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Effect of Epidural Compared to Patient-Controlled Intravenous Analgesia on Outcomes for Patients Undergoing Liver Resection for Neoplastic Disease

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Abstract

Background—Epidural analgesia is routinely used for postoperative pain control following abdominal surgeries, yet data regarding the safety and efficacy of epidural analgesia is controversial.

Methods—Pain-related and clinical perioperative data were extracted and correlated with baseline clinicopathologic data and method of analgesia (epidural versus intravenous patient-controlled analgesia) in patients who underwent hepatectomy from 2012 to 2014. Chronic pain was defined by specific narcotic requirements preoperatively.

Results—Eighty-seven patients underwent hepatectomy with 60% having epidurals placed for postoperative pain control. Epidural patients underwent more major hepatectomies and open resections. Comparison of pain scores between both groups demonstrated no significant difference (all $p>.05$). A significantly lower proportion of TEA patients required additional IV pain medications than those with IVPCA ($p<0.001$). There was no major effect of epidural analgesia on time to ambulation or complications (all $p>0.05$). After adjusting for perioperative factors, and surgical extent and approach, no significant differences in fluids administered or length of stay were detected.

Conclusions—Overall postoperative outcomes were not significantly different based on method of analgesia after adjusting for type and extent of hepatic resection. Though patients with epidurals underwent more extensive operations they required less additional IV pain medications than IVPCA patients.

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Keywords

epidural; hepatectomy; analgesia

INTRODUCTION

Epidural analgesia is routinely used at many institutions to provide postoperative pain control for patients undergoing major abdominal surgery. Although epidural analgesia has often been considered the gold standard for postoperative pain control, there is conflicting data regarding surgical outcomes and complications related to epidural analgesia. Previous studies have indicated that epidural use improves surgical outcomes by inhibiting the surgical stress response and thus reduces rates of postoperative cardiac complications, thromboembolism, and respiratory distress.[1,2] Epidural anesthesia has also been associated with earlier return of bowel function[2] and superior pain control compared to parenteral opioids.[3,4] However, there is limited data regarding the efficacy of epidurals in oncology patients undergoing complex hepatobiliary surgeries. Hepatectomy patients in particular may be at risk for complications due to coagulopathy,[5] yet other studies have concluded that there is no significant difference between epidural and intravenous (IV) patient-controlled analgesia rates of complications and overall morbidity and mortality.[6] Because of the limited and conflicting data regarding pain outcomes in patients undergoing liver resection, we conducted a retrospective study of hepatectomy patients at our institution over a two-year period to assess pain control, fluid administration, length of stay, and surgical complications. We compared patients who received thoracic epidural analgesia (TEA) to those who received intravenous patient-controlled analgesia (IVPCA). We hypothesized that TEA would prove superior to IV PCA in terms of pain control and postoperative complications.

MATERIALS AND METHODS

With approval from the Wake Forest University Health Sciences Institutional Review Board, a retrospective review of a prospective database was performed on patients who underwent hepatectomy between 2012 and 2014 at our institution and who had either IVPCA or TEA for postoperative pain control. Chronic pain was defined as having taken more than 30 mg of oxycodone or its equivalent per day for greater than one week prior to surgery, or having been on an extended-release opioid prior to surgery. A minimally invasive procedure was defined as either a pure laparoscopic or hand-assisted laparoscopic procedure. A minor resection was defined as removal of no more than two liver segments, while a major resection was the removal of three or more segments. Intraoperative and postoperative data were collected for each patient, and Clavien-Dindo postoperative complication grade[7] was recorded. Hypotension was defined as systolic blood pressure <90 mm Hg. A TEA adjustment was defined as either pausing the epidural during infusion or decreasing the infusion rate. Postoperative pain was assessed using the Numeric Rating Scale (NRS), in which patients rate pain on a scale from 0 to 10. NRS scores were recorded at 6, 12, 24, and 48 hours postoperatively.

Patient characteristics were summarized using frequencies and percentages or medians and ranges. Demographic information and surgical characteristics were compared by method of postoperative pain control using Chi-squared tests. Pain scores at 6, 12, 24, and 48 hours were compared by receipt of a TEA using ANOVA. Next, the total number of fluids (mL) and length of stay (days) was compared using ANOVA by method of post-operative pain control and, if a TEA was administered, by functional TEAs and by intraoperative TEA infusion. In patients who received a TEA, univariate logistic regression was used to assess odds of functional TEA and hypotension.

The average total fluid was compared between TEA and IV PCA patients by the presence of cardiac disease, vasopressor infusion, TEA status, TEA performed during the procedure, and by whether not the TEA was functioning using ANOVA. The relationship between total fluids and other continuous variables was evaluated using Pearson's correlations. Variables with univariate p values less than 0.20 were selected for a multivariate linear regression model assessing associations with the total number of fluids. The same analysis was repeated for length of stay (log transformed for normality). We determined the relationship between various factors on First Clear Liquid Intake, First Solid Food Intake, and First Walk (all categorized as 0,1 or 2+ days), Complication Grade (none, I, II, III, IV, or V) and TEA or IPVCA administration. Lastly, linear regression was used to determine if differences in pain scores, total fluids, and length of stay by method of pain control (TEA vs IV PCA) existed after adjusting for operating room time, estimated intraoperative blood loss, postoperative vasopressor requirement, surgical approach (minimally invasive vs. open), and extent of liver resection (major vs. minor). All analysis was performed in SAS Version 9.4 (Cary, NC), and p values less than 0.05 were considered significantly associated with the outcome of interest.

RESULTS

Eighty-seven patients met the inclusion criteria, of which sixty percent (n=53) had TEA for postoperative pain control. Of those 53 patients, 13 percent had nonfunctional TEAs and 25 percent experienced hypotension, requiring a median of 2 adjustments (range 0-5). Univariate logistic regression models indicated that a performance status of 2 (versus 0) was a predictor of a nonfunctional TEA (p=0.033). Univariate regression models indicated no significant predictors of hypotension (p>0.05 for all variables). Patients with TEA tended to have more major resections and open surgeries instead of minimally invasive surgeries (Table 2). Of the 53 patients who had TEA, 7.5 percent (n=4) had delayed removal of the catheter due to coagulopathy or low platelet count.

Excluding patients with chronic pain, there was no statistically significant difference in NRS pain scores at 12, 24, and 48 hours postoperatively between the TEA and IVPCA groups, but a significant difference in NRS pain scores at 6 hours postoperatively (mean pain score was 3.23 in patients without TEA vs. 1.95 in patients with TEA, p=0.046) was detected. However after adjustment for perioperative factors, there was no significant difference in mean pain scores at all time points. (Table 3)

Vasopressor infusion and the presence of a TEA were associated with higher amounts of perioperative fluid administration (p=0.021 and 0.014, respectively; Table 3).

Patients with TEA had significantly longer hospital stays than those with IVPCA (median 6 days vs. 4 days, p=0.039; Table 3). After adjustment for receipt of a TEA, age, length of operation, and total fluids; preoperative Eastern Cooperative Oncology Group (ECOG) performance status of zero was associated with a significantly shorter length of hospital stay versus patients with a performance status of two (p=0.046).

Of the 53 patients who had TEAs placed, 14 (26.4%) required the addition of an IVPCA or adjunctive IV pain medications, most commonly ketorolac or acetaminophen. The mean time to addition of the IVPCA was 0.57 days (range 0-2 days). Of the patients with IVCPA, 24 (70.5%) required additional IV pain medications, a significantly higher proportion than patients with TEA (p<0.001). Postoperative outcomes did not differ significantly by type of analgesia or with the addition of IV medications for pain control. Overall, a higher percentage of patients with TEA than those with IV PCA had their first solid intake by postoperative day 2. However, when stratified by postoperative day, there was no significant difference in time to first solid in terms of method of analgesia and addition of IV pain medications (p=0.4576 for POD 1 and p=1 for POD 2).

After adjusting for operating room time, estimated intraoperative blood loss, postoperative vasopressor requirements, and surgical extent and approach, fluids administered and length of stay did not differ significantly by method of pain control (TEA vs. IVPCA) (Table 3). Seven of 53 patients with TEA required intraoperative blood transfusions (13%), compared to 4 of 34 patients with IVPCA (11%) (p=0.805).

DISCUSSION

Although epidural analgesia has been shown to be beneficial in many types of abdominal surgeries, there is special concern for its use in hepatectomy patients due to complications related to coagulopathy and increased transfusion requirements. Multiple studies have indicated that changes in coagulation profiles occur in patients undergoing liver resections[8,9,10], leading to a theoretical increased risk for epidural hematoma formation following epidural catheter removal. However, Elterman and Xiong reported that in spite of increased PT and INR and decreased platelet counts, none of the hepatectomy patients in their study who received epidurals developed epidural hematomas.[8] Another study reported an increased risk of packed red blood cell transfusion associated with epidurals in hepatectomy patients, as compared to patients receiving intravenous analgesia.[11]

However regional anesthesia may also have benefits in abdominal surgery. Epidural analgesia may block the sympathetic stress response to surgery, allowing for faster return of bowel function, decreased cardiac work and myocardial oxygen demand, and reduced pulmonary complications.[12, 13] Also, effective epidural analgesia reduces opioid requirements for postoperative pain control. Although still an area of controversy, some studies have indicated that opioids have the potential to upregulate the inflammatory response and promote tumor growth.[14] Thus, protocols for enhanced recovery after surgery

(ERAS) have recommended the use of regional anesthesia and NSAIDs for pain control in hepatectomy patients to limit opioid requirements, decreasing their negative potential immunomodulatory effects.[15] These potential benefits of epidural analgesia must be weighed against the theoretical risks of coagulopathy and increased transfusion in hepatectomy patients.

The selection of pain control method for the patients in our study was not based on a standardized pain management protocol. The decision of whether to administer a TEA or IV PCA for postoperative pain control was made at the discretion of the operative surgeon.

None of the patients in our study developed TEA hematomas or abscesses, although 7.5 percent had delayed catheter removal due to changes in coagulation profiles. These results are in agreement from a study by Elterman and Xiong[8], indicating that epidural analgesia can be safe in patients undergoing liver resection.

Of the 60 percent of patients in our study who had TEA for postoperative pain control, 13 percent had nonfunctional TEAs and 25 percent experienced hypotension. We attempted to identify specific factors that were predictors of nonfunctional TEAs and hypotension by performing a univariate analysis, but the only significant finding was an ECOG performance status of 2. As this was not the primary objective the study, the study was likely underpowered for this specific analysis.

Our data indicate that there is no significant difference in pain scores between patients who received TEA and those who received IVPCA for postoperative pain control after adjusting for confounding factors. This was true among patients with or without chronic pain. After adjusting for extent and approach of resection, OR time, and postoperative vasopressor requirement, there was no statistically significant difference in pain scores between patients who had TEA and those who had IVPCA. Patients with TEA who underwent more extensive and invasive resections had similar pain scores to those with IVPCA who underwent less invasive and less extensive surgeries. In addition, a significantly lower proportion of patients with TEA required additional IV pain control than IVPCA patients. This suggests that epidural analgesia may actually be superior to IVPCA in terms of pain control for this patient population. A randomized trial by Revie et al compared epidural analgesia to IVPCA with local anesthetic wound infiltration in hepatectomy patients.[16] They found that patients in the epidural group had lower pain scores in the first 48 hours after surgery both at rest and with movement. However there was no difference in complication rates or time to first mobilization.

We analyzed the amount of fluids received by each patient intraoperatively and in the initial 24 hours postoperatively, as well as the length of hospital stay. Initial analysis indicated that TEA patients received significantly more fluids than patients who had IVPCA (8.6 L vs. 6.6 L, $p = 0.014$). This is probably due to the significantly higher rate of open and major hepatectomies in the TEA cohort, leading to higher insensible fluid and blood loss, as well as the fact that 25% of TEA patients experienced postoperative hypotension. Patients with TEA were also found to have a significantly longer length of hospital stay– a median of 6 days for TEA vs. a median of 4 days for IVPCA ($p = 0.039$). However, after adjusting for

potential confounding factors such as extent and approach of surgery, estimated intraoperative blood loss, OR time, and postoperative vasopressor requirement, there was no significant difference in either fluid requirements or length of hospital stay between TEA patients and IVPCA patients (Table 3). Page et al reported no difference in length of hospital stay between epidural patients and those receiving IV analgesia; there was also no significant difference in extent of resection (major vs. minor) between epidural and non-epidural patients in their study. [11] They did not report surgical approach (open vs. minimally invasive). This suggests that our finding of an association between longer hospital stays and TEA analgesia is not a direct result of epidural usage, but is instead due to the tendency of patients undergoing larger resections and more invasive surgeries to be selected for TEA in this study.

There was no statistically significant difference between the percentage of TEA patients and the percentage with IVPCAs who required packed red blood cell transfusions intraoperatively. Our threshold for transfusion was generally hemoglobin less than 7.0 g/dL, however this varied intraoperatively depending on many factors that included the hemodynamic stability of the patient, estimated blood loss during the case, and concern for future excessive blood loss. Page et al reported a significant association between epidural analgesia and transfusion requirements, which they theorized was due to low central venous pressure technique in the face of hypotension caused by epidural use, leading to more aggressive fluid resuscitation and transfusions.[11] However, their results included the postoperative period, whereas our results are for the intraoperative period alone.

Overall, a higher percentage of TEA patients had their first solid intake by POD2. But when the data are stratified by postoperative day, there is no significant difference in time to first solid between patients with either IV PCA or TEA alone and those with additional pain medications. Patients undergoing hepatectomy can generally advance their diet early in their postoperative course and type of analgesia appears to have a negligible effect on this.

There was no difference in overall Clavien-Dindo complication grade between TEA patients and IVPCA patients in our study. These results are in agreement with those in the prospective study by Revie et al.[16]

The limitations of this study are a small sample size and lack of a standardized protocol for management of TEA in hepatectomy patients. In addition, there was selection bias in choosing patients for TEA versus IVPCA. Patients with more extensive surgeries tended to be selected for TEA. Furthermore, the pain scores did not account for the specific quantities of pain medication or intraoperative local anesthetic administered. In addition, we feel that a cost analysis of IV PCA vs epidural would be beneficial in future studies. An advantage of this study was the ability to collect a substantial amount of data on postoperative outcomes and perioperative pain scores. Collaboration with the anesthesiology pain service faculty allowed the extraction and interpretation of intraoperative data.

CONCLUSIONS

After adjusting for extent and approach of surgery, there were no differences in outcomes between patients with TEA and those with IVPCA, and none of the patients in our study experienced major complications related to epidural use. In addition, pain scores did not differ between patients with TEA and those with IVPCA, even though patients with TEA tended to have larger and more extensive surgeries. Patients with TEA also had a lower requirement for additional IV pain medications than patients with IVPCA alone. These results suggest that epidural analgesia can be a safe and effective method of perioperative pain control in patients undergoing liver resection. A prospective study is necessary to further explore the use of epidural analgesia in hepatectomy patients, as well as a cost analysis.

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Synopsis

The use of epidural analgesia in patients undergoing liver resection remains an area of controversy. This analysis compared postoperative outcomes between hepatectomy patients who received thoracic epidural analgesia and those who received intravenous patient-controlled analgesia for postoperative pain control.

Table 1

Demographic information by method of postoperative pain control.

	TEA		IVPCA		P value
	n	%	n	%	
Sex					
Male	24	27	17	19	0.667
Female	29	33	17	19	
ECOG Performance Status					
0	30	34	20	23	
1	19	22	13	15	
2	4	5	1	1	
Extent of surgery					
Major	24	27	6	7	0.008
Minor	29	33	28	32	
Surgical approach					
Open	42	48	20	23	0.040
Minimally invasive	11	12	14	16	
Chronic pain preoperatively					
Yes	8	9	4	5	0.660
No	45	52	30	34	
Additional non-PCA[a] IV pain medications					
Yes	22	27	24	30	0.015
No	31	30	10	13	

IVPCA: intravenous patient-controlled analgesia; ECOG: Eastern Cooperative Oncology Group

[a]14 TEA patients required a PCA for additional pain control

Table 2

Adjusted[a] mean outcomes by method of pain control.

	6 hr postoperative pain score		12 hr postoperative pain score		24 hr postoperative pain score		48 hr postoperative pain score		Length of stay[b]		24 hr postoperative fluids (mL)	
	Adjusted Mean	P value	Adjusted Mean	P value	Adjusted Mean	P value	Adjusted Mean	P value	Adjusted Mean	P value	Adjusted Mean	P value
IVPCA	2.42	0.201	2.40	0.859	2.21	0.169	2.54	0.857	1.62	0.252	4196	0.336
TEA	1.51		2.55		3.20		2.42		1.76		4505	

IVPCA: intravenous patient-controlled analgesia

[a]Models are adjusted for OR time, estimated intraoperative blood loss, postoperative vasopressor requirement, surgical approach (minimally invasive or open), and extent of liver resection (major or minor).

[b]Log-transformed to satisfy normality assumption.

Table 3

Effects of TEA and IVPCA on total fluids administered intraoperatively and within the first 24 hours postoperatively, and on the length of hospital stay.

	Total Fluids (L)			Length of Stay (days)		
	Mean	**SD**	**P value**	**Median**	**Min, Max**	**P value**
TEA	8.2	3.2	0.014	6	1,26	0.039
IVPCA	6.6	2.3		4	2,24	
Functional TEA	8.3	3.3	0.722	6	5,13	0.452
Nonfunctional TEA	7.8	2.5		6	1,26	
Intraoperative TEA infusion	8.0	3.6	0.207	6	1,26	0.093
No intraoperative TEA infusion	7.2	2.5		5	2,24	