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ORIGINAL ARTICLE

Coagulation profile changes and safety of epidural analgesia after hepatectomy: a retrospective study

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Abstract
Purpose We aimed to review post-hepatectomy coagulation profile changes, to assess outcomes of epidural catheter placement in post-hepatectomy patients, and to make justifications regarding use of epidural analgesia in patients undergoing hepatectomy.
Methods We performed a retrospective study of 141 patients undergoing liver resection at Brigham and Women's Hospital between January 1, 2007 and December 31, 2011. All patients were between 21 and 85 years old, with ASA physical status classification of II or III, and Child-Pugh scores ≤6. Patients undergoing laparoscopy or resection of less than three hepatic segments were excluded. We examined pre-operative hematocrit, platelet count, coagulation studies, and liver function tests, and trended values for 7 post-operative days. We examined frequency of epidural placement, use of peri-operative anticoagulation, and incidence of epidural-related complications.
Results We demonstrated statistically significant decreases in hematocrit and platelet counts, as well as statistically significant increases in prothrombin time and international normalized ratio (INR) values. Thirty-two percent of patients required vitamin K or fresh frozen plasma to achieve an INR ≤1.3. No patient required platelet transfusion to achieve platelets ≥100,000 prior to catheter removal. Changes in post-operative partial thromboplastin time were not significant. Epidural catheters were placed in 90 % of liver resections performed at our institution. We noted no epidural hematomas, even in the 7 % of patients in whom the epidural catheter was inadvertently removed before coagulation criteria were met. The latter group was monitored with hourly neurologic exams for 24 h.
Conclusion Epidural analgesia may be safely used in patients undergoing major hepatic resection, providing that they have normal pre-operative coagulation and catheters are removed only when resection-induced perioperative coagulopathy has resolved or has been corrected.

Keywords Hepatectomy · Coagulopathy · Epidural anesthesia

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Introduction

Over the past few decades, hepatic resection has become the mainstay of treatment for both primary and secondary (metastatic) liver malignancies [1]. Procedure-related morbidity and mortality has dropped significantly, partly due to the overall advances in surgical and anesthetic techniques, better understanding of hepatic pathophysiology, and improvement in peri-operative management [2, 3]. However, post-operative pain management remains a challenge after hepatic resection due to the presence of a large surgical incision. Compared with several other post-operative pain modalities, such as patient controlled analgesia (PCA) and the On-Q Pain Buster System, epidural analgesia is logically far superior for a large laparotomy because it provides excellent pain relief as well as reducing pulmonary complications and the duration of post-operative ileus [4]. However, post-hepatectomy alterations of coagulation profiles such as increases in the prothrombin

time/international normalized ratio (PT/INR) and the partial thromboplastin time (PTT), as well as decreases in platelet counts (PLT) have been reported [5–8] and thus epidural anesthesia is not universally used due to the risk of epidural hematoma formation.

In this study, we conducted a chart review of patients undergoing major hepatic resection at our institution over 5 years, and examined post-operative coagulation profile changes as well as the anesthetic management and post-operative outcomes at our center to assess the safety of epidural catheters in patients undergoing liver resection. We present our experience with these patients and our strategies to reduce post-operative neurological complications associated with epidural analgesia in patients undergoing major hepatic resection.

An abstract of this work showing preliminary data was presented at the 2013 American Society of Anesthesiologists Annual Meeting (A3122; Washington DC, October, 2013).

Materials and methods

Design and setting

After obtaining approval by the Institutional Review Board of Partners Health Care, Boston, MA, we conducted a retrospective study to review all patients undergoing hepatic resection from January 1, 2007 to December 31, 2011. This chart review study was conducted at Brigham and Women's Hospital, a Harvard Medical School-affiliated tertiary-care center and member of the Partners Healthcare organization. We obtained the complete list of patients who underwent liver resection during this time frame by querying our electronic medical record and operating room systems.

All patients undergoing hepatic resection between the ages of 21 and 85, with ASA physical status classification of II or III, and Child-Pugh scores $\leq$6, were considered eligible for this study. Patients with ASA physical status of greater or equal to IV, as well as those with a Childs-Pugh score >6, were excluded. Patients who did not have daily post-operative lab values, or had values only for 1 or 2 days post-operatively, were also excluded.

Since the amount of liver tissue resected has been shown to influence the degree of post-operative coagulopathy [7], we focused only on cases of major hepatic resection. Thus, unless stated otherwise, all patients undergoing hemi-hepatectomy with laparotomy, defined by either right hepatectomy that involved the resection of segments V through VIII, or left hepatectomy that involved the resection of segments II through IV, with or without segment I [9], were included in this study. Hepatectomy with resection of three segments were also included. Patients undergoing laparoscopic hepatic resection, minor hepatic resection, such as single segment or wedge resection, or hepatic resection combined with other abdominal surgery (e.g. Whipple procedure or bowel resection), were excluded.

Patients

We found a total of 680 liver resection patients from our institution's database from 2007 to 2011. Based on our protocol design criteria (see above), we identified 141 eligible patients. The majority of these cases required liver resection due to metastatic hepatic lesions from colorectal cancer, although some involved other lesions, such as hepatoma and hemangioma. All patients underwent general anesthesia with endotracheal intubation, with or without epidural analgesia. For those who received epidural analgesia, the epidural catheter was placed pre-operatively. Epidural analgesia (except the initial "test dose" of 3 ml 2 % lidocaine with 1:200,000 μg epinephrine) was not initiated until after completion of the surgical procedure. All patients had a radial arterial catheter placed for hemodynamic monitoring intra-operatively, and some had a central venous line placed for better IV access.

Measures of variables

We examined pre-operative hematocrit, platelet count, PT/INR, and PTT, as well as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). We then examined the immediate post-operative (POD 0) values, and trended these values for a total of 7 post-operative days (POD 1–POD 7). The lab values of patients who were discharged or whose last known values were prior to the 7th post-operative day were trended as far as the last known values. Additionally, we collected data regarding the frequency of epidural placement in these procedures, the use of peri-operative anticoagulation, the total estimated blood loss (EBL) for the procedure, the amount of hepatic tissue resected, the post-operative day on which the epidural was removed, whether blood products were administered to correct INR or platelets prior to epidural removal, and the incidence of epidural-related complications, specifically hematoma formation, neurologic injury, or the need for frequent neurologic monitoring due to concern for potential neurologic injury.

Statistical analysis

Data were summarized and analyzed using SAS version 9.3 software (SAS Institute, NC, USA). All results are presented as percentages for categorical variables and as mean $\pm$ standard deviation (SD) for continuous variables. For each variable of the post-hepatectomy coagulation

profile, differences were analyzed by repeated measures ANOVA. A series of Bonferroni-adjusted pair-wise comparisons were performed to study the effect. All statistical tests were two-sided, with a type I error of 0.05. A $P < 0.05$ was considered statistically significant.

Results

Our results demonstrated that epidurals were placed in 90 % of liver resections (127 out of 141 patients) performed at our institution. As our primary goal was to determine the safety of epidural analgesia in patients undergoing hepatectomy, the remaining 14 patients were excluded from the data analysis.

All 127 patients included in this study underwent major hepatic resection, as previously defined, by two experienced surgeons. The demographic characteristics and essential intra-operative patient data are summarized in Table 1.

The average operative time was 6.02 ± 1.5 h and the average amount of hepatic tissue resected was 450 g (range 230–800 g). All patients remained normothermic intra-operatively (temperature 36.4 ± 0.5 °C). The average EBL was 837 ± 818 ml, and the average maximal decrease of hematocrit was 25 %, occurring on POD 3 (28.62 ± 3.62 on POD 3 compared with 38.29 ± 3.97 pre-operatively). Twenty-one percent of patients required transfusion of packed red blood cells intra-operatively or immediate post-operatively (Table 1). We observed a statistically significant decrease in platelet count of 46 % occurring on POD 3, and then a gradual return to baseline level on POD 7 (Fig. 1). In addition, PT and INR values increased significantly after hepatectomy, with a peak elevation in PT of 37 % on POD 2 (18.78 ± 2.47 on POD 2 compared with 13.76 ± 1.44 pre-operatively). By POD 7, these values, while still elevated, appeared to decrease towards their baseline (Fig. 2). Of note, 40 of 127 patients required vitamin K or FFP to correct PT/INR prior to epidural catheter removal, and therefore were removed during the determination of this trend so as not to confound the results. Changes in post-operative PTT were not clinically significant. Liver function tests (ALT and AST) were elevated post-operatively, but these changes were self-limited and resolved within 5–8 days post-operatively (Fig. 3).

Table 1 Demographic and perioperative data of patients undergoing hepatectomy

Age (years)	58 ± 13
Gender (female/male)	65/76
Body mass index	27.4 ± 4.9
Surgical duration (h)	6.02 ± 1.5
Core body temperature (°C)	36.4 ± 0.5
Liver tissue resected	450 g (range 230–800 g)
Estimated blood loss (ml)	837 ± 818
Crystalloids administered (ml)	4,936 ± 1,980
Colloids administered (ml)	608 ± 545
% Requiring blood product transfusion	21
Blood or cell saver transfused (units)	2.3 ± 1.5
Fresh frozen plasma transfused (units)	3.9 ± 1.8
Day of epidural catheter removal	POD 4.45 (POD1–POD13)

Demographic data and perioperative procedure details of all patients included in study

No patient received subcutaneous heparin pre-operatively, and initiation of 5,000 units of heparin dosed subcutaneously every 8 h for DVT prophylaxis was held for 8 h post-operatively, as is the standard practice in our institution. Per the guidelines of our institution, platelets and INR were confirmed to be ≥100,000, and ≤1.3, respectively, prior to epidural placement. For the majority of patients with epidural catheters, these same criteria were met at the time of catheter removal. Specifically, on the day of epidural catheter removal (usually between POD 4 and POD 5, mean POD 4.45), the mean platelet count and INR values were approximately 220,000 (80,000–662,000) and 1.26 (1.0–1.8), respectively. As evidenced by the lower limit of the platelet range and the upper limit of the INR range, not all patients met all epidural catheter removal criteria on the day of epidural catheter removal. This is because 9 patients (7 % of total) experienced inadvertent epidural catheter removal in the setting of inappropriately low platelets or high INR. Additionally, 40 out of 127 patients (32 %) required vitamin K or FFP to correct the INR prior to epidural removal. On the day of FFP or vitamin K administration, the INR and platelet values of these 40 patients were 190,000 (97,000–509,000) and 1.52 (1.1–2.0), respectively. No patient required platelet transfusion.

The incidence of epidural hematoma was zero, although the 7 % of patients with inadvertent epidural catheter removal mentioned above did require hourly neurologic exams over the course of a 24-h period. The mean platelet count on the day of inadvertent catheter removal in these patients was 192,000, and the mean INR was 1.4. Despite the need for monitoring, no epidural-related neurologic complications were identified.

Discussion

Post-operative coagulopathy after liver resection is a well-known phenomenon that results from the combination of blood loss, consumption of coagulation factors, and transient hepatic synthetic insufficiency [10]. Typically, it manifests as an increase in the prothrombin time and a

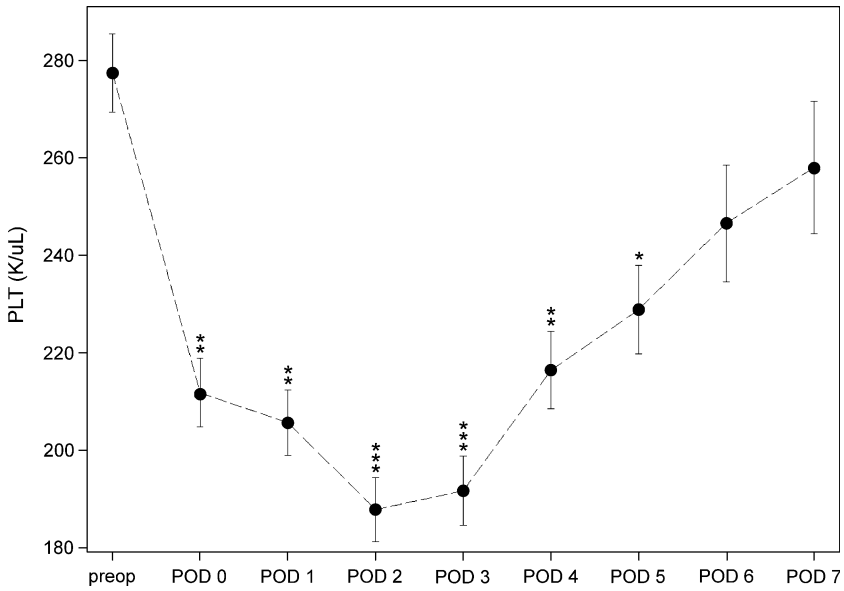

Fig. 1 Change in platelet (PLT) count after hepatectomy. All data points are expressed as mean (*filled circles*) ± SD (*bars*). Preop denotes pre-hepatectomy; POD denotes post-operative day(s). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, all compared with preop value ($N = 127$)

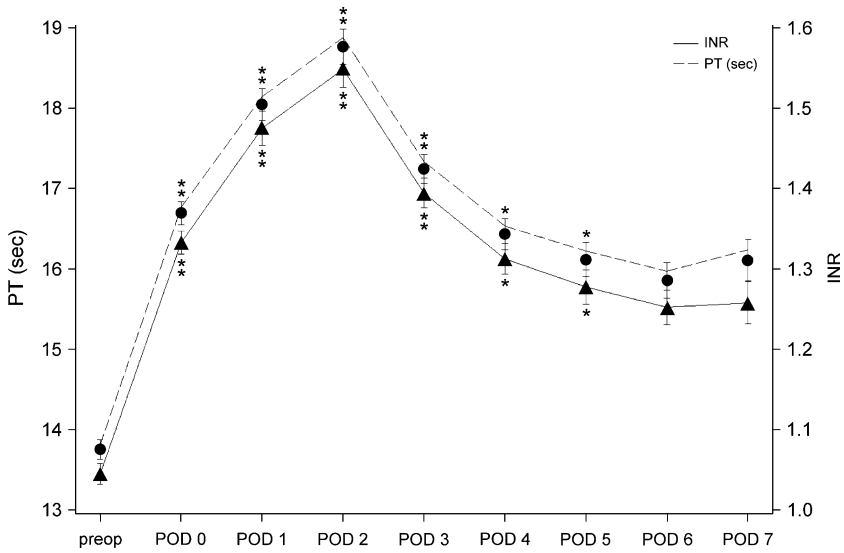

Fig. 2 Change in PT and INR after hepatectomy. All data points are expressed as mean (*filled symbols*) ± SD (*bars*). *Filled circles* and *dotted line* represent PT, and *filled triangles* and *solid line* represents INR. Preop denotes pre-hepatectomy; POD denotes post-operative day(s). $*P < 0.05$, $**P < 0.01$, compared with preop value. *Note* $N = 87$ in this figure because 40 patients who received FFP or vitamin K were excluded

decrease in platelets, as confirmed by this study. While the degree of change varies from patient to patient, a clinically significant difference has been documented in several studies [5, 7, 8, 10–14]. This difference poses a dilemma for anesthesiologists caring for patients undergoing liver resection in that as the procedure is a major abdominal operation, patients would benefit from epidural analgesia, however, the presence of concomitant or expected post-operative coagulopathy imposes an increased risk for epidural hematoma [15].

Because of this increased risk, the topic of epidural analgesia for patients undergoing liver resection has been much debated. For patients with underlying liver disease, pre-operative coagulopathy may not only prevent the safe placement of an epidural catheter, but also predispose to increased post-operative coagulopathy [11]. Additionally, those undergoing major hepatic resection are also at increased risk [12]. In the presence of elevated PT/INR post-operatively, epidural catheter removal may need to be delayed [16, 17], potentially increasing the risk for infection. Importantly, as approximately 7 % of epidural catheters can become inadvertently dislodged [17], placing an epidural catheter in a patient who will likely become coagulopathic post-operatively could be considered problematic. Further, while post-operative coagulopathy can be partially reversed with administration of FFP, INR cannot be easily decreased below 1.3, and transfusion of blood products is certainly not without its own risks. For all of these reasons, several clinicians choose to avoid epidural analgesia in patients undergoing liver resection.

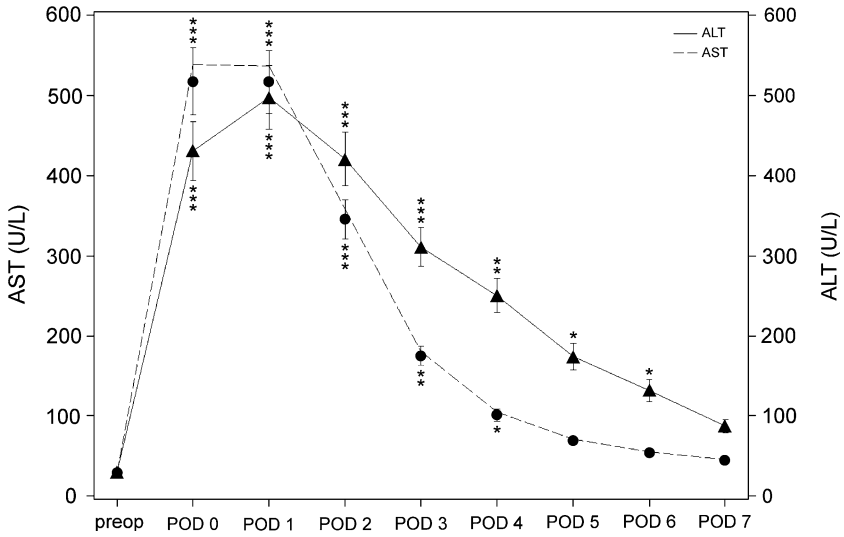

Fig. 3 Change in AST and ALT after hepatectomy. All data points are expressed as mean (*filled symbols*) ± SD (*bars*). *Filled circles* and *dotted line* represent AST, and *filled triangles* and *solid line* represents ALT. Preop denotes pre-hepatectomy; POD denotes post-operative day(s). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with preop value ($N = 127$)

However, these concerns, while certainly relevant in patients with extensive hepatic disease or cirrhosis, may not necessarily contraindicate epidural analgesia for all patients undergoing liver resection. First, while it is true that nearly all patients develop clinically significant coagulation abnormalities as early as post-operative day 1, these aberrations often resolve by the 4th or 5th post-operative day (see Fig. 2) [5, 7, 13] which is within a reasonable timeframe for epidural catheter duration. Of note, post-operative coagulopathy in these patients is frequently determined by PT/INR prolongation. Despite this well-established post-operative hemostatic abnormality, Barton et al. [18] showed that thromboelastography (TEG) actually demonstrates transient hypercoagulability and unchanged clot strength after liver resection. Fazakas et al. [19] have also suggested that the presence of a normal TEG may be useful in guiding the decision to pursue epidural analgesia in patients undergoing hepatectomy. Regardless of whether coagulation dynamics are assessed by PT/INR or TEG, no epidural or spinal hematomas have been reported in patients undergoing liver resection without pre-operative coagulation abnormalities [20]. Choi et al. [8] demonstrated this as well in their study of 242 healthy liver donors undergoing hepatic resection with epidural catheters in which no epidural hematomas were observed despite post-operative changes in coagulation profiles.

Although guidelines regarding neuraxial instrumentation in the setting of elevated PT/INR have been set forth by the American Society of Regional Anesthesia and Pain Medicine (ASRA) [21], the recommendations to avoid epidural placement or catheter removal when INR is greater than 1.5 were developed for patients on anticoagulants, rather than those with coagulopathy as a result of liver disease or resection. Nonetheless, these recommendations are often applied to patients with coagulopathy for any reason.

At our center, epidural analgesia was only offered to those relatively healthy patients (ASA class II or III) undergoing liver resections as a post-operative pain management modality, since these patients are less likely to develop profound coagulation abnormalities as compared to their cirrhotic counterparts. In managing epidural catheters in these patients, our approach is more conservative than that suggested by Horlocker et al. [21]. We typically do not place nor remove epidural catheters unless the INR is $\leq$1.3. Similarly, we do not remove epidural catheters if the platelet count is <100,000. Often, simply delaying catheter removal until POD 4 or 5 is sufficient to achieve these goals. Rarely, if that is not enough, we would transfuse FFP or platelets in an effort to normalize the INR or platelet count.

We performed this retrospective chart review to determine the safety of our management strategy. As described, we reviewed 141 patients, ASA class II–III, undergoing either right or left hepatectomy at our institution between 2007 and 2011. Our findings as far as mean blood loss and percent change in post-operative hematocrit, platelets, and PT/INR values are on par with those of other studies. Interestingly, we did note that epidurals were placed in 90 % of our patients, which is only slightly higher than that reported elsewhere in the literature [14]. Despite a higher rate of epidural placement, our present study did not find a single case that developed an epidural hematoma post-operatively. Seven percent, however, did require q1h neurologic examinations to monitor for hematoma development due to unintended epidural catheter removal in the setting of platelets <100,000, or INR >1.3. None of these patients were found to have any neurologic complications. Similar to the findings of Yuan et al. [11], hemostatic goals for epidural removal in our study were achieved by POD 4 or 5.

We believe our safe use of epidural analgesia for patients undergoing hepatectomy is due to our conservative management strategies. While a small portion of our patients required FFP, vitamin K, or platelet transfusion to meet the goals for epidural removal, none developed a transfusion reaction. Additionally, no pre-operative nor immediate post-operative subcutaneous heparin was administered to any patient.

The limitations of this study are those inherent to retrospective study design, mainly reliance on accuracy of chart documentation and limitations of available data. Despite these limitations, our data indicate that epidural analgesia can be safely performed for patients undergoing liver resection. Adherence to ASRA guidelines, or an even more conservative approach, regarding epidural placement and removal, may be important to the safety of such practice. Based on our experience, we recommend the use of epidural analgesia for otherwise relatively healthy patients undergoing liver resection.

Conclusion

Patients undergoing elective major hepatic resection inevitably become moderately coagulopathic. However, this phenomenon is typically self-limited and often resolves within 7 post-operative days. While many clinicians are understandably concerned about using epidural analgesia in patients expected to become coagulopathic, when used cautiously, with stringent post-operative monitoring and conservative hemostatic goals surrounding catheter placement and removal, epidural analgesia can be a safe and effective modality for post-operative pain management in these patients.

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Conflict of interest No author has financial interests to disclose.

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