-authors.

Aniko Faluhelyi, MD, and Emese Bakò, MD, Semmelweis Egyetem Ortopéd Klinika, Budapest, Hungary; Guido Fanelli, MD, Giorgio Danelli, MD, Antonia Gennari, MD, Simone Di Cianni, MD, University of Parma, Parma Italy; Sandor Illes, MD, Orszagos Baleseti es Surgossegi Intezet Hungary Budapest, Hungary; Illona Kerenyi, MD, and Gabriella Kamarás, MD, Orszagos Sportegeszsegugyi Intezet, Budapest, Hungary; Xenia Kovacs, BS, Abbott, Chicago, USA; Juan Medina, MD, Isabel Riobo, MD, and Santiago Fernandez, MD, Hospital de Conxo, Santiago de Compostela, Spain; Antonio Montero, MD, Tomás Domingo, MD, Hospital Bellvitge, Barcelona, Spain; Tamas Papp, MD, and Rita Schmidt, MD, Budai Irgalmas Korhaz, Budapest, Hungary; Concepcion Pérez, MD, Blanca Tapia, MD, Carlos Valera, MD, and Delia Cornejo, MD, Hospital la Princesa, Madrid, Spain; Francisco Rey, MD, Ignacio Tobìo, MD, and Bélen Bobillo, MD, Hospital Xeral Cies, Vigo, Spain; Javier Rodrigo, MD, Victorino Leal, MD, and Monserrat Aranzubia, MD, Fundación Jiménez Díaz, Madrid, Spain; Francisco Lopez-Timoneda, MD, Siro Tato, MD, Lourdes Durán, MD, Jesus Hurtado, MD, Luis Santé, MD, Jose Marugán, MD, Hospital Clínico San Carlos, Madrid, Spain; Giorgio Torri, MD, and Roberta Santorsola, MD, Vita-Salute University, Milano, Italy; Kristina Unnebrink, Ph.D. and Detlef Nehrlich, Ph.D., Abbott, Ludwigshafen, Germany; Eva Varga, MD, Szent Janos Korhaz, Budapest.