Original Article

AOSPINE

Global Spine Journal
2019, Vol. 9(2) 133-137

DOI: 10.1177/2192568218755684
journals.sagepub.com/home/gsj

SAGE

Can Liposomal Bupivacaine Be Safely Utilized in Elective Spine Surgery?

Luke Brown, MD, MBA[1], Tristan Weir, MD[1], Scott Koenig, MD[1], Mark Shasti, MD[1], Imran Yousaf, DO[1], Omer Yousaf, MD[1], Oliver Tannous, MD[1], Eugene Koh, MD, PhD[1], Kelley Banagan, MD[1], Daniel Gelb, MD[1], and Steven Ludwig, MD[1]

Abstract

Study Design: Single-blinded prospective randomized control trial.

Objectives: To compare the incidence of adverse events (AEs) and hospital length of stay between patients who received liposomal bupivacaine (LB) versus a single saline injection, following posterior lumbar decompression and fusion surgery for degenerative spondylosis.

Methods: From 2015 to 2016, 59 patients undergoing posterior lumbar decompression and fusion surgery were prospectively enrolled and randomized to receive either 60 mL injection of 266 mg LB or 60 mL of 0.9% sterile saline, intraoperatively. Outcome measures included the incidence of postoperative AEs and hospital length of stay.

Results: The most common AEs in the treatment group were nausea (39.3%), emesis (18.1%), and hypotension (18.1%). Nausea (23%), constipation (19.2%), and urinary retention (15.3%) were most common in the control group. Patients who received LB had an increased risk of developing nausea (relative risk [RR] = 1.7; 95% confidence interval [CI] = 0.75-3.8), emesis (RR = 2.3; 95% CI = 0.51-10.7), and headaches (RR = 2.36; 95% CI = 0.26-21.4). Patients receiving LB had a decreased risk of developing constipation (RR = 0.78; 95% CI = 0.25-2.43), urinary retention (RR = 0.78; 95% CI = 0.21-2.85), and pruritus (RR = 0.78; 95% = 0.21-2.8) postoperatively. Relative risk values mentioned above failed to reach statistical significance. No significant difference in the hospital length of stay between both groups was found (3.9 vs 3.9 days; $P = .92$).

Conclusion: Single-dose injections of LB to the surgical site prior to wound closure did not significantly increase or decrease the incidence or risk of developing AEs postoperatively. Furthermore, no significant difference was found in the hospital length of stay between both groups.

Keywords

postoperative pain, opioid, liposomal bupivacaine, lumbar decompression and fusion, degenerative spondylosis, adverse events, safety

Introduction

Spine surgeries are among the most common procedures to cause severe postoperative pain.[1] Local tissue trauma—including damage to the vertebrae, intervertebral discs, and nerve root sleeves—generate complex neuropathic and nociceptive signals that can prolong the sensation of pain well throughout the postoperative recovery period.[2] Inadequate pain control can contribute to longer hospital stays and potentially increase the risk of postoperative complications secondary to immobilization, such as deep vein thrombosis, pulmonary emboli, and sepsis.[3] Providing effective postoperative analgesia can therefore promote early mobilization and reduce many hospital-related adverse events (AEs).[4]

[1] University of Maryland School of Medicine, Baltimore, MD, USA

Corresponding Author:
Steven Ludwig, Department of Orthopaedics, University of Maryland Medical Center, 110 South Paca Street, 6th Floor Suite 300, Baltimore, MD 21201, USA.
Email: sludwig@umoa.umm.edu

Despite advancements in pain management regimens across the United States, differences of opinion continue to exist regarding optimal treatment plans for controlling postoperative pain.[5] Common therapies include the use of nonsteroidal anti-inflammatory drugs, acetaminophen, and corticosteroids, often used separately or in combination with one another to achieve adequate analgesia.[6] The cornerstone of pain control therapy, however, has traditionally been opiate analgesics due to their effectiveness in providing rapid pain relief following complex operative procedures.[7] Yet such analgesics are also known to cause many opioid-related AEs (or ORAEs), such as nausea, constipation, and emesis.[8,9] The severity of these and many other ORAEs have ultimately driven the development of novel therapies with the goal of achieving adequate analgesia and healing in the postoperative period.[10]

In 2011, liposomal bupivacaine (LB) was approved by the US Food and Drug Administration for the exclusive use of single-dose infiltrations into the surgical site.[11] The extended release formulation has been shown to provide postoperative analgesia for up to 72 hours and reduce patient pain scores after various surgical procedures.[12,13] It is for these reasons that LB has been incorporated into current multimodal pain control protocols alongside attempts to determine its most predictable side effects.[14] Recent clinical trials have reported emesis, nausea, constipation, pyrexia, headaches, and dizziness to be the most common, with hypotension and bradycardia being cited as the most severe.[15,16]

In light of these recent findings, attempts have been made to thoroughly review the safety profile of LB in order to determine its optimal utilization.[17] In 2014, Portillo et al sought to compare the AEs of LB with a placebo or control drug, and determined that it is relatively safe to use in therapeutic doses.[18] In 2016, Grieff et al assessed the efficacy of LB versus bupivacaine HCl in the postoperative management of cervical or lumbar decompression surgeries.[19] They mentioned that the medication did not significantly reduce AEs postoperatively; however, neither the type of side effect, nor risk of acquiring them, were discussed. Since the safety of LB has never been thoroughly evaluated in patients undergoing lumbar spine surgery, we attempted to evaluate the incidence and relative risk of AEs among patients receiving LB compared with those receiving only saline injections, in a cohort undergoing posterior laminectomy and instrumented spinal fusion surgery. A secondary aim was to assess the hospital length of stay between both groups.

Methods

Study Design

After obtaining institutional review board approval, 59 patients were enrolled in a prospective randomized control trial from August 2015 to October 2016. Candidates for the study were patients 18 years of age or older undergoing a primary, 1- or 2-level elective open posterior lumbar decompression and instrumented fusion for degenerative spondylosis. Patients were included if they had any number of laminectomies, a 1- or 2-level fusion, with at least 1 level involving a lumbar vertebrae. Patients were excluded if they had an active infection, metastatic malignancy of the spine, fracture of a lumbar vertebrae, history of substance abuse, impaired cardiovascular function, or severe hepatic disease. All procedures were performed by 4 fellowship-trained orthopedic spine surgeons at a tertiary referral center. All procedures included decompression plus or minus medial facetectomies and foraminotomies, as well as posterior instrumentation with pedicle screws and rod constructs. Fusion techniques included posterolateral, posterior lumbar interbody, and transforaminal interbody fusions with local bone autograft, morselized allograft bone, and/or demineralized bone matrix in any combination.

Patients were randomized in a 1:1 fashion by our hospital research pharmacy to ensure that they were equally allocated to either a treatment or control group. Computer randomization was used to assign patients in their respective groups. Depending on the patients' random assignment, the research pharmacy staff delivered either LB or the placebo medication to the operating room. The treatment arm received 266 mg of LB in a 60 mL suspension, while the control group received 60 mL of 0.9% sterile saline. Local injections were made prior to wound closure into the exposed paraspinal muscles and surrounding soft tissues, as similarly performed by Grieff and colleagues.[19] Due to the noticeable appearance of LB suspension compared with placebo saline, research staff and investigators administering the injections were not blinded to patient group assignments. All other providers involved in postoperative care including nurses, pain management team members, and physical therapists were blinded to patient group assignments. All patients had a patient-controlled analgesia pump initiated shortly after surgery that was discontinued at 6 AM on postoperative day 1. Intravenous and oral (PO) opioid-based pain medications were used only as necessary for adequate pain control throughout the postoperative period in conjunction with other nonopioid medications.

Data Collection and Statistical Analysis

Cumulative data was entered into an electronic data sheet (Microsoft Excel, Microsoft Office, Redmond, WA). Demographic data included age, sex, body mass index, and Charlson Comorbidity Index scores.[20] Surgical data included operation length (minutes), estimated blood loss, and number of vertebra levels decompressed and fused. The primary outcome measured was the incidence of postoperative AEs that occurred between the treatment and control groups. For the purpose of this study, an AE was defined as any undesired event occurring within 72 hours, postoperatively. A literature review of published randomized controlled trials was conducted to identify a list of common AEs of LB (Table 2).[18] Data regarding hospital length of stay was collected from the day of admission until the patient was successfully discharged.

Statistical analysis was done with the aid of JMP Pro Version 13 STATS Software (SAS Institute Inc, Cary, NC).

Table 1. Patient Characteristics[a].

	Liposomal Bupivacaine Group (N = 33)	Control Group (N = 26)	P
Male: female	21:12	9:17	.652
Age	59.8 (12.22)	63.1 (10.6)	.271
BMI	29.9 (6.38)	30.5 (6.3)	.736
CCI scores	3.0 (0.39)	2.5 (0.37)	.29
Length of stay (days)	3.9 (1.62)	3.9 (1.46)	.92
Number of vertebrae fused	2.7 (1.0)	2.4 (0.50)	.093
Number of vertebrae decompressed	3.1 (1.0)	3.7 (0.91)	.036
EBL (mL)	428.9 (337.7)	450.9 (262.5)	.780
Operation length (minutes)	147.4 (54.3)	168.7 (56.2)	.161

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index[20]; EBL, estimated blood loss.
[a]Values presented as means (SDs).

Table 2. Adverse Events[a].

	Liposomal Bupivacaine Group (N = 33)	Control Group (N = 26)	P
Nausea	13 (39.3)	6 (23.0)	.263
Vomiting	6 (18.1)	2 (7.6)	.445
Constipation	5 (15.1)	5 (19.2)	.736
Urinary retention	4 (12.1)	4 (15.3)	.721
Hypotension	6 (18.1)	4 (15.3)	1.000
Arrhythmias	0 (0)	0 (0)	—
Pruritus	4 (12.1)	4 (15.3)	.721
Headache	3 (9.0)	1 (3.8)	.623
Acute mountain sickness	1 (3.0)	0 (0)	1.00
Acute respiratory distress	0 (0)	0 (0)	—
Desaturation	1 (3.0)	0 (0)	1.00
Pyrexia	1 (3.0)	0 (0)	1.00

[a]Values presented as n (%).

Statistical tests that were performed included a 2-tailed Fischer's exact test for proportional differences in dichotomous variables and a 2-tailed student *t* test for the means of normally distributed continuous variables. Nonparametric data means were compared using the Wilcoxon rank sum test. An α error of 5% was set as the threshold for significance for all tests.

Results

A total of 59 patients were enrolled in this study with 33 patients randomized to the treatment group and 26 patients randomized to the control group. Both groups were similar with regard to age, sex, body mass index, and Charlson Comorbidity Index scores[20] (Table 1). With regard to surgical parameters, there was no difference in operation length, number of vertebrae fused, and estimated blood loss between the treatment and control group (Table 1).

A list of AEs between the treatment and control groups is shown in Table 2. The most common AEs in the treatment group were nausea (39.3%), emesis (18.1%), hypotension (18.1%), constipation (15.1%), urinary retention (12.1%), and pruritus (12.1%). With regard to the control group, the most common AEs were nausea (23%), constipation (19.2%), urinary retention (15.3%), hypotension (15.3%), and pruritus (15.3%). No significant difference in the rates of AEs was appreciated between both groups.

Patients who received LB intraoperatively had an increased risk of developing nausea (relative risk [RR] = 1.7; 95% confidence interval [CI] = 0.75-3.8), vomiting (RR = 2.3; 95% CI = 0.51-10.7), and headaches (RR = 2.36; 95% CI = 0.26-21.4). Patients receiving LB had a decreased risk of developing constipation (RR = 0.78; 95% CI = 0.25-2.43), urinary retention (RR = 0.78; 95% CI = 0.21-2.85), and pruritus (RR = 0.78; 95% CI = 0.21-2.8) postoperatively. Relative risk values failed to reach statistical significance. With regard to the secondary outcome measure, there was no statistically significant difference in the hospital length of stay between the treatment and control groups (3.9 vs 3.9 days; $P = .92$).

Discussion

Complex spine surgeries often involve extensive trauma to underlying musculoskeletal and periarticular tissues of the spine. The degree of postoperative pain during the recovery process is difficult to manage without the use of potent analgesics.[21,22] This has chiefly driven the consumption of large amounts of opioids among patients, protracting their in-hospital length of stay, as well as burdening them with many deleterious and costly AEs.[7] In an effort to address, and possibly resolve, the many complications associated with opioid use, current therapeutic strategies now endorse a multimodal approach to postoperative pain control. The regimen includes the use of nonopioid analgesics and local anesthetics, such as LB.[23] The latter has been of particular interest since its approval as an infiltrative anesthetic by the Food and Drug Administration in 2011.[11,24] With a single administration given during surgery, the newly extended release formulation may prolong analgesia and possibly limit opioid dependence in the postoperative period.[15,25] Both LB and bupivacaine HCl are contraindicated in obstetrical paracervical block anesthesia, since the latter has been shown to result in fetal bradycardia and death.[11]

Recent studies have also demonstrated a favorable safety profile of LB when used within therapeutic doses in the setting of various surgical procedures, including inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, breast augmentation, and bunionectomy.[26] And while it has been shown that LB did not significantly reduce AEs following cervical or lumbar decompression surgery,[19] no study has thoroughly examined the safety profile of LB in the exclusive setting of operative lumbar spine procedures. The primary purpose of this study was to therefore determine the incidence and risk of AEs among patients receiving LB compared with those receiving only saline injections, in the setting of posterior laminectomy and

instrumented spinal fusion surgery. A secondary aim was to assess the hospital length of stay between both groups.

With regard to the treatment group, our results demonstrate the most common AE to be nausea, followed by emesis or hypotension (both having the same incidence), constipation, urinary retention, and pruritus. A relatively similar incidence of AEs was found in the control group, with nausea likewise being the most common, followed by constipation, urinary retention, hypotension, and pruritus. When comparing the rates of AEs between both groups, however, no statistically significant difference was found. Despite these findings, our results slightly mirror those of previous reports involving the use of LB ($\leq$266 mg) in nonspinal procedures; the majority revealed nausea to be the most common AE experienced in the postoperative period, followed by constipation, emesis, and pyrexia.[18,26] Since many of these AEs have been firmly grounded in studies assessing the exclusive use of opioids, and considering that all patients had access to a controlled analgesic pump, it is likely that most of these events are related to the perioperative and postoperative use of general anesthetic medicines and opioids.[9,27] Our findings further reveal that the intraoperative administration of LB neither increased nor decreased the relative risk of developing any of the above-mentioned AEs, nor had any significant effect on the hospital length of stay for patients undergoing spine surgery. The presence and severity of certain comorbidities, in addition to the postoperative use of other analgesics, may likely hinder attempts at discerning the unequivocal impact of LB in spine surgery.

To our knowledge, this report serves as the first randomized prospective trial assessing the safety profile of LB in spine surgery. However, several limitations still challenge our analysis. The number of patients randomized to this study was relatively small (n = 59), which may obscure relevant findings across the treatment and control groups. Controlling the study population more strictly by including 1-level, rather than 1- or 2-level, posterior lumbar decompression and fusion surgeries would also reveal more clearly the postoperative safety profile of LB. In addition to the impact of patients' preoperative narcotic requirements on their postoperative course, the co-administration of other postoperative medications, such as sedatives, antispasmodics, or anticholinergics, many of which have been shown to augment the incidences of ORAEs, makes it particularly difficult in determining any association between the use of LB and the outcomes studied. This is further compounded by our study design wherein only single-dose injections of LB were directly administered to the surgical site. Last, preexisting comorbidities and other concomitant medications may potentiate the rate and risk of developing any of the AEs, further stressing the need to adjust for independent and combined variables that could affect primary and secondary outcomes, such as hospital length of stay and patient readmission rates. Since this study focused on the safety profile of LB, it is also difficult to assess whether the medication be recommended for relieving postoperative pain following lumbar spine surgery. In summary, a robustly powered, randomized double-blind prospective study with a larger sample size will be necessary in order to identify meaningful associations between LB and the incidence of AEs in patients undergoing spine surgery.

Conclusion

In this prospective randomized pilot study of 59 patients who underwent posterior laminectomy and instrumented spinal fusion surgery, single-dose injections of LB into the surgical site prior to wound closure did not significantly increase or decrease the incidence and risk of developing AEs in the immediate postoperative period, nor had any significant effect on the hospital length of stay. To better assess the safety profile of LB in spine surgery, carefully designed studies involving a larger sample size are warranted.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: *LB*, *TW*, *SK*, *MS*, *IY*, *OSY*, OT: No disclosures. *SL*: American Board of Orthopaedic Surgery, Inc: Board or committee member; American Orthopaedic Association: Board or committee member; AO Spine North America Spine Fellowship Support: Research support; ASIP, ISD: Stock or stock options; Cervical Spine Research Society: Board or committee member; DePuy, A Johnson & Johnson Company: IP royalties; Paid consultant; Paid presenter or speaker; Globus Medical: Paid consultant; Research support; *Journal of Spinal Disorders and Techniques*: Editorial or governing board; K2M spine: Research support; K2Medical: Paid consultant; OMEGA: Research support; Pacira: Research support; SMISS: Board or committee member; Synthes: Paid consultant; Paid presenter or speaker; Thieme, QMP: Publishing royalties, financial, or material support. *DG*: Advanced Spinal Intellectual Property: Stock or stock options; Depuy-Synthes Spine: IP royalties; Paid presenter or speaker; Globus Medical: IP royalties. *EK*: Biomet: Paid consultant; DePuy, A Johnson & Johnson Company: Paid presenter or speaker. *KB*: K2M: Employee; Orthofix, Inc: Research support.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Pacira Pharmaceutical, Inc.

Ethical Approval

Institutional review board approval was obtained before conducting this research study.

References

1. Gerbershagen HJ, Aduckathil S, van Wijck AJM, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology*. 2013;118:934-944. doi:10.1097/ALN.0b013e31828866b3.
2. Tsuda M, Koga K, Chen T, Zhuo M. Neuronal and microglial mechanisms for neuropathic pain in the spinal dorsal horn and anterior cingulate cortex. *J Neurochem*. 2017;141:486-498. doi:10.1111/jnc.14001.

3. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97: 534-540. doi:0.1213/01.ANE.0000068822.10113.9E.
4. Kehlet H, Dahl JB. Anesthesia, surgery, and challenges in postoperative recovery. *Lancet*. 2003;362:1921-1928. doi:10.1016/S0140-6736(03)14966-5.
5. Penprase B, Brunetto E, Dahmani E, Forthoffer JJ, Kapoor S. The efficacy of preemptive analgesia for postoperative pain control: a systematic review of the literature. *AORN J*. 2015;101:94-105. doi:10.1016/j.aorn.2014.01.030.
6. Dahl JB, Nielsen RV, Wetterslev J, et al; Scandinavian Postoperative Pain Alliance (ScaPAlli). Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anesthesiol Scand*. 2014;58: 1165-1181. doi:10.1111/aas.12382.
7. Gottschalk A, Durieux ME, Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. *Anesth Analg*. 2011;112:218-223. doi:10.1213/ANE.0b013e3181d8a095.
8. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain*. 2002;3:159-180. doi:10.1054/jpai.2002.123652.
9. Pizzi LT, Toner R, Foley K, et al. Relationship between potential opioid-related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery. *Pharmacotherapy*. 2012;32:502-514. doi:10.1002/j.1875-9114.2012.01101.x.
10. Bajwa SJS, Haldar R. Pain management following spinal surgeries: an appraisal of the available options. *J Craniovertebr Junction Spine*. 2015;6:105-110. doi:10.4103/0974-8237.161589.
11. US Food and Drug Administration, Center for Drug Evaluation and Research. EXPAREL NDA 022496 Approval letter. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/022496s000ltr.pdf. Published October 28, 2011. Accessed January 11, 2018.
12. Ilfeld BM, Viscusi ER, Hadzic A, et al. Safety and side effect profile of liposome bupivacaine (Exparel) in peripheral nerve blocks. *Reg Anesth Pain Med*. 2015;40:572-582. doi:10.1097/AAP.0000000000000283.
13. Bergese SD, Ramamoorthy S, Patou G, Bramlett K, Gorfine SR, Candiotti KA. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. *J Pain Res*. 2012;5:107-116. doi:10.2147/JPR.S30861.
14. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. *J Clin Neurosci*. 2015;22: 930-938. doi:10.1016/j.jocn.2015.01.003.
15. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoamÒ bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. *Adv Ther*. 2011; 28:776-788. doi:10.1007/s12325-011-0052-y.
16. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. *Knee*. 2012;19:530-536. doi:10.1016/j.knee.2011.12.004.
17. Viscusi ER. The safety of liposome bupivacaine 2 years post-launch: a look back and a look forward. *Expert Opin Drug Saf*. 2015;14:1801-1803. doi:10.1517/14740338.2015.1089232.
18. Portillo J, Kamar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. *Front Pharmacol*. 2014;5:90. doi:10.3389/fphar.2014.00090.
19. Grieff AN, Ghobrial GM, Jallo J. Use of liposomal bupivacaine in the postoperative management of posterior spinal decompression. *J Neurosurg Spine*. 2016;25:88-93. doi:10.3171/2015.11.SPINE15957.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
21. Bogduk N. The innervation of the lumbar spine. *Spine (Phila Pa 1976)*. 1983;8:286-293. doi:10.1097/00007632-198304000-00009.
22. McGrath B, Elgendy H, Chung F, Kamming D, Curti B, King S. Thirty percent of patients have moderate to severe pain 24 hr after ambulatory surgery: a survey of 5,703 patients. *Can J Anaesth*. 2004;51:886-891. doi:10.1007/BF03018885.
23. Mathiesen O, Dahl B, Thomsen BA, et al. A comprehensive multimodal pain treatment reduces opioid consumption after multilevel spine surgery. *Eur Spine J*. 2013;22:2089-2096. doi:10.1007/s00586-013-2826-1.
24. Saraghi M, Hersh EV. Three newly approved analgesics: an update. *Anesth Prog*. 2013;60:178-187. doi:10.2344/0003-3006-60.4.178.
25. Smoot JD, Bergese SD, Onel E, Williams HT, Hedden W. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammaplasty: a randomized, double-blind, active-control study. *Aesthet Surg J*. 2012;32:69-76. doi:10.1177/1090820X11430831.
26. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain*. 2014;30:102-110. doi:10.1097/AJP.0b013e318288e1f6.
27. Tramèr MR. A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part II. Recommendations for prevention and treatment, and research agenda. *Acta Anaesthesiol Scand*. 2001;45:14-19.