Randomized Trial

Perioperative Lidocaine Infusion Reduces the Incidence of Post-Mastectomy Chronic Pain: A Double-Blind, Placebo-Controlled Randomized Trial

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Disclaimer: The study was funded by the Department of Anesthesiology, University of Virginia, Charlottesville, VA

Manuscript received: 08-01-2014 Revised manuscript received: 10-22-2014 Accepted for publication: 11-21-2014

Free full manuscript: www.painphysicianjournal.com

Background: Chronic post-surgical pain (CPSP) is a not uncommon complication after mastectomy, with a reported incidence between 20% and 68%. Careful dissection, the use of minimally invasive surgical techniques, and attempts to reduce the associated inflammatory and hyperalgesic responses are suggested methods to prevent CPSP.

Objective: To determine if the use of perioperative lidocaine infusion is associated with decreased incidence of CPSP after mastectomy.

Study Design: Double-blind, placebo-controlled randomized trial.

Methods: This is a secondary analysis of data from 61 out of 71 patients who underwent mastectomy for breast cancer. Patients were randomized to either placebo (Group P; n = 27) or intravenous lidocaine (Group L; n = 34, bolus 1.5 mg/kg at induction, then infusion at 2 mg/kg/hr, up to 2 hours after the end of surgery) in a prospective double-blind design. CPSP was assessed at 6 months after surgery. Stepwise logistic regression analysis was performed to assess the efficacy of lidocaine.

Results: Overall 12 (20%) patients developed CPSP, 8 (30%) in the placebo group and 4 (12%) in the lidocaine group. Predictive factors for CPSP that remained significant after multivariate analysis included lidocaine (associated with a 20-fold decrease in CPSP, $P = 0.013$), breast implant placement (associated with a 16-fold increase in CPSP, $P = 0.034$), and radiotherapy (associated with a 29-fold increase in CPSP, $P = 0.008$).

Limitations: Small sample size.

Conclusion: Perioperative lidocaine administration was associated with a decreased incidence of CPSP, while breast implant placement and radiotherapy were associated with an increased incidence. These findings suggest a protective effect of lidocaine on CPSP development in mastectomy patients.

Key words: Lidocaine, chronic pain, breast surgery, radiotherapy, breast implant

Pain Physician 2015; 18:E139-E146

Chronic post-surgical pain (CPSP) is defined by the International Association for the Study of Pain (IASP) as pain that persists more than 3 months after surgery (1). CPSP after breast surgery is also known as post-mastectomy pain syndrome (2) and persistent post-mastectomy pain (3). CPSP is a common complication after mastectomy, with a reported incidence between 20% (4) and 68% (5). The variation in incidence in the literature results from heterogeneity in the time when the diagnosis was made and the specific definition used for CPSP. CPSP after breast cancer surgery has a pronounced negative impact on the patient's physical activity, general and mental health (2), and quality of life (1).

It is also associated with increased risk of depression, sleep disturbances, and increased anxiolytic use (6). This pain is not static and it can either progress or regress with time, while it may remain for many years after surgery (7).

Many theories have been postulated for the development of CPSP, including peripheral nociceptor sensitization at the site of injury (primary hyperalgesia), central neuronal sensitization at spinal and supraspinal sites innervating the injured area (central hyperalgesia), and central nervous system inflammatory changes triggered by injury (8). Suggested methods to prevent CPSP include careful dissection, reduction of inflammatory responses, and use of minimally invasive surgical techniques (4), as well as preventing peripheral and central neuronal sensitization.

Lidocaine has several properties that can make it a potentially useful drug for prevention of CPSP: 1) it blocks sodium channels in the neuronal cell membrane, 2) it has anti-inflammatory properties, and 3) it has anti-hyperalgesic effects. This led us to consider the possibility that intravenous lidocaine may prevent chronic pain development. The present study investigated this possibility, and tests the hypothesis that the use of perioperative lidocaine infusion reduces the incidence of CPSP after mastectomy.

Methods

Enrollment

After we obtained institutional review board approval, and registered the study in ClinicalTrials.gov (identifier NCT01204242), we approached patients scheduled for mastectomy for cancer at the University of Virginia Health System. The study was conducted between January 2009 and January 2014. Patients aged 18 to 80 years, of American Society of Anesthesiologists (ASA) physical classification classes I – III were eligible for the study. Exclusion criteria were allergy to local anesthetics, fentanyl, or morphine; myocardial infarction within 6 months; profoundly decreased left ventricular function (ejection fraction < 40%) or high-grade arrhythmias; severe liver disease (AST or ALT or billirubin > 2.5 times the upper limit of normal); renal impairment (creatinine clearance < 60 mL/min); pregnancy or breast feeding; enrollment in another clinical trial within the last 30 days; and pre-existing pain at the site of surgery.

Randomization

Both the patients and research team remained blinded until after all data were analyzed. The patients were randomized at 1:1 ratio to receive either lidocaine (prepared blinded by our investigational pharmacy as 8 mg/mL) or placebo (0.9% NaCl). All patients received lidocaine as a bolus prior to anesthetic induction, at a dose of up to 1.5 mg/kg, with a maximum of 150 mg (i.e., patients 100 kg and above received a fixed dose of 150 mg). This bolus was followed by a lidocaine infusion at 2 mg/kg/hr (to a maximum upper limit of 200 mg/hr) or equal volume of placebo. Infusions were continued until 2 hours after arrival in the post-anesthesia care unit (PACU), or PACU discharge (whichever was earlier). If the patient stayed in PACU less than 2 hours, the study drug infusion was terminated and the patient was analyzed per intention to treat. We selected a 2-hour postoperative infusion regimen as we felt it is clinically applicable; furthermore, changes in duration of postoperative infusion do not result in major differences in benefit of intravenous lidocaine (9), suggesting that the intraoperative administration provides the majority of the effect. A website random number generator was used (www.randomization.com). Numbers were concealed in opaque sealed envelopes and the patient was asked to select one envelope on the morning of surgery.

Anesthesia Standardization and Protocol

Sevoflurane in air/oxygen was used for maintenance. Intraoperative analgesia was limited to fentanyl IV (5 mcg/kg maximum). The use of pre-medication, choice of induction drug, and muscle relaxant were left to the discretion of the attending anesthesiologist. After surgery, all patients were transported to the PACU and monitored per institutional PACU protocol. Pain was assessed every 15 minutes, and scores greater than 3 treated with either fentanyl 50 mcg every 10 minutes or morphine 4 mg every 20 minutes as needed. Postoperative analgesia was not standardized; this was done in order to mimic realistic clinical scenarios. Further protocol details are provided in a previous publication (10).

Outcome measurements

The primary outcome for this analysis was whether the use of perioperative lidocaine infusion reduced the incidence of CPSP after breast surgery.

A research associate, who was blinded to treatment group and management, conducted a telephone interview with the patients 6 months after surgery. The interview started by asking the patient if she experienced chronic or persistent pain as a result of her breast

surgery? If her answer was "yes," then she was labeled as having chronic pain and further questions were asked as follows: When did the pain begin? Can you rate your pain on the scale from 0 to 10, where zero is no pain and 10 the worst pain imaginable? Where is the pain located? Please choose from the following what best describes your pain: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, splitting, sickening, tearful? Is your pain constant or intermittent? If the pain is intermittent, how long does it last? Do you take any medication to relieve your pain? If yes, what medications? In addition, we asked the patients if they had any comments to add. If patients did not respond to their initial follow-up phone call, 3 additional phone calls were made over a period of one week and at different times of day in an effort to maximize likelihood of reaching the patients. If patients still could not be reached, a final phone call was attempted 2 weeks later. If the patient could not be reached then, she was dropped from the study.

Statistical Analysis

This study is a secondary analysis of a trial of the effect of intraoperative lidocaine on postoperative opioid requirements (10), which required a sample size of 27 patients per group to achieve an alpha of 0.05 and obtain 90% power using a two-sample t-test to compare 24-hour morphine requirements and assuming an expected 25% reduction in opioid consumption. Based on a previous study of postoperative pain and morphine requirements in patients following breast cancer surgery under general anesthesia showed that mean 24 hours opioid requirements were 21.7 mg morphine equivalents (11).

Data were first evaluated for normality of distribution. Parametric and non-parametric comparisons were used as appropriate. Mean and standard deviation were used for descriptive analysis of normally distributed variables. Two-sample t-test was used to compare the mean difference between the 2 groups for normally distributed data. Categorical variables were compared with chi-square test or Fisher exact test, as appropriate. As the development of CPSP in breast surgery is known to be caused by a variety of factors (12), and the outcome (CPSP: no pain vs. pain) is categorical, we used forward stepwise (likelihood ratio) logistic regression analysis, after we checked the data using a cross-tabulation table to satisfy the assumptions of goodness-of-fit tests in logistic regression (13). A number of potential confounders were included. Age (7) and body mass index (BMI) (14) have previously been linked with CPSP in breast surgery. Other potentially clinically meaningful confounders included type of surgery (15), axillary dissection (7), breast implant placement (15), pain severity at 2 hours after surgery (early postoperative pain) (5), chemotherapy, radiotherapy (12), and hormonal therapy. Models were evaluated based on their -2 Log likelihood (-2LL), Cox & Snell R Square, Nagelkerke R Square, overall predictive ability of the model, and the model driven *P*-value by Omnibus test. The model with the lowest -2LL, highest R squares, and the best overall prediction accuracy was selected as the best model. A *P*-value of 0.05 was considered statistically significant. SPSS 21 software (SPSS, Chicago, IL) was used for the analysis.

Results

A CONSORT flow diagram is presented in Fig. 1. Seven patients in the placebo group and 3 in the lidocaine group could not be reached for follow-up, despite multiple phone call attempts (14% dropout). Therefore, we analyzed 61 patients, 27 in the placebo group and 34 in the lidocaine group. Table 1 shows the demographic and clinical characteristics of the study sample; no statistically significant differences were observed, which indicates good randomization of the cohort between groups.

A total of 12 patients (20%) out of those 61 who answered their follow-up phone call at 6 months developed chronic post-mastectomy pain. Eight (30%) of these were in the placebo group, and 4 (12%) in the lidocaine group. Table 2 summarizes the differences between patients who developed chronic post-mastectomy pain and those who did not, with regard to confounders that may affect the incidence of pain. Only one patient (in the placebo group) developed lymphedema, while no post-surgery infection or other complications were reported. None of the patients had additional surgery within the 6 months follow-up period.

The best logistic regression model is presented in Table 3. The use of perioperative lidocaine infusion was found to be associated with a 20-fold decrease in the incidence of CPSP ($P = 0.013$) in this study population. The use of breast implants and radiotherapy were found to increase the incidence of chronic post-mastectomy pain by 16-fold and 29-fold, respectively ($P = 0.034$, and $P = 0.008$, respectively). This model had the ability to predict outcome in 84% of patients. In order to take into account potential effects due to age and BMI, these 2 variables were used as control variables

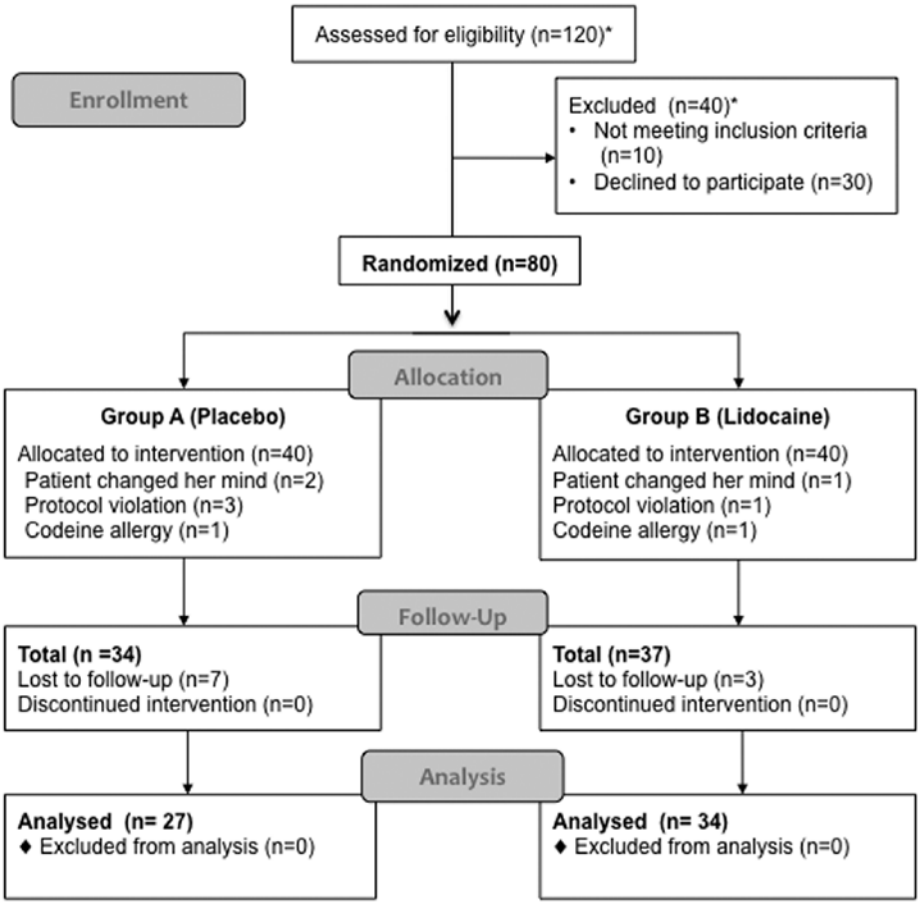

Fig. 1. *CONSORT flow diagram.*
*Indicate estimated numbers.

Table 1. *Demographic and clinical characteristics of the study cohort.*

Characteristic	Placebo group (n = 27)	Lidocaine group (n = 34)	*P*-value
Age (year)	55.2 ± 10.9	55.0 ± 13.7	0.401
BMI (kg/m2)	28.0 ± 6.8	29.5 ± 6.7	0.743
ASA score I II III	 3 21 3	 2 25 7	 0.652 1 0.501
Type of surgery Simple mastectomy Modified radical	 19 (70.3%) 8 (29.6%)	 20 (58.8%) 14 (41.2%)	 0.817 0.695
Axillary dissection	3 (11.1%)	13 (38.2%)	0.085
Breast implant	5 (18.5%)	8 (23.5%)	0.766
Chemotherapy	11 (40.7%)	18 (52.9%)	0.733
Radiotherapy	9 (33.3%)	14 (41.1%)	0.859
Hormone therapy	10 (37.0%)	7 (20.6%)	0.430

Table 2. *Demographic and clinical comparison between patients who had CPSP and those who did not.*

Characteristic	CPSP (n = 12)	No CPSP (n = 49)	*P*-value
Age (year)	53.3 ± 8.6	54.6 ± 13.0	0.668
BMI (kg/m2)	29.5 ± 6.6	29.0 ± 7.0	0.668
ASA score I II III	 1 9 2	 4 37 8	 1 1 1
Type of surgery Simple mastectomy Modified radical	 6 (50.0%) 6 (50.0%)	 33 (67.3%) 16 (32.6%)	 0.781 0.548
Axillary dissection	2 (16.6%)	14 (28.5%)	0.721
Breast implant	4 (33.3%)	9 (18.3)	0.459
Chemotherapy	8 (66.6%)	21 (42.8%)	0.566
Radiotherapy	7 (58.3%)	16 (32.6%)	0.447
Hormone therapy	5 (41.6%)	11 (22.4%)	0.326

Table 3. *Logistic regression model (Best model).*

	B	S.E	OR (95% CI)	*P*-value
Intercept	- 0.39	3.26	0.67	0.903
Age	- 0.04	0.05	0.95 (0.87 – 0.05)	0.401
BMI	- 0.00	0.07	0.99 (0.86 – 1.15)	0.981
Lidocaine	- 2.85	1.14	0.05 (0.00 – 0.54)	0.013
Breast implant	2.78	1.31	16.19 (1.23 – 16.19)	0.034
Radiotherapy	3.35	1.26	28.62 (2.40 – 341.19)	0.008

Model statistics: -2 Log likelihood = 29.87, Cox & Snell R Square = 0.36, Nagelkerke R Square = 0.54, overall model prediction = 84.4%, model significance (using Omnibus test) = 0.001; B = beta coefficient for the intercept (constant), S.E. = standard error around the coefficient and OR = odd ratio, with 95% confidence interval.

(i.e., held constant while estimating the effect of other predictors on pain at 6 months). As shown in Table 3, age (P = 0.401) and BMI (P = 0.981) were not significant predictors of chronic post-mastectomy pain incidence. Factors excluded by the final model were type of surgery (P = 0.265), axillary dissection (P = 0.865), and chemotherapy (P = 0.273).

Pain severity, site, character, quality, and pain medications are summarized in Table 4.

Discussion

This study demonstrates a decreased incidence of CPSP in patients who received perioperative lidocaine infusion (12%) versus those who received placebo (30%). The reported incidence of CPSP in our control group echoes the incidence in the literature. We used stepwise logistic regression analysis to test the efficacy of perioperative lidocaine infusion on the incidence of CPSP in breast cancer surgery in the presence of other well-documented CPSP confounders. The best model indicated that the use of breast implants (submuscular tissue expander) and radiotherapy favor the occurrence of CPSP, while perioperative lidocaine infusion mitigates this incidence. Interestingly, although we did not find a statistically significant difference between patients who received lidocaine versus placebo in acute post-operative pain or morphine consumption in this study population (10), lidocaine use was associated both with a lower incidence of CPSP and a protective effect in the logistic regression analysis. This finding is supported by a recent, smaller study of Grigoras et al (16) who found the incidence of CPSP after breast surgery after 3-month follow-up to be 11% in the lidocaine group (n = 2 out of 17) and 47% in placebo (n = 8 out of 19).

Theories of Chronic Pain Development

Understanding the mechanisms and causes for development of CPSP will help in establishing better prevention and treatment strategies. There are multiple mechanisms that may affect the transition to chronic pain, which are not necessary applicable to all types of surgery (8). These include, but are not limited to: 1)

Table 4. *Pain characteristics*.

Pain characteristics	Placebo group (n = 8)	Lidocaine group (n = 4)	Total (n = 12)
Severity			
Mild (≤ 3)	2	1	3 (25.0%)
Moderate (4 – 6)	6	3	9 (75.0%)
Severe (≥ 7)	0	0	0
Site			
Scar	3	1	4 (33.3%)
Chest wall	2	2	4 (33.3%)
Upper arm	3	1	4 (33.3%)
Character			
Throbbing	1	2	3 (25.0%)
Heaviness	2	1	3 (25.0%)
Aching	3	1	4 (33.3%)
Burning	1	0	1 (8.33%)
Tearful	1	0	1 (8.33%)
Quality			
Constant	3	1	4 (33.3%)
Intermittent	5	3	8 (66.6%)
Medications			
None	2	2	4 (33.3%)
Oral NSAIDs	2	2	4 (33.3%)
Oral opioids	4	0	4 (33.3%)

Peripheral nociceptor sensitization at the site of injury (primary hyperalgesia); 2) central neuronal sensitization at spinal and supraspinal sites innervating the injured area (secondary or central hyperalgesia) (The latter is a form of synaptic plasticity in the spinal cord that amplifies pain signaling. When it occurs, the responsiveness of the neurons increases sufficiently that even normally ineffective synaptic inputs, including those elicited by innocuous stimuli, activate pain transmission neurons.); 3) central nervous system inflammatory changes triggered by injury, which induce proliferation of immunologically active microglia (CNS macrophages) and astrocytes; 4) impaired nociceptive inhibitory modulation; 5) enhanced nociceptive facilatatory modulation; 6) nerve damage can cause increases in Na channel expression, and development of ectopic nerve discharges (e.g., neuroma formation at the injured site); 7) reactive or compensatory musculoskeletal changes following surgery (e.g., frozen shoulder or lymphedema); 8) genetic and epigenetic factors may predispose the patient to chronic pain (4,8,17,18). Prevention of these mechanisms may offer an effective strategy for reduction in CPSP.

Rationale for Lidocaine Use

Lidocaine blocks sodium channels in the neuronal cell membrane that may play a role in the pathogenesis and maintenance of both inflammatory and neuropathic pain (19). Lidocaine has anti-inflammatory properties: It blocks neutrophil accumulation at the injury site of injury and reduces the release of inflammatory mediators (20). Lidocaine has shown anti-hyperalgesic effects both in the peripheral and the central nervous system. Koppert et al (21) found that low-dose (2 mg/kg/hr) lidocaine reduces secondary hyperalgesia by a central mode of action. Furthermore, Kawamata et al (22) found that treatment with lidocaine prior to a surgical incision reduces the excessive inputs from the injured peripheral nerves, consequently suppressing development of flare formation and secondary hyperalgesia through peripheral and central mechanisms, respectively. Lidocaine has been successfully used in the treatment of central and peripheral neuropathic pain, complex regional pain syndrome, as well as fibromyalgia (19).

Other Management Modalities for CPSP After Breast Surgery

Many investigators tried different approaches to perioperative analgesia in order to reduce the incidence of CPSP in breast cancer surgery, but with a poor success rate. Fassoulaki et al (23) tested the effect of a regimen of gabapentin, eutectic mixture of local anesthetics cream, and ropivacaine in the wound versus placebo, and found a decreased incidence of chronic pain at 3 months. However, it is difficult to know if this effect is related to one of these treatments or all of them together. On the other hand, Albi-Feldzer et al (24) in a large multicenter study, did not observe a decrease in the incidence of chronic pain at 3, 6, and 12 months after the use of ropivacaine wound infiltration. A small thoracic paravertebral block (TPVB) study showed a promising effect in mitigating the incidence of CPSP (25). Chiu et al (26), in a recent and larger study, tested the efficacy of TPVB and local anesthetic infiltration on CPSP at one year following breast cancer surgery. They failed to show a significant effect of either modality; the study was stopped after the interim analysis suggested rates of CPSP much lower than anticipated (26). Karmakar et al (27) in a recent study, also did not find a significant difference in the incidence of chronic pain at 3 and 6 months in patients who received TPVB, but noticed that patients with TPVB reported less severe chronic pain.

The results of these studies do not support a protective effect of topical or regional administration of local anesthetic on CPSP.

Risk Factors for CPSP in Breast Surgery

Many risk factors were identified that influence the occurrence of CPSP in breast cancer surgery. However, there is little consistency across studies. For instance, while some studies found radiotherapy to increase the risk of CPSP (12,28,29), others did not (3,30). The type of surgery (use of reconstruction or breast implants) (15), was reported to be a major determinant of CPSP incidence, but others did not find it to increase risk (31,32). Axillary dissection and younger age were associated with increased risk (5,7,28,30), while others did not find axillary dissection to be a risk factor (3). Severity of acute postoperative pain was found to increase the incidence in some studies (5,29). A number of risk factors are associated with the development of pain, including chemotherapy, hormonal therapy, and genetic polymorphisms (28). In contrast, in another study, chemotherapy was not found to increase risk (33).

Therefore, it is very important that any study of interventions for CPSP should consider the role of these factors. Among all the confounders that we tested, we found radiotherapy and breast implant to affect the incidence of CPSP in this study population.

Our study has some limitations: 1) The sample size was not determined to assess the effect of lidocaine on chronic post-mastectomy pain. However, we used a multivariate logistic regression model that takes into account the presence of other "uncontrollable" confounders and the model assessment statistics results were reassuring (e.g., the model had the ability to predict outcome in 84% of patients, Nagelkerke R square = 0.54, P = 0.001). 2) This study did not evaluate possible psychological factors influencing chronic pain (e.g., pain catestrophizing) (3). However, in one study preoperative emotional functioning (depression and anxiety) variables did not independently contribute to the contribution of CPSP in breast cancer surgery (29). 3) It is also worth mentioning that we faced 14% dropout during the follow-up, which needs to be accounted for when calculating sample size for any future study. The large difference in dropout rates between the groups may have affected our results as well. Given the small sample size, if the dropout had been comparable between groups, our results might have been different.

In conclusion, perioperative lidocaine administration was associated with a decreased incidence of CPSP, while breast implant use and radiotherapy were associated with an increased incidence. These findings suggest a protective effect of lidocaine for CPSP in mastectomy patients.

Acknowledgments

We are thankful to Siny Tsang, M.A, StatLab at the University of Virginia, Charlottesville, for her help with the data statistics. We also would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

Author Contributions:

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Abdullah S. Terkawi did the statistical analysis and wrote the manuscript, Dr. Sonal Sharma collected the data, Dr. Marcel E. Durieux, Dr. Mohamed Tiouririne, and Dr. David Brenin designed the study and wrote the manuscript, and Dr. Swapna Thammishetti collected the data. All authors participated in writing the manuscript.

Conflict of Interest: The authors declare no conflict of interest. The study was funded by the Department of Anesthesiology, University of Virginia, Charlottesville, VA.

Note

The abstract of this article was presented at the American Society of Anesthesiologists annual meeting, October 2014, New Orleans, LA.

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