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# Anesthesia and Hepatic Resection

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**The emergence of partial hepatectomy as a safe and effective treatment for both benign and malignant liver disease is relatively recent due to the high mortality rate traditionally associated with the surgery. Currently, the surgical literature still questions the mortality and morbidity incidence and prevention techniques associated with hepatectomy. Improved knowledge of hepatic anatomy makes it possible to limit the extent of the resection and reduce blood loss. From an anesthetic standpoint, a number of questions are relevant. How can blood loss during the operation be reduced? How can safe postoperative analgesia be assured? Hepatic resection temporarily disrupts hemostasis. Is an epidural safe in these circumstances?**

## HEPATIC ANATOMY

An adult liver weighs approximately 1.5 kg. Its anatomy seems simple: a right and left lobe when viewed from above, and a quadrate and caudate lobe underneath. But a complex segmentary structure lies below the surface: parenchyma with few guide points and a tangle of three vessels that can bleed profusely. The liver consists of eight segments, each containing a stem of portal and bile vessels. These segments correspond to the functional anatomy, on which resections are primarily based.

## HISTORICAL BACKGROUND

The first hepatectomy was successfully performed by Carl von Langenbuch in the 19th century. A 30-year-old woman had a 370 g tumour removed. She returned that night for control of hemorrhaging and, fortunately, survived. From 1960 to 1970, hepatic surgery retained a high morbidity rate, with a mortality rate of close to 18% for a left hepatectomy and 50% for a right hepatectomy. The main causes of death were liver failure and hemorrhage. Today, the mortality rate is about 5% in large centres and as low as 2% to 3% in highly specialized ones.

From a surgical point of view, segmentary resections are now performed that preserve a maximum amount of hepatic parenchyma, while reducing tumour size and blood loss. From an anesthetic standpoint, maintaining a low central venous pressure (CVP) allows for better control of vascular bleeding and reduced blood loss.

## PATIENTS

Patients undergoing a hepatectomy range in age from 19 to 85 years. Approximately 10% of hepatectomies are for benign lesions and 90% are for malignant lesions. Of the latter, 20% are primary and 80% metastatic, and the origin of most of the latter is colorectal cancer.

## PRE-OPERATIVE ASSESSMENT

Patients in good health simply need a routine preoperative assessment, including a complete blood count and standard biochemical and coagulation tests.[1] With chronic liver disease, multisystemic complications have to be ruled out. When examining the lungs, look for pulmonary hypertension or arterial hypoxia caused by ascites or an intrapulmonary shunt. Heart disease is frequent (caused by alcohol abuse or vitamin deficiency) and a dobutamine stress echocardiogram can determine cardiac capacity for dealing with vascular clamping. Any infection and/or hepatic decompensation must be

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treated, since their presence increases mortality. Kidney dysfunction is associated with chronic liver disease and must be investigated.

The American Society of Anesthesiologists (ASA) classification does not take into account the importance of hepatic function in patients with chronic liver disease. The Child-Turcotte classification is better at predicting the mortality of cirrhotic patients who have to undergo liver surgery.

## ANESTHETIC TECHNIQUE

All patients require general anesthesia with tracheal intubation. The presence of ascites might justify rapid sequence induction. Distribution volume is increased for the induction agents, but metabolism is slowed in patients with liver failure. The induction doses remain essentially the same.[2,3]

Isoflurane is the most commonly used agent to maintain anesthesia. Sevoflurane reduces the increase in postoperative liver enzyme levels, but the clinical significance of this finding remains unknown.[4] As for neuromuscular blocking agents, the traditional recommendation is to use those that do not depend on hepatic metabolism yet, in practice, in the literature on this subject, rocuronium and vecuronium are the most commonly used agents. Two large-calibre venous accesses are preferable because of high and unpredictable blood loss. In addition to basic monitoring, an arterial canula and central venous catheter are installed. Prophylactic antibiotic treatment is indicated due to the length of the operation, the creation of dead space, and tissue devitalisation.

## MAINTAINING A LOW CVP

Two articles published in the *British Journal of Surgery* in 1998[5,6] reported a correlation between a low CVP and blood loss during hepatic resection. A study by Jones et al reported blood loss of 200 mL when the CVP was < 6 cm $H_2O$ and 1,000 mL when the CVP was above that level.[5] The transfusion rate increased from 5% to 48%. A CVP of ≤5 cm $H_2O$ not only reduces blood loss, but also the morbidity associated with multiple transfusions and the consequences of hemorrhaging. This approach restricts fluids until the vessels are controlled and the parenchymal resection is finished.

At the Memorial Sloan-Kettering Cancer Center,[7] this objective is achieved by administering only maintenance fluids during the resection and small crystalloid boluses (250 mL) as needed to maintain systolic pressure >90 mm Hg and diuresis at 25 mL/hr. With this approach, the average blood loss is 641 mL and the transfusion rate is 47%. A slight (~15º) Trendelenburg position reduces the impact of hypovolemia, increases glomerular filtration, and protects against gas embolism. Occasionally, intravenous morphine or nitroglycerine is necessary to reduce the CVP even further. Euvolemia is restored at the end of the procedure.

A low CVP exposes the patient to hypovolemia with the risk of inadequate perfusion of the vital organs and a lack of volemic reserve in the event of bleeding, as well as the risk of an air embolism. Aside from a transient rise in postoperative creatinine levels in a few patients, the Memorial Sloan-Kettering Cancer Center encountered no major problems with this technique. A 0.1% incidence of air embolism was found in 1,803 patients. Other studies,[9] however, reveal a 10% risk of temporary and about 3% permanent kidney dysfunction following a major resection.

Not all centres monitor CVP. At New York Presbyterian Hospital,[1] the fluid treatment is adjusted to maintain diuresis at >0.5 mL/kg/hr, with fluids restricted before and during hepatic resection. Nitroglycerine is used when the liver is distended or if seepage from the resected surface appears excessive. Blood loss and transfusion rates at that hospital are comparable to those where low CVP is used.

A European review of hepatic resection[9] warns against relying on CVP during this operation. The pressure of the retractors on the diaphragm increases intrathoracic pressure and, thereby, CVP. Clamping of liver vessels and mobilization of the liver by compressing the portal vein and vena cava reduces venous return and lowers the CVP. Compression of the liver, by releasing a significant quantity of blood, increases it. A review of 30 living donors who underwent a right or left hepatectomy for a transplant found no correlation between maintaining a low CVP and blood loss.[10] The average CVP was 7.7±2.8 cm $H_2O$ and blood loss was 55 mL. According to the authors, maintaining a low CVP is desirable (but not essential) to reduce hepatic venous bleeding and improve hemostatic control during resection. Meticulous surgical hemostasis appears to be more important.

## HEMOSTATIC CONTROL

Given the hemorrhagic potential of liver surgery, are there measures to diminish blood loss and reduce the number of transfusions other than restricting fluids?

Desmopressin[11] is used in treating von Willebrand disease hemophilia, as well as reducing prolonged bleeding times associated with uremia, cirrhosis, and other pathologies involving platelet dysfunction. However, desmopressin does not appear to be useful for reducing blood loss and transfusion requirements in patients undergoing hepatectomy. With aprotinin,[9] the conclusions appear to be the same. Tranexamic acid and epsilon-aminocaproic acid have not been studied in this population. Recently, recombinant activated factor VII was studied specifically in liver resection cases, but it did not reduce the number of units transfused.[12] In a 2002 prospective controlled study, Matot et al demonstrated the effectiveness of normovolemic hemodilution in a group of 39 patients undergoing a major hepatectomy.[13] Although blood loss was comparable in both study groups (ie,

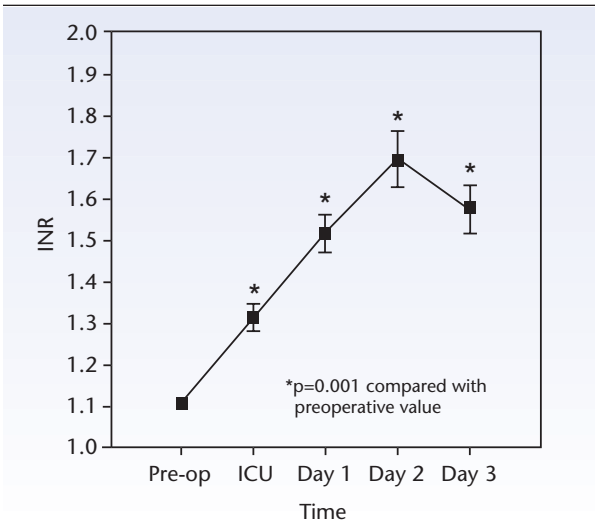
1,442 mL in the hemodiluted group and 1,528 mL in the control group), the proportion of transfused patients dropped from 36% to 10% (P = 0.014).

Surgically, blood loss can be diminished through use of perioperative echography, which can pinpoint vascular and biliary structures, as well as tumours. New instruments such as the ultrasonic dissector, harmonic scalpel, and radiofrequency coagulator can reduce bleeding. Some surgical teams prefer to occlude vascular flow to limit bleeding. This procedure results in hepatic ischemia, but can be tolerated by a healthy liver for up to 90 minutes. Hilar clamping (Pringle's maneuver) increases vascular resistance by 40% and, as a result, cardiac output drops by 10%. The net effect is an increase in systemic pressure by about 15%.[1] However, clinically, hilar clamping does not result in the hemodynamic change that might be expected. The consequences of hepatic vascular exclusion are more dramatic. In addition to portal triad clamping, there is clamping of suprahepatic veins and the inferior vena cava. This decreases venous return by 50% and, despite the increase in pulse rate and systemic resistance, cardiac output drops. As a precaution against total vascular exclusion, adequate volemic repletion is necessary to avoid hypotension.

## POSTOPERATIVE ANALGESIA

The literature on postoperative analgesia following a hepatic resection is scarce. It appears to be an unresolved issue. Some authors suggest that postoperative coagulopathy is so crucial that insertion of an epidural catheter is contraindicated. These authors use only patient-controlled analgesia (PCA). However, others regularly use epidural analgesia. One hundred and fifty patients undergoing a hepatectomy had their prothrombin time (International Normalized Ratio – INR) monitored until the third day after surgery.[14] Figure 1 shows the rise in INR which peaked at 1.69 on Day 2 and remained above 1.4 on Day 3. This persistent elevation in INR led to the use of morphine PCA at this centre and, according to the authors, patient convalescence was acceptable.

FIGURE 1: Changes in the INR before and after a partial hepatectomy[14]



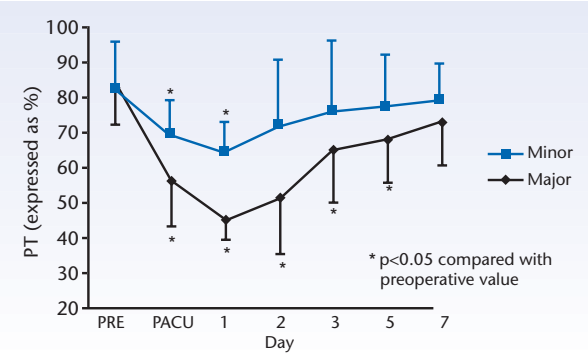

INR = international normalized ratio; ICU = intensive care unit

### *Epidural analgesia*

Matot et al consider epidural analgesia to be an acceptable technique for hepatic resection even though there can be postoperative coagulation anomalies.[15] The size of the resection can affect both the extent and duration of the coagulation disorder and, therefore, the timing of removal of the epidural catheter. These authors assessed the safety of an epidural in patients undergoing hepatectomy based on their coagulation profiles; 136 patients undergoing a hepatic resection were divided into 2 groups (major and minor hepatectomy) and all were given a thoracic epidural. Patients in the minor hepatectomy group underwent a resection of 1 or 2 segments (231 g on average) and the major group had resection of ≥3 segments (894 g on average). Blood loss was 445 mL and 885 mL, respectively.

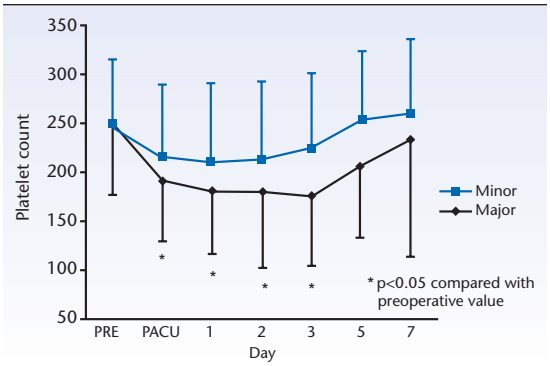
The rise in prothrombin time (PT) was more pronounced in the major hepatectomy group. Following surgery, 1.4% of patients in the minor hepatectomy group had a PT <60% (INR>1.3) on Day 5 compared to 12% of the major hepatectomy group (Figure 2). Only the major hepatectomy group had a significant reduction in platelet count: 5% of patients had a platelet count of <100 G/L on Day 3 and 1% on Day 5 (Figure 3). The authors found an inverse relation between PT, platelet count, and the quantity of liver removed. Because of coagulation disorders, the epidural catheter remained in place for 7 days in 9% of the patients in the major hepatectomy group and fresh frozen plasma was administered to 2 patients to normalize their coagulation profile before removal of the catheter. The authors concluded that it is relatively safe to use a continuous epidural in these

FIGURE 2: Changes in postoperative prothrombin time (PT) in patients undergoing major or minor liver resections[15]




PRE = preoperative; PACU = postoperative anesthesia care unit

FIGURE 3: Changes in postoperative platelet count (x $10^3/mm^3$) in patients undergoing major or minor liver resections[15]




PRE = preoperative; PACU = postoperative anesthesia care unit

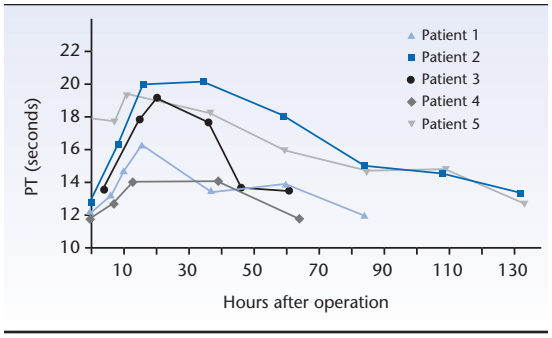
patients, but the rare incidence of spinal hematoma makes relative risk difficult to establish. In this study of 136 patients, the maximum risk of epidural hematoma was estimated at 2.2%. If this analgesic technique is used, one must realize that removal of the catheter may have to be delayed due to coagulopathy, blood products might have to be administered when the catheter is removed, coagulation values have to be monitored closely postoperatively as well as before the epidural catheter is removed, and the patients have to be checked daily for early signs of medullar compression.

A letter published in *Anesthesia and Intensive Care*[16] reports the safe use of epidural anesthesia in 5 patients undergoing a left hepatectomy. The author suggests this technique is beneficial in selected patients. Although the coagulation values were reported only in part, it might be expected that these patients retained sufficient hepatic parenchyma to avoid coagulopathy. The resected hepatic mass was not mentioned, but blood loss ranged from 250 to 800 mL. Finally, at New York Presbyterian Hospital,[1] an epidural was used only in patients undergoing a limited resection who had normal liver function and normal coagulation.

Epidural analgesia has also been studied in living donors. Choudhry et al reported postoperative analgesic techniques for 22 patients who underwent a left donor hepatectomy.[17] Nine patients received a thoracic epidural, 5 a lumbar epidural, 6 an injection of intrathecal morphine, and 2 were managed with PCA. In all cases, the return of intestinal flow, the length of time in intensive care, and total hospital stay was the same, regardless of the type of analgesia.

Epidural analgesia and the rise in PT after a right hepatectomy have also been studied in living donors.[18] This type of surgery enables us to study the effects of a major liver resection on coagulation in the absence of hepatic pathology,

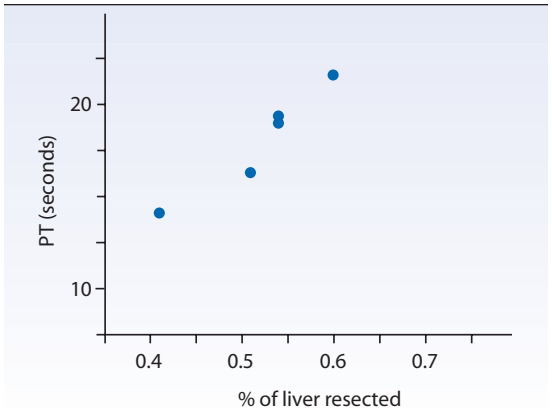
FIGURE 4: Postoperative prolongation of the prothrombin time (PT) in 5 patients after donor right lobectomy[18]




vascular occlusion, or massive transfusion. An epidural catheter was inserted preoperatively at T7-T8 and used during the operation. Figure 4 shows the variations in PT in 5 patients, while Figure 5 shows the variation in PT as a function of the mass of liver resected. As demonstrated, the relationship is direct. The authors observed postoperative hemostatic disorders, although there was no massive transfusion or disseminated intravascular coagulation. These disorders appear to be directly related to the extent of the resection. As a general rule, the PT returns to normal in 3 to 6 days. A temporary alteration in the hepatic synthesis of coagulation factors probably explains the PT changes. The authors therefore suggest monitoring the PT postoperatively and before the catheter is removed, as well as neurological signs while the epidural is in place and several hours after its removal. Until we have a better understanding of hemostatic disorders associated with partial hepatectomy, the risks and benefits of epidural analgesia must be weighed carefully.

Schumann et al reported their findings on the use of an epidural for postoperative analgesia in 8

FIGURE 5: Extent of resection (ratio of graft mass to total liver mass) versus maximum prothrombin time (PT) for each patient[18]



right hepatectomy donors.[19] All had an epidural inserted preoperatively between T6 and T11. Over a 5-day period, the authors monitored changes in pain intensity, as well as the following variables: platelet count, INR, ALT (alanine aminotransferase) and AST (aspartate aminotransferase). For the epidural catheter to be removed, the INR had to be ≤1.3. No patient had an epidural hematoma and none required fresh plasma. This study confirms that extensive hepatic resections alter hemostasis, but also introduces the concept of an alteration in postoperative hepatic metabolism in these patients. An unexpected sensitivity to systemically administered opiates (total dose of 2 mg of hydromorphone) was found in a female patient who remained in pain despite a functioning epidural.

An increase in the plasma concentration of lidocaine during continuous epidural infusions in patients undergoing hepatic resection has already been demonstrated.[20] It might be expected that in this group, postoperative drug metabolism would also be abnormal. The authors concluded that until we have a better knowledge of the physiological changes associated with hepatic resection, forms of analgesia other than epidural are preferable.

Change in PT and platelet counts was studied in 36 living right hepatectomy donors.[21] Thirty patients agreed to receive an epidural. The study investigated the possible causes of coagulation disorders and the potential implications for epidural analgesia. Blood loss averaged 820 mL, although one donor lost over 2,000 mL. The average volume of crystalloids and colloids administered was 5,970 mL. The rise in PT directly correlated to blood loss and quantity of fluids administered. The authors found the same hemostatic changes as Schumann et al,[19] ie, an immediate postoperative rise in PT peaking on Day 1 that improved (although not back to normal) on Day 5. The decline in platelet count was 30% immediately following surgery, reached a nadir on Day 3, and returned to normal on Day 5. The platelet count directly correlated to blood loss and the quantity of fluids administered. The epidural catheter was removed from 22 patients on Day 3 and 8 others on Day 4 when their INR reached 1.3. No patient required fresh plasma.

In brief, anesthesiologists face a dilemma in selecting postoperative analgesics for these patients. Coagulation abnormalities run the risk of an epidural hematoma, whereas systemic opiates carry a risk of toxicity.

### *PCA*

In a study of 35 living donors, 6 received an epidural, 24 a morphine PCA, and 5 a continuous infusion of morphine followed by PCA.[22] It is interesting to note that from Day 1 to 3, the authors found no difference in the assessment of pain between the groups. Postoperative morbidity was unrelated to the type or quality of analgesia. The average postoperative dose of morphine was 0.024 mg/kg/hr.

### *Other forms of postoperative analgesia*

The elimination half-life of acetaminophen has not been studied in patients undergoing a major hepatic resection. Since the clinical and biological signs characteristic of toxicity cannot be detected postoperatively, acetaminophen should be avoided.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with liver failure because they can aggravate pre-existing kidney dysfunction. About 50% of patients develop transient post-operative ascites that develop at the expense of intravascular volume and cause hypovolemia. The presence of an NSAID can precipitate kidney failure.

Redai et al prefer the use of a single dose of 0.5 to 0.7 mg intrathecal morphine in patients undergoing hepatectomy.[1] A Spanish group[23] reported the effectiveness of a single dose of epidural morphine ranging from 3.5 to 5 mg, with or without 20 to 30 mg ketamine, in 107 Child class A cirrhotic patients. Analgesia was adequate for 16.4 hr. in the morphine and 27.2 hr. in the morphine-ketamine group.

The use of paravertebral blocks in order to improve postoperative analgesia has been reported in two hepatectomy patients.[24] In both cases, morphine consumption in the postoperative period was reduced.

## CONCLUSION

Hepatic resection is a major surgical procedure. The surgical incision is large and blood loss is substantial. Maintaining a low CVP can reduce blood loss; however, not all patients are able to tolerate it. Sometimes a low CVP can lead to anuria and hemodynamic instability if hydration is insufficient. A number of studies report the use of isoflurane to maintain a low CVP during the operation. Nitroglycerine and intravenous morphine have also been used. Postoperative kidney dysfunction may occur, but rarely if systemic pressure is adequate and minimal diuresis is maintained.

All studies report postoperative changes in hemostasis that may result from perioperative hemodilution, as well as from dysfunction of coagulation protein synthesis by the liver. These changes appear to be directly proportional to the mass of resected liver. In the case of a major

hepatic resection, the INR rises on the first day after the operation and returns to acceptable values for removal of the epidural catheter in 4 or 5 days, although not completely to normal. Nonetheless, patients requiring fresh plasma to normalize their INRs are rare. Platelet count bottoms out on Day 3 and returns to normal on Day 5.

While no case of epidural hematoma has been reported with a hepatic resection or living donor hepatectomy, epidural analgesia remains controversial. Due to the low incidence of epidural hematoma, it would require a very large number of patients to establish the incidence of this complication. Epidural analgesia is a better analgesic modality during the first 3 days post-op and modestly reduces the incidence of respiratory failure.[25] However, the question remains – do the benefits outweigh the risks?

Quality postoperative analgesia seems possible with other methods, such as PCA or use of a single-dose neuraxial narcotic. Further studies will be necessary before more definitive recommendations can be made.

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