Rev Bras Anestesiol. 2014;64(3):145–151

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

SCIENTIFIC ARTICLE

Randomized, controlled trial comparing the effects of anesthesia with propofol, isoflurane, desflurane and sevoflurane on pain after laparoscopic cholecystectomy

Jaime Ortiz[a,*], **Lee C. Chang**[a], **Daniel A. Tolpin**[a], **Charles G. Minard**[b], **Bradford G. Scott**[c], **Jose M. Rivers**[a]

[a] *Department of Anesthesiology, Baylor College of Medicine, Houston, TX, United States*
[b] *Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, TX, United States*
[c] *Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, United States*

Received 11 December 2012; accepted 20 March 2013
Available online 11 October 2013

KEYWORDS
Laparoscopic cholecystectomy;
Pain;
Propofol;
Inhalational anesthetics

Abstract
Background: Pain is the primary complaint and the main reason for prolonged recovery after laparoscopic cholecystectomy. The authors hypothesized that patients undergoing laparoscopic cholecystectomy will have less pain four hours after surgery when receiving maintenance of anesthesia with propofol when compared to isoflurane, desflurane, or sevoflurane.
Methods: In this prospective, randomized trial, 80 patients scheduled for laparoscopic cholecystectomy were assigned to propofol, isoflurane, desflurane, or sevoflurane for the maintenance of anesthesia. Our primary outcome was pain measured on the numeric analog scale four hours after surgery. We also recorded intraoperative use of opioids as well as analgesic consumption during the first 24 h after surgery.
Results: There was no statistically significant difference in pain scores four hours after surgery ($p = 0.72$). There were also no statistically significant differences in pain scores between treatment groups during the 24 h after surgery ($p = 0.45$). Intraoperative use of fentanyl and morphine did not vary significantly among the groups ($p = 0.21$ and 0.24, respectively). There were no differences in total morphine and hydrocodone/APAP use during the first 24 h ($p = 0.61$ and 0.53, respectively).
Conclusion: Patients receiving maintenance of general anesthesia with propofol do not have less pain after laparoscopic cholecystectomy when compared to isoflurane, desflurane, or sevoflurane.

Introduction

Pain is the primary complaint and the main reason for prolonged recovery after laparoscopic cholecystectomy.[1]

* Corresponding author.
E-mail: jaimeo@bcm.edu (J. Ortiz).

0104-0014/$ - see front matter
http://dx.doi.org/10.1016/j.bjane.2013.03.011

Previous studies investigating postoperative pain after laparoscopic cholecystectomy reported large amounts of inter-individual variation.[2] Pain after laparoscopic cholecystectomy has three components: incisional pain, visceral pain, and referred shoulder pain.[2] Over the past 20 years, several studies have examined this issue using a multimodal approach to postoperative pain management after laparoscopic cholecystectomy.[3–8]

The inhalational anesthetics isoflurane, desflurane and sevoflurane are commonly used to provide maintenance of general anesthesia during surgery. Certain inhalational agents reportedly increase sensitivity to pain at lower concentrations as present during emergence, but relieve pain at higher concentrations.[9] The differential effects of inhalational agents on nociceptive pathways may influence postoperative pain development. Specifically, investigators have shown that isoflurane hyperalgesia may be modulated by the nicotinic receptor.[10]

Clinical studies examining propofol versus inhalational agents for the maintenance of general anesthesia reveal potential benefits to propofol administration which include: improvements in well-being, decreased postoperative pain scores, and decreased incidence of postoperative nausea and vomiting (PONV).[11–14] However, not all of these studies were designed or powered to look specifically at postoperative pain. A study by Fassoulaki[15] did not show any difference in postoperative pain scores after abdominal hysterectomy or myomectomy when comparing propofol, desflurane, and sevoflurane for maintenance of anesthesia. The conflicting findings with regard to the potential analgesic benefit of propofol use for maintenance of anesthesia have resulted in a number of varying opinions within the anesthesiology literature.[16–18]

To our knowledge, no study investigating differences in postoperative pain following laparoscopic cholecystectomy has been reported in the literature comparing maintenance of anesthesia with propofol, isoflurane, desflurane, or sevoflurane. The authors felt it would be important to compare propofol to all three of the commonly used inhalational agents in this study, as different results have been found when comparing propofol to each of the separate agents.[11–15] Our hypothesis was that maintenance of anesthesia with propofol will result in less pain four hours after laparoscopic cholecystectomy when compared to isoflurane, desflurane, or sevoflurane.

Patients, materials and methods

Patient recruitment

The study protocol was approved by the Baylor College of Medicine IRB in August 2009 and registered at ClinicalTrials.gov (NCT00983918, September 2009). Informed, written consent was obtained from 80 inpatients between the ages of 18 and 64 classified as American Society of Anesthesiologists (ASA) physical status I, II, or III, scheduled to undergo laparoscopic cholecystectomy at Ben Taub General Hospital in Houston, Texas. Patients were excluded if any of the following applied: scheduled for outpatient surgery, scheduled for open cholecystectomy, renal dysfunction (Cr > 1.2), allergy to any of the study medications, chronic opioid use at home, or inability to properly describe postoperative pain to investigators (e.g., language barrier, neuropsychiatric disorder). Patients were enrolled by study investigators from September 23, 2009 to June 10, 2010. Study recruitment was placed on hold from December 23, 2009 to March 9, 2010 due to a local shortage of propofol.

Randomization

Patients were assigned to one of four study groups using a computer randomization scheme generated by a department administrator using the website Randomization.com (http://www.randomization.com). Patients had an equal 25% chance of assignment to any of the groups. Group assignments were placed inside numbered opaque envelopes as follows: Group P – maintenance of anesthesia with propofol infusion; Group I – maintenance of anesthesia with isoflurane; Group D – maintenance of anesthesia with desflurane; and Group S – maintenance of anesthesia with sevoflurane. Upon enrollment, all subjects were familiarized with the numerical analog scale (NAS) and the postoperative pain routine. It was explained that a score of ''0'' represented no pain and a score of ''10'' represented the worst pain imaginable. Patients, surgeons and nurses assessing pain scores were blinded with regard to group assignment and anesthetic agent. The members of the anesthesia team performing the general anesthetic were not blinded.

Anesthetic technique

After placement of a peripheral venous catheter, a lactated ringer's infusion was started. A preoperative pain score at rest was recorded at this time. Standard monitoring and Bispectral index (BIS) (Aspect Medical Systems, Norwood, MA) monitoring were applied for all groups. Midazolam 1–2 mg IV was given for anxiolysis as needed. After pre-oxygenation with 100% oxygen, anesthesia was induced with fentanyl 2 mcg/kg, lidocaine 1 mg/kg, and propofol 2.5 mg/kg. Tracheal intubation was facilitated with either succinylcholine 1–2 mg/kg or rocuronium 0.6 mg/kg.

Maintenance of anesthesia was provided as follows: Group P – propofol infusion, Group I – isoflurane, Group D – desflurane, and Group S – sevoflurane. The amount of anesthetic for all groups was titrated to maintain a BIS value between 30 and 50 during the procedure. Muscle relaxation was maintained with rocuronium. Additional administration of fentanyl 50–100 mcg was given at the discretion of the anesthesia team during the procedure. All patients received ondansetron 4 mg IV and ketorolac 30 mg IV after removal of the gallbladder. Neuromuscular blockade was antagonized with neostigmine and glycopyrrolate at the end of surgery. The anesthesia team was instructed to give morphine as needed at the end of the procedure to assist with emergence.

All patients received a standard laparoscopic cholecystectomy with pneumoperitoneum pressures maintained at 15 mm Hg throughout. A total of 10 mL of bupivacaine 0.25% was injected subcutaneously at the trocar insertion sites after wound closure by the surgical team as follows: 3 mL for each of the 10 mm trocar incisions, and 2 mL for each of the 5 mm trocar incisions.

Postoperative care and pain assessment

Time of arrival to the post-anesthesia care unit (PACU) became Time 0 for our pain assessments. Pain at rest was recorded for each patient using the NAS (0–10) at Time 0, and at 1, 2, 4, 8, 12, and 24 h after the surgery was completed. All patients were placed on a postoperative analgesic regimen which included hydrocodone 5 mg/acetaminophen 500 mg tablets, 2 tablets given for mild pain (NAS 3–5) every 6 h with a maximum of 6 tablets in a 24 h period, and morphine 4 mg IV, given every 3 h for severe pain (NAS 6–10). Pain scores were recorded by the PACU and floor nurses taking care of the patient without knowledge of patient group assignment. In addition, analgesic use and PONV events during the first 24 h were recorded.

Statistics

The primary outcome was postoperative pain scores on the NAS from 0 to 10 four hours after surgery. The secondary outcome was pain scores during the first 24 h after surgery. A study by Gupta[19] reported that pain after laparoscopic cholecystectomy had a standard deviation of ± 2 on the visual analog scale. Assuming a common standard deviation of 2.5 units since we used a numerical analog scale, a total of 18 patients per group would be required to detect a 3 unit difference between two groups with 80% power assuming alpha = 0.01. An alpha = 0.01 level was assumed to maintain an overall Type I error rate of 0.05 for multiple comparisons. To account for any patient dropouts or missing patient data, we planned to enroll 20 patients per study group for a total of 80 patients.

Patient demographics, surgery characteristics, analgesic use, and pain scores were compared across treatment groups. A one-way ANOVA model was used to compare mean postoperative pain scores at four hours after surgery across treatment groups as well as continuously measured baseline and surgical covariates. Categorical variables were compared using Fisher's exact test. The overall effect of treatment groups during the first 24 h after surgery was compared using a general linear mixed model assuming an unstructured covariance matrix of correlated errors. The model included fixed effects for treatment group,

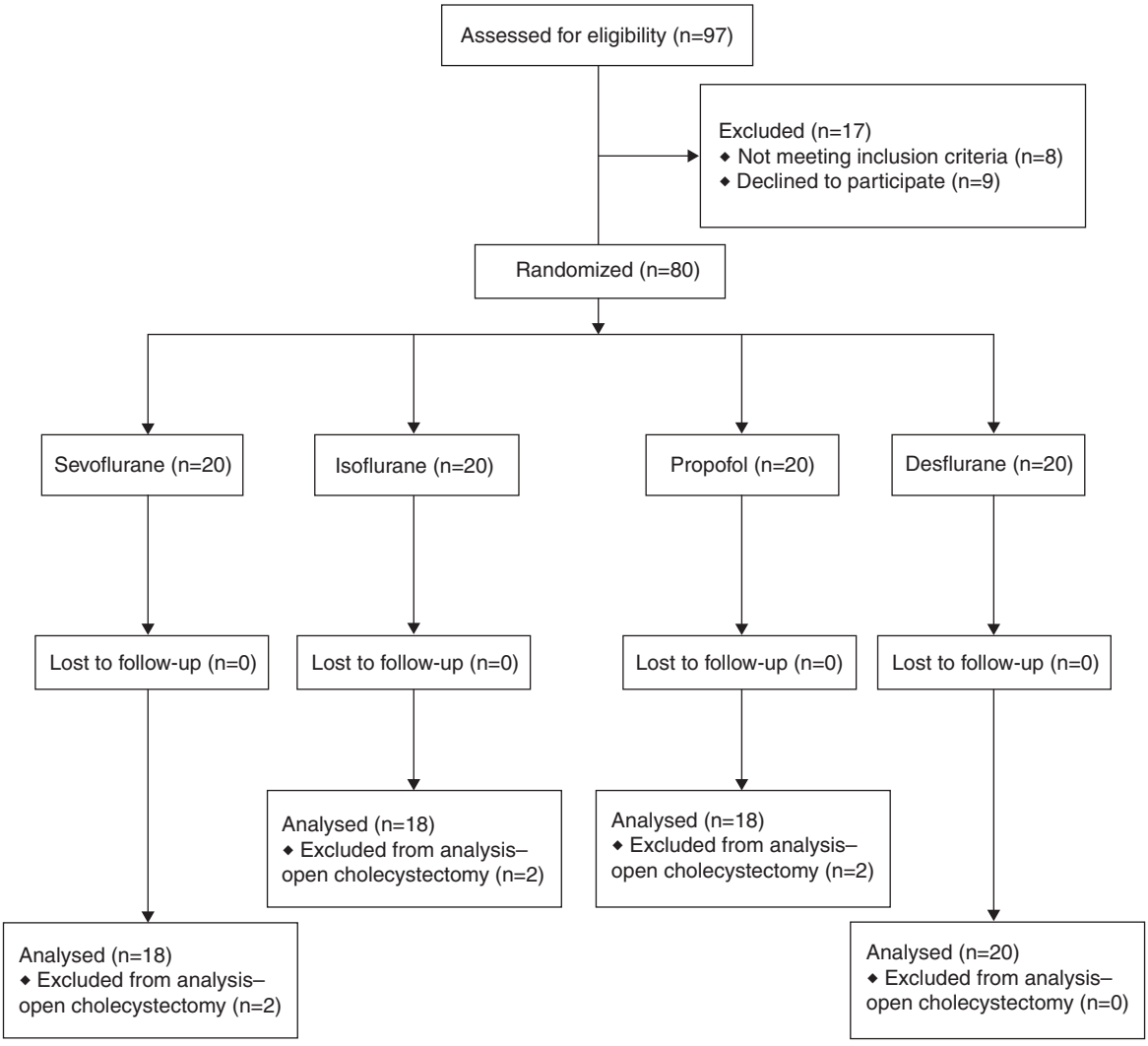

Figure 1 CONSORT flow diagram.

Table 1 Patient demographics and surgical characteristics.

	PROP ($n=18$)	ISO ($n=18$)	DES ($n=20$)	SEVO ($n=18$)
Age	29(7)	34(12)	33(12)	34(14)
Weight (kg)	76(22)	80(16)	77(27)	74(16)
Height (in.)	62(2)	63(3)	63(3)	63(4)
Female	18(100)	16(89)	14(70)	15(83)
ASA class				
1	10(55)	5(28)	5(25)	7(39)
2	7(39)	13(72)	14(70)	10(55)
3	1(6)	0(0)	1(5)	1(6)
Diagnosis				
AC	11(61)	10(55)	12(60)	9(50)
BC	4(22)	5(28)	3(15)	8(44)
GP	3(17)	3(17)	5(25)	1(6)
Surgery time (min)	93(16)	102(45)	88(23)	86(28)
Anesthesia time (min)	148(19)	155(47)	142(24)	142(33)
Estimated blood loss (mL)	39(25)	47(54)	42(34)	37(28)
Nausea				
No	15(83)	13(72)	16(80)	16(89)
Yes	3(17)	5(28)	4(20)	2(11)

Continuous variables are presented as mean(SD) and categorical variables are presented as *n*(%).

time, and group–time interaction term. Treatment and time were modeled as categorical variables. The model was also adjusted for covariates including age, weight, height, sex, ASA classification, diagnosis, intraoperative morphine, intraoperative fentanyl, surgery time, anesthesia time, and estimated blood loss. Statistical significance was assessed at $\alpha = 0.05$. All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

The CONSORT patient flow diagram is shown in Fig. 1. A total of 80 patients were prospectively enrolled in the study. Six patients were subsequently excluded from the final analyses because they met one of the exclusion criteria (conversion of laparoscopic to open procedure). The remaining 74 patients included in the final analyses were distributed as follows: 20 patients in the desflurane group, and 18 patients each in the propofol, isoflurane, and sevoflurane groups.

Our overall patient population was 85% female. The population was 85% Latin American, 6.25% Caucasian, 6.25% African American, and 2.5% Asian. The preoperative diagnoses were distributed as follows: acute cholecystitis in 56%, biliary colic in 28%, and gallstone pancreatitis in 16% of the patients.

A summary of demographic and surgical data is shown in Table 1. Table 2 summarizes the analgesic consumption data. We did not find a statistically significant difference in the intraoperative use of fentanyl and morphine between the groups ($p = 0.21$ and 0.24, respectively). Additionally, there were no differences in total morphine and hydrocodone/APAP use during the first 24 h ($p = 0.61$ and 0.53, respectively).

Fig. 2 shows pain scores for the first 24 h for all groups. There was no statistically significant difference in pain scores four hours after surgery ($p = 0.72$). Differences in pain scores between treatment groups did not depend on time ($p = 0.43$), and the interaction term was removed from the model. There were no statistically significant differences in pain scores between treatment groups ($p = 0.45$). Time was significantly associated with pain score ($p < 0.001$). Even after adjusting for preoperative pain scores, treatment groups were not statistically different ($p = 0.42$). Patient age was significantly associated with pain score ($p < 0.001$). On average, pain scores decreased by 0.7 units for every 10-year increase in age. Otherwise, no other covariates were significantly associated with postoperative pain scores ($p >= 0.16$).

The largest differences between mean pain scores occurred one hour after arrival to PACU. All pairwise comparisons were tested for significant differences using an independent, two-sample *t*-test. After adjusting for multiple comparisons using the Bonferroni correction, only the difference between propofol and desflurane was statistically significant ($p = 0.04$). All other comparisons were not significant ($p >= 0.07$) assuming an overall Type 1 error rate of 0.05.

Discussion

The results of this study do not support the hypothesis that patients receiving maintenance of anesthesia with propofol have less pain four hours after laparoscopic cholecystectomy when compared to isoflurane, desflurane, or sevoflurane.

Our findings differ from recent studies that reported lower pain scores after surgery in patients anesthetized with propofol when compared to isoflurane or sevoflurane.[11,12] A study by Cheng[11] showed an analgesic benefit of propofol

Table 2 Analgesic comparison.

	PROP ($n=18$)	ISO ($n=18$)	DES ($n=20$)	SEVO ($n=18$)	p
Preop pain score (0–10)	1.3(2.4)	0.4(1.1)	1.7(2.1)	1.1(2.1)	0.28
Intraop fentanyl					
>250 mcg	6(33)	11(61)	8(40)	5(28)	
<250 mcg	12(67)	7(39)	12(60)	13(72)	0.21
Intraop morphine (mg)	6.1(4.3)	5.1(4.1)	3.6(4.0)	6.1(4.8)	0.24
24 h morphine (mg)	16(8)	15(11)	12(7)	13(8)	0.61
Hydrocodone/APAP (#)	1.9(1.8)	1.9(2.1)	2.2(1.6)	1.3(1.8)	0.53

Continuous variables are presented as mean(SD) and categorical variables are presented as n(%). p-values obtained by comparing summary measures across treatment groups using one-way ANOVA for continuously measured variables and Fisher's exact test for categorical variables.

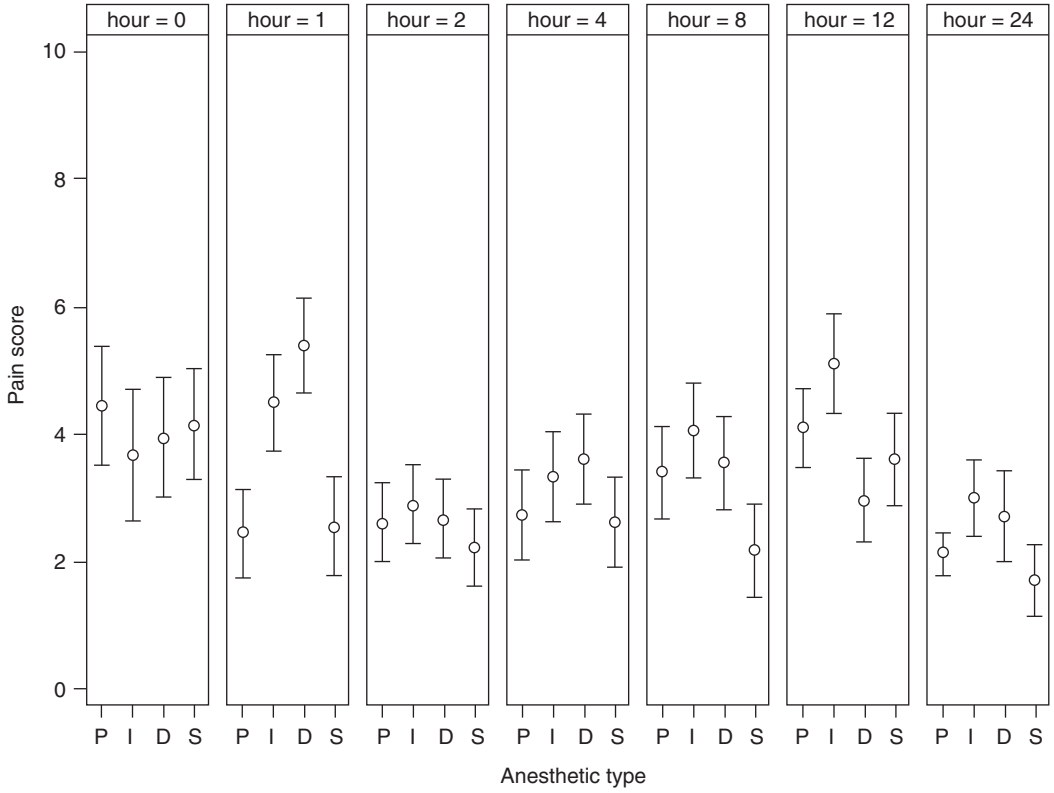

Figure 2 Mean pain scores and standard errors by time and anesthetic type.

when compared to isoflurane, but only two pain scores were recorded after the first hour, at 2 and 24 h after surgery. The study by Tan[12] showed patients had less pain with propofol when compared to sevoflurane, but only looked at pain scores during the first four hours after surgery. In contrast, our study showed no significant difference in pain scores for the sevoflurane and propofol groups throughout the 24 h postoperative period.

Advocates of utilizing propofol for maintenance of anesthesia often refer to studies linking inhaled anesthetics and pain on the biochemical level. For example, Zhang[9] and Flood[10] both reported on the hyperalgesic qualities of isoflurane. Recently, isoflurane and desflurane were found to activate transient receptor potential (TRP)-A1 in a concentration-dependent manner.[20] TRP-A1 is present in peripheral nociceptors. This same effect was not observed with halothane or sevoflurane, suggesting that activation of TRP-A1 may play a role in the development of hyperalgesia by the irritant volatile anesthetics.[20] Although patients in our study that were anesthetized with desflurane were found to have more pain one hour after surgery when compared to propofol, this difference was not found to be statistically significant at any of the other measured time points during the first 24 h.

Although we were unable to show that propofol has analgesic benefits when compared to the inhalational agents, our study has limitations. This study was powered based on the primary outcome of postoperative pain scores and not on

analgesic consumption over the first 24 h. Although we found no statistically significant differences in the use of fentanyl, morphine, or hydrocodone/APAP in our study groups, this may need further investigation using a study powered for that specific outcome. Some of the statistical methods used to analyze the data make normality assumptions, but the NAS is inherently non-normal. However, nonparametric analysis using Kruskal–Wallis and Kolmogorov–Smirnov tests yielded nearly identical results. The only notable difference was that the Bonferroni adjusted *p*-value comparing propofol and desflurane one hour after surgery was no longer significant ($p = 0.12$).

In addition, we modeled our protocol based on the common postoperative pain management of patients at our institution, which includes a multimodal approach with local anesthetics, NSAIDS and opioids. These analgesic agents affect postoperative pain and could mask any differences between propofol and the inhalational agents. For comparison purposes, patients received postoperative PCA morphine in the study by Cheng[11] which showed that patients anesthetized with propofol had less pain compared to isoflurane after open uterine surgery. Patients undergoing diagnostic laparoscopic gynecological surgery in the study by Tan[12] had less pain after propofol when compared to sevoflurane, but received paracetamol, diclofenac, dexamethasone, morphine and oxycodone as part of their multimodal regimen.

We chose to use propofol as the IV induction agent for all groups in this study since this is common practice at our institution. Although it can be argued that an inhalation induction would be the best study design for the patients receiving maintenance of anesthesia with isoflurane, desflurane, or sevoflurane, the risk of aspiration in this patient population and difficulties with inhalation inductions in adult patients made this impractical. Therefore, we cannot disregard any potential effects on pain that an induction dose of propofol could have on all groups.

Another potential confounder is that some of our patients received succinylcholine at the anesthesiologist's discretion. We felt it was important to allow this choice as many patients in our study population have risk factors for aspiration or difficult ventilation and intubation, and as such, the use of succinylcholine may be preferred over rocuronium for induction and intubation. It is possible that some of our patients may have had post fasciculation muscle pain caused by succinylcholine which could have affected our postoperative pain assessments.

Many previous clinical studies on pain after laparoscopic cholecystectomy commonly have a patient population with a primary diagnosis of biliary colic and surgery is usually performed in the outpatient setting. A majority of patients in our study were undergoing operation for acute cholecystitis. This subgroup of patients may have more pain during the perioperative period when compared to patients with a primary diagnosis of biliary colic or gallstone pancreatitis. This increased perioperative pain in our patient population could mask any potential difference between the maintenance agents. However, this heterogeneous population is a common patient mix at many community hospitals.

In conclusion, maintenance of general anesthesia with propofol did not lead to decreased pain scores four hours after laparoscopic cholecystectomy when compared to isoflurane, desflurane, or sevoflurane. Further, well-designed studies are needed to ascertain whether propofol has any beneficial effect on postoperative pain when compared to the inhalational agents after other surgical procedures in the setting of multimodal analgesia.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

We are grateful to Dr. Robert M. Bryan Jr., Professor of Anesthesiology at Baylor College of Medicine, for assisting us with data analysis. This study was supported, in part, by the Dan L. Duncan Institute for Clinical and Translational Research.

References

1. Bisgaard T, Klarskov B, Rosenberg J, et al. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Arch Surg. 2001;136:917–21.
2. Bisgaard T, Klarskov B, Rosenberg J, et al. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90:261–9.
3. Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology. 2006;104:835–46.
4. Jensen K, Kehlet H, Kund CM. Post-operative recovery profile after laparoscopic cholecystectomy: a prospective, observational study of a multimodal anaesthetic regimen. Acta Anaesthesiol Scand. 2007;51:464–71.
5. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg. 1996;82:44–51.
6. Munoz HR, Guerrero ME, Brandes V, et al. Effect of timing of morphine administration during remifentanil-based anaesthesia on early recovery from anaesthesia and postoperative pain. Br J Anaesth. 2002;88:814–8.
7. Sinha S, Munikrishnan V, Montgomery J, et al. The impact of patient-controlled analgesia on laparoscopic cholecystectomy. Ann R Coll Surg Engl. 2007;89:374–8.
8. Zajaczkowska R, Wnek W, Wordliczek J, et al. Peripheral opioid analgesia in laparoscopic cholecystectomy. Reg Anesth Pain Med. 2004;29:424–9.
9. Zhang Y, Eger 2nd EI, Dutton R, et al. Inhaled anesthetics have hyperalgesic effects at 0.1 minimum alveolar anesthetic concentration. Anesth Analg. 2000;91:462–6.
10. Flood P, Sonner JM, Gong D, et al. Isoflurane hyperalgesia is modulated by nicotinic inhibition. Anesthesiology. 2002;97:192–8.
11. Cheng SS, Yeh J, Flood P. Anesthesia matters: patients anesthetized with propofol have less postoperative pain than those anesthetized with isoflurane. Anesth Analg. 2008;106:264–9.
12. Tan T, Bhinder R, Carey M, et al. Day-surgery patients anesthetized with propofol have less postoperative pain than those anesthetized with sevoflurane. Anesth Analg. 2010;111:83–5.
13. Hofer CK, Zollinger A, Büchi S, et al. Patient well-being after general anaesthesia: a prospective, randomized, controlled multi-centre trial comparing intravenous and inhalation anaesthesia. Br J Anaesth. 2003;91:631–7.
14. Raeder JC, Mjaland O, Aasbo V, et al. Desflurane versus propofol maintenance for outpatient laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 1998;42:106–10.

15. Fassoulaki A, Melemeni A, Paraskeva A, et al. Postoperative pain and analgesic requirements after anesthesia with sevoflurane, desflurane or propofol. Anesth Analg. 2008;107:1715–9.
16. Shafer SL, Nekhendzy V. Anesthesia matters: statistical anomaly or new paradigm? Anesth Analg. 2008;106:3–4.
17. Flood P. Pro: accumulating evidence for an outrageous claim. Anesth Analg. 2010;111:86–7.
18. White PF. Con: anesthesia versus analgesia: assessing the analgesic effects of anesthetic drugs. Anesth Analg. 2010;111:88–9.
19. Gupta A, Thörn SE, Axelsson K, et al. Postoperative pain relief using intermittent injections of 0.5% ropivacaine through a catheter after laparoscopic cholecystectomy. Anesth Analg. 2002;95:450–6.
20. Eilers H, Cattaruzza F, Nassini R, et al. Pungent general anesthetics activate transient receptor potential-A1 to produce hyperalgesia and neurogenic bronchoconstriction. Anesthesiology. 2010;112:1452–63.