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Impact of continuous paravertebral blockade infusion type on pain management over time for video-assisted thoracoscopic surgery: a pilot study.

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Abstract

This pilot study was designed to examine the impact of two different (PVB) infusion types compared to a control (no PVB) on pain management in video-assisted thoracoscopic surgery. Acute and chronic pain over time, perioperative oral morphine milligram equivalent (MME) consumption and patient satisfaction were measured. A protracted enrollment period and participant attrition precluded target enrollment and subsequent power analysis. Further, there was no increased efficacy of the intervention groups over the control group. In fact, the patient-controlled analgesia only group (control) had lower mean and median MME consumption postoperatively. Pain and patient satisfaction scores were similar among all treatment groups at all time points assessed. We characterize our study population, report our results for each treatment group and highlight challenges encountered and lessons learned to aid in the development of future research.

Keywords

Thoracoscopic Surgery; Thoracic Regional Anesthetic Techniques; Postoperative Analgesia; Paravertebral Block; Programmed Intermittent Bolus; Pilot Study

INTRODUCTION

Postoperative pain after thoracotomy can be severe and lead to chronic pain^[1–3]. Adequate postoperative pain control is an important factor in determining immediate recovery, hospital length of stay, and the severity and incidence of chronic pain^[1, 4]. Regional anesthesia has been shown to be superior to systemic analgesics (nonsteroidal anti-inflammatory drugs and patient-controlled analgesia with opioids) for postoperative pain relief following open thoracotomy^[4, 5]. Although epidural analgesia (EPA) for open thoracotomy has the benefit

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of decreased inflammation and decreased incidence of deep vein thrombosis, it does carry the risk of epidural hematoma with prophylactic anticoagulation and causes hypotension. Continuous paravertebral nerve blocks (PVB) have also been shown to decrease surgical inflammation, but when compared to EPA they boast an improved safety profile^[6], equivalent acute postoperative analgesia^[6, 7], and decreased pain with cough following open thoracotomy^[8]. Chronic pain after video-assisted thoracoscopic surgery (VATS) has a prevalence of 22% to 63%, which is similar to open thoracotomy^[3, 4]. This is surprising given the minimally invasive nature of the procedure. A gap exists in the literature with respect to the optimal analgesic regimen for VATS.

The purpose of this pilot study was two-fold: to compare two different continuous thoracic PVB infusion techniques, programmed intermittent bolus (PIB) and continuous rate, to intravenous patient-controlled analgesia (PCA) only regarding acute postoperative analgesia and to investigate the incidence and severity of chronic post-VATS pain amongst the study groups out to 12 months postoperatively. Primary outcomes were postoperative visual analog scale (VAS) pain scores and opioid consumption. Postoperative patient satisfaction and the incidence and severity of chronic post-VATS pain were secondary outcomes of interest.

METHODS

A literature review was conducted to determine the study design and review outcomes of similar clinical research investigations that have evaluated the efficacy of regional anesthesia techniques for thoracotomy. This prospective, single-blind (allocation concealment from investigators) randomized control trial was conducted in a university setting after institutional review board approval. Informed consent was required for participation in the study. Inclusion criteria were ASA physical status 1–3 patients aged 18–90 undergoing VATS for unilateral wedge resection, partial lobectomy, and lobectomy. Exclusion criteria were patient refusal, pregnancy, diabetic or other significant neuropathies, neurologic or neuromuscular disease, current coagulopathy, skin infection at needle insertion site for PVB placement, systemic infections, local anesthetic or hydromorphone allergy, significant renal or hepatic impairment, unsuccessful PVB or catheter placement, catheter dislodgement after placement, inability to understand visual analog scales or inability to use a PCA pump, and requirement for postoperative mechanical ventilation.

A simple randomization technique was utilized. A study coordinator communicated the group allocation to the anesthesia care team on the day of surgery. The intervention groups received a thoracic PVB and catheter placement preoperatively. The postoperative catheter infusion technique was either a programmed intermittent bolus (PIB) or continuous rate. The control group (PCA only) did not receive a PVB or catheter. The patients could not be blinded between the intervention and control groups. Blinding between the intervention groups (PIB versus continuous rate) also could not be guaranteed due to the mechanical sounds of the infusion pumps. All three groups were prescribed a hydromorphone PCA for postoperative analgesia. We intended to enroll 10 patients in each of the three arms for this pilot study and then perform a power analysis to determine the final number of patients needed to complete the study depending on the effect size of the PVB infusions. Similar studies had enrollments between 40–100 patients.

Premedication in the preoperative holding area was limited to 5 mg midazolam and 100 micrograms fentanyl. The PVBs were placed using the classic landmark technique using the loss of resistance with a Tuohy needle at the T5 vertebral level. An initial bolus of 5 mL 0.75% ropivacaine was administered. The catheter was threaded 4–5 cm beyond the needle tip and secured to the skin using sterile technique. The catheter was then bolused with an additional 10 mL 0.75% ropivacaine (not to exceed a total dose of 3 mg/kg).

Intraoperatively, general anesthesia with endotracheal intubation was performed. Induction medications and maintenance anesthetics prescribed were at the discretion of the attending anesthesiologist. Intraoperative analgesia was achieved with fentanyl. No long-acting opioids and no other supplemental analgesics (e.g. gabapentin, nonsteroidal anti-inflammatory drugs, ketamine, dexmedetomidine or local anesthetics) were to be given. After emergence, all patients were transferred to the post-anesthesia care unit (PACU) for recovery and initiation of their PVB infusion and intravenous PCA according to their randomization group.

Upon admission to the PACU, a study coordinator provided the nurse with an appropriate preprogrammed infusion pump for the PVB catheter groups. All PVB patients were also given a hydromorphone PCA postoperatively. The PVB infusion technique was either a continuous rate of 12.1 mL/hr (continuous group) or a bolus dose of 6 mL every 30 min (PIB group) with a negligible basal rate of 0.1 mL/hr to ensure catheter patency. The continuous infusion was started immediately upon catheter to pump connection for the continuous rate group. In order to keep total local anesthetic dose over time equivalent between intervention groups, the first bolus of the PIB group was 30 min after connection. The PCA only patients (control group) received a hydromorphone PCA upon arrival to the PACU. CADD-Legacy PLUS 6500 (Deltec, Inc. St. Paul, MN) pumps and tubing were used for the PVB infusions.

The only allowable change to the pump infusion protocols was to discontinue the infusion, such as for catheter malfunction or dislodgement, suspected toxicity or other adverse event related to the infusion. If supplemental bolus of the PVB catheter was needed for pain control, the physician or nurse anesthetist administering the bolus was allowed to disconnect the catheter from the pump tubing and manually administer the syringe-injected bolus using sterile technique. The catheter would then be reconnected to the pump and the infusion continued at its initial programmed infusion setting. All such events and interventions were to be documented as secondary outcomes. The PVB catheters were removed by an anesthesia provider after the patient's chest tube had been removed (typically on POD 2).

Visual analog scale (VAS) pain scores with respect to overall pain experience were assessed by a study coordinator preoperatively on the day of surgery and postoperatively prior to the catheter to pump connection in the PACU. Procedure-related chest wall pain (i.e. incisional and chest tube-related) at rest and with coughing were also assessed postoperatively using a VAS. A study coordinator or the patient's nurse performed subsequent interval pain assessments within 3 hours of nursing shift change (0700 and 1900 daily) until the patient's chest tube was removed. The VAS used was the standard 100 mm horizontal line with 0 mm = "no pain" and 100 mm = "worst pain imaginable". A new and unmarked VAS was used for each time point over the assessment period to avoid bias. Opioid consumption was

documented by a study coordinator at each pain assessment. Patient satisfaction with pain control was also obtained using a 6-point Likert rating scale from 1 equaling “completely satisfied” to 6 equaling “completely dissatisfied”.

The patients were contacted via telephone by a study coordinator at 1, 6 and 12 months from the date of their operation to assess for the presence of chronic post-VATS incisional pain. They were asked a standardized set of questions including a numeric rating scale (NRS) pain score (0 = “no pain” and 100 = “worst pain imaginable”). The McGill Pain Questionnaire Short Form was administered if the incisional pain was present.

Additional outcomes data collected were hospital length of stay, the incidence of any postoperative acute pain service anesthesia provider interventions, and complications involving the PVB catheters. Demographic data collected included age, gender, weight, height, BMI, ASA physical status, anesthesia duration, surgery duration, type of VATS (e.g., partial lobectomy, lobectomy, or wedge resection) and the total amount of preoperative and intraoperative opioids administered. The time-table for enrollment of patients sufficient to complete the study was estimated to be 12 months with an additional 12 months of follow-up required for the chronic pain assessments. Actual recruitment occurred from December 2010 until August 2015 and data collection ended in August 2016.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all variables in the data. The primary outcomes of interest were patient self-reported pain over time and oral morphine milligram equivalent (MME) consumption. Given the pilot nature of this study, the goal was to estimate patient self-reported pain and MME consumption by treatment group rather than to conduct formal hypothesis testing comparing the different treatment groups. Median, minimum, and maximum patient self-reported VAS pain score by treatment group was estimated for arrival to PACU, at POD 0 (1900), POD 1 (0700 and 1900), and POD 2 (0700). Mean preoperative, intraoperative, postoperative, and total MME consumption within each treatment group was estimated as well as the standard deviation. Median patient self-reported patient satisfaction with pain control at rest and with coughing was estimated on POD 1 and 2. We also report the number of patients for whom pain assessment is missing post-operatively and at long-term follow-up. All analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

The final study population included 23 participants of whom 8 received PCA only (control group), 8 received a PIB technique, and 7 received a continuous rate of infusion through the PVB catheter. Seven patients were withdrawn from the study for the following reasons: surgical procedure not performed due to presence of metastatic disease (n = 1), conversion to open thoracotomy (n = 2), misplaced PVB catheter (n = 2), epidural placed in PACU (n = 1), and postoperative ICU admission (n = 1).

Patient characteristics across all patients and within each treatment group are reported in Table 1. Approximately half of the patients were male (52.2%) and the mean age was 66.5 ±

7.9 years. A majority of the patients underwent VATS lobectomy (65.2%). The overall median preoperative VAS pain score was 0 mm (0 to 50 mm). Anesthesia and surgery durations, estimated blood loss and intraoperative MME consumptions were similar across all groups.

The PCA only group had a higher percentage of ASA physical status 2 patients (62.5%) whereas the intervention groups had higher percentages of ASA physical status 3 patients: PIB (62.5 %) and continuous (57.1%). There were no apparent meaningful differences in the demographic characteristics between groups.

The overall (all groups combined) mean postoperative MME consumption was 300.4 ± 261.9 and the overall total perioperative (pre-, intra-, and postoperative) MME consumption was 413 ± 270.8 (Table 2). There was no trend towards increased efficacy of the intervention groups over the control group. In fact, the PCA only group had a lower mean (Table 2) and median (Figure 1) MME consumption postoperatively.

Figure 1 shows the distribution of MME consumption by treatment group preoperatively, intraoperatively, postoperatively, and overall. The PIB group had the highest preoperative and intraoperative MME consumption. The continuous infusion group had the highest postoperative and total MME consumption. An extreme outlier potentially skewed the continuous infusion group data. This patient consumed more than twice the MME of any other patient in the study.

Figures 2–4 show the distribution of patient self-reported pain scores (on a 100 mm VAS) over time overall, at rest, and while coughing by treatment group. There was not a clear trend in pain scores within or across treatment groups over time.

We also examined patient satisfaction on POD 1 and 2 by treatment group both while resting and while coughing. Table 2 shows the overall median patient satisfaction on POD 1 was 2 (moderately satisfied) both at rest and while coughing. On POD 2 overall median patient satisfaction at rest (1 or completely satisfied) was marginally better relative to coughing (2 or moderately satisfied). The continuous infusion group reported slightly better median satisfaction at rest and while coughing on POD 1 and at rest on POD 2 relative to the PCA only and PIB groups. This difference was small and not clinically relevant.

Finally, we also had some data regarding post-VATS incisional pain with long-term follow-up (up to 12 months) on a smaller number of patients in each group. Results of patient self-reported pain at 2 days, 1 month, 6 months, and 12 months are presented in Table 3. Median VAS pain scores were similar between groups on POD 2. The PCA only group at 1 month following surgery was the only group and time point with a median pain score greater than zero (median NRS pain score was 25). The McGill Pain Questionnaire results are not reported due to the small incidence of chronic postoperative pain in this cohort and insignificance of these results.

Missingness in terms of incomplete acute postoperative pain scores (Table 4) as well as attrition or long-term lost to follow-up (Table 5) were impediments to the data analysis. For preoperative and postoperative assessments, pain scores were more likely to be correctly

collected and include pain overall, at rest, and while coughing. However, the PACU assessments were less likely to collect pain at rest and with coughing. Additionally, there was twice the amount of missing data for the postoperative 1900 assessments than at 0700. With respect to long-term follow-up, an approximate 30% attrition rate was experienced across all treatment groups out to 12 months postoperatively.

DISCUSSION

This pilot study encountered many obstacles. Some were intrinsic due to the design and execution of the protocol and others were external and unforeseen. We feel it important to publish our findings in hopes of communicating our scientific process and lessons learned with the hope of helping other investigators to learn from our experience.

Internal validity is essential to the research process. One weakness of our protocol was the inability to completely ensure allocation concealment among the two intervention groups. Blinding could not be guaranteed due to the differing mechanical noises created by a pump running a continuous rate of infusion versus one delivering intermittent boluses. Obviously, the PCA only group participants were aware that they were the control group. We did keep the investigators properly blinded, but the single-blind design falls short of the gold standard.

Data collection was another challenge for our research team. We had built some flexibility into our protocol, which we thought would aid the collection process and offset the workload of our staff. We allowed for a 3-hour window before or after the planned postoperative assessment times at 0700 and 1900 each day to collect the outcome data. Also, we allowed the coordinators to enlist the nursing staff to complete the assessments if needed. A lack of nursing education and buy-in could account for the increased missing data at the 1900 assessments when our research team was more likely to be off of work. All assessments were obtained using standardized forms that the patients were required to complete on their own. However, the forms were not always completed properly so certain data points were missing. We did not anticipate having such a high degree of missingness with this allowance, but perhaps our collection methods were too relaxed. We lost scientific rigor by not standardizing who collects the data thus ensuring that it is completed appropriately. A recommendation for future research to limit missingness is to design assessment methods and time points that are aligned with the available resources to optimize data collection.

Patient attrition is expected with any long-term study, but our approximate 30% loss to follow-up rate is rather high. It is likely that a large number of participants would be needed to assess for statistical differences in chronic post-VATS pain in this population since minimal to no pain was present across all three groups greater than 1 month out from surgery. Future studies should probably focus on acute postoperative endpoints only.

One external factor that could not be anticipated or controlled for was the sudden death of one of our thoracic surgeons, who was the primary participating surgical co-investigator at the time. Another factor was staff turnover within our department's own research department. Both of these led to a protracted recruitment period (57 months versus planned

12 months) and substantially prolonged the duration of the study. Research coordinator turnover could have also adversely affected data collection in both the acute and chronic pain assessments. Ensuring proper handoffs when there is research staff turnover is advisable to minimize missingness.

The landmark-based “blind” loss of resistance technique utilized for placement of the PVBs and catheters may not be the best in terms of ensuring proper placement. It is possible that we had an even higher number of misplaced blocks and/or catheters that went undiagnosed. This could be one reason to explain why there was no discernible benefit seen with the treatment groups. Ultrasound-guided techniques and even hybrid techniques using the thoracoscope to visually confirm proper percutaneous catheter placement of the catheter by the surgeon in the paravertebral space^[9, 10] may be more reliable techniques to investigate in future research.

Other criticisms include the small number of participants in the pilot study, which allows outliers to have a larger impact in the data analysis. These data suggest that the amount of variability in pain scores and MME consumption might require a very large trial to detect any differences. Also, we did not collect baseline (outpatient) chronic opioid consumption in the demographic data. This would be important to consider as patients with chronic pain may exhibit opioid tolerance or may have other pain generators outside of the surgical site and thoracostomy tube which could account for increased postoperative opioid consumption. It would be advisable to have exclusion criteria for certain chronic pain syndromes and for a high baseline daily opioid requirement (e.g., more than 60 oral MME daily).

Another potential confounding factor to consider is the possibility that not all VATS incisions and procedures are created equal. For example, some may not be that painful and a multimodal analgesic regimen without a regional anesthetic approach may be adequate to treat acute post-VATS pain in these less invasive cases. This point may be controversial as some studies have shown benefit to continuous PVBs over multimodal analgesics only in three ports’ VATS for pneumothorax or solitary pulmonary nodule^[9], which are not as invasive as a VATS lobectomy for example. Our group has had discussions about our practice and it has been proposed to perform PVBs for VATS lobectomies only since there is a larger incision made (mini-thoracotomy) in order to remove the resected lung tissue. Our research protocol allowed for the inclusion of VATS wedge resections, partial lobectomies and lobectomies, which may have altered the internal validity of the study. We had intentionally included a broader case mix in order to recruit more patients and shorten the study duration, but this may have been detrimental if the postoperative pain differs significantly between these procedures.

Unfortunately, we do not feel that there is any new knowledge to be learned from this study to apply to daily clinical practice. The value of this research effort lies in process improvement initiatives for our research department (and hopefully others as well). Further, we want to educate others who are interested in similar research about our lessons learned.

CONCLUSION

Our pilot study did not find a trend toward increased efficacy of either intervention group over the control group, therefore a power analysis was not able to be performed as intended. Further, pain and patient satisfaction scores were similar among all treatment groups at all time points assessed. We hope that by highlighting the challenges we encountered and subsequent lessons learned that this research will aid in the successful development of future studies.

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Figure 1:

Opioid consumption in oral morphine milligram equivalents (MME) by treatment group preoperatively, intraoperatively, postoperatively, and overall. The line in each box in the figure represents the median MME, the edges of the box represent the 25th and 75th percentiles of the distribution, the whiskers represent 1.5 times the inner-quartile range (IQR) and points represent all values outside 1.5 x IQR.

Figure 2: Patient self-reported overall postoperative pain over time on a 100 mm VAS scale by treatment group. The line in each box in the figure represents the median pain score, the edges of the box represent the 25th and 75th percentiles of the distribution, the whiskers represent 1.5 times the inner-quartile range (IQR) and points represent all values outside 1.5 x IQR.

Figure 3:

Patient self-reported post-operative pain while resting over time on a 100 mm VAS scale by treatment group. The line in each box in the figure represents the median pain score, the edges of the box represent the 25th and 75th percentiles of the distribution, the whiskers represent 1.5 times the inner-quartile range (IQR) and points represent all values outside 1.5 x IQR.

Figure 4: Patient self-reported post-operative pain while coughing over time on a 100 mm VAS scale by treatment group. The line in each box in the figure represents the median pain score, the edges of the box represent the 25th and 75th percentiles of the distribution, the whiskers represent 1.5 times the inner-quartile range (IQR) and points represent all values outside 1.5 x IQR.

Table 1:

Patient characteristics overall and by treatment group.

Demographic category	Overall (n = 23)	Treatment Group		
		PCA only (n = 8)	PIB (n = 8)	Continuous (n = 7)
Male (%)	12 (2.2)	4 (50.0)	6 (75.0)	2 (28.6)
Age (years)	66.5 (7.9)	64.8 (7.7)	65.4 (9.2)	69.7 (6.6)
BMI	28.1 (7.1)	29.1 (9.8)	28.8 (6.7)	26.3 (3.7)
ASA: 2	11 (47.8)	5 (62.5)	3 (37.5)	3 (42.9)
3	12 (52.2)	3 (37.5)	5 (62.5)	4 (57.1)
Surgery Type				
Lobectomy	15 (65.2)	6 (75.0)	4 (50.0)	5 (71.4)
Wedge Resection	8 (34.8)	2 (25.0)	4 (50.0)	2 (28.6)
Anesthesia duration (min)	251.2 (67.4)	252.5 (58.5)	252.3 (96.4)	248.6 (42.3)
Surgery duration (min)	209.6 (70.8)	215.5 (51.7)	180.1 (136.3)	208.1 (43.6)
Estimated Blood Loss (mL) *	175 (1, 400)	150 (50, 350)	150 (1, 400)	200 (100,
Preop VAS Overall (mm) *	0 (0, 50)	50 (0, 50)	0 (0, 50)	20 (0, 50)
Preop VAS Resting (mm) *	0 (0, 50)	50 (0, 50)	0 (0, 50)	20 (0, 50)
Preop VAS Coughing (mm) *	10 (0, 50)	50 (0, 50)	0 (0, 50)	10 (0, 50)
Preop MME	34.9 (28.9)	40.3 (16.5)	76.9 (38.8)	15.0 (17.3)
Intraop MME	77.3 (44.1)	79.3 (34.1)	82.8 (62.9)	68.9 (32.2)

Categorical variables are reported as n (%) and continuous variables are reported as mean (SD) or median (min, max) when denoted by a *.

PIB = programmed intermittent bolus, PCA = patient controlled analgesia (intravenous), MME = morphine milligram equivalents

Table 2:

Postoperative (PACU through hospital discharge) and total (pre-, intra- and postoperative combined) oral morphine milligram equivalent (MME) consumption reported as mean (SD) and patient satisfaction with pain control at rest and while coughing reported as median (min, max). A satisfaction score of 1 equates to “completely satisfied” and a score of 6 equates to “completely dissatisfied”. PIB = programmed intermittent bolus, PCA = patient controlled analgesia (intravenous), MME = morphine milligram equivalents, POD = postoperative day

		Treatment Group		
Outcome	Overall (n = 23)	PCA only (n = 8)	PIB (n = 8)	Continuous (n = 7)
Postop MME	300.4 (261.9)	203.1 (169.9)	273.7 (127.1)	438.2 (393.3)
Total MME	413.2 (270.8)	322.7 (180.8)	407.7 (161.1)	522.1 (409.5)
POD 1 Satisfaction				
At Rest	2 (1, 6)	2 (1, 6)	2 (1, 4)	1.5 (1, 6)
While Coughing	2 (1, 6)	3 (1, 6)	3 (1, 6)	2 (1, 3)
POD 2 Satisfaction				
At Rest	1 (1, 5)	2 (1, 5)	1.5 (1, 2)	1 (1, 2)
While Coughing	2 (1, 6)	2 (1, 6)	2 (2, 4)	2 (1, 2)

Table 3:

Self-reported pain on postoperative day 2 (POD 2) and at long-term follow-up at 1, 6 and 12 months postoperatively. Pain scores reported as median (min, max). PIB = programmed intermittent bolus, PCA = patient controlled analgesia (intravenous), VAS = visual analog scale administered in person, NRS = numeric rating scale administered over phone

Treatment	Postoperative Evaluation Time			
	POD 2 (7 am) VAS	1 month NRS	6 months NRS	12 Months NRS
PCA only	25 (0, 60)	25 (0, 50)	0 (0, 50)	0 (0, 30)
PIB	20 (0, 50)	0 (0, 50)	0 (0, 50)	0 (0, 0)
Continuous	30 (10, 80)	0 (0, 40)	0 (0, 0)	0 (0, 20)

Table 4:

Missingness – number (%) of patients missing pain scores overall and by treatment group at the preoperative holding area (preop), post-anesthesia care unit (PACU), and 7 am (POD 1/POD 2) and 7 pm (POD 0/POD 1) follow-up times. Note the missing number of postoperative 7 am and 7 pm checks are averaged from the POD 1/POD 2 and POD 0/POD 1 assessments, respectively. PIB = programmed intermittent bolus, PCA = patient controlled analgesia (intravenous)

		Treatment Group		
Time	Overall (n = 23)	PCA Only (n = 8)	PIB (n = 8)	Continuous (n = 7)
Preop	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
PACU				
Overall	4 (17.4)	2 (25.0)	2 (25.0)	0 (0.00)
At rest	8 (34.8)	2 (25.0)	3 (37.5)	3 (42.9)
While coughing	15 (65.2)	4 (50.0)	6 (75.0)	5 (71.4)
Postop 7 am	3 (13.0)	1 (12.5)	1 (12.5)	1 (14.3)
Postop 7 pm	6.5 (28.2)	2.5 (31.3)	2 (25.0)	2 (28.6)

Table 5:

Attrition – number (%) of participants lost to long-term follow-up when collecting information about pain occurrence and type of long-term pain. PIB = programmed intermittent bolus, PCA = patient controlled analgesia (intravenous), POD = postoperative day

		Treatment Group		
Time	Overall (n = 23)	PCA Only (n = 8)	PIB (n = 8)	Continuous (n = 7)
POD 2	6 (26.1)	2 (25.0)	2 (25.0)	2 (28.6)
1 Month	8 (34.8)	3 (37.5)	2 (25.0)	3 (42.9)
6 Months	8 (34.8)	2 (25.0)	3 (37.5)	3 (42.9)
12 Months	7 (30.4)	2 (25.0)	2 (25.0)	3 (42.9)