REVIEW ARTICLE

Portal triad clamping versus other methods of vascular control in liver resection: a systematic review and meta-analysis

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Abstract

Background: Portal triad clamping (PTC) is the most commonly used method of achieving vascular control during liver resection. However, the efficacy and safety of PTC, compared with those of other methods of vascular control, are uncertain.

Methods: A systematic review was conducted to identify randomized controlled trials (RCTs) comparing PTC with other methods of vascular control during liver resection. Endpoints included in-hospital mortality, need for transfusion, number of complications and length of hospital stay. Meta-analyses were performed using a random-effects model.

Results: Ten RCTs were identified; these included a total of 820 patients. No statistically significant differences between PTC and other forms of vascular control in liver resection were demonstrated.

Conclusions: There is no evidence, on the basis of this meta-analysis of RCTs, of any difference between PTC and other forms of vascular control in liver resection.

Keywords

resection, liver, haemorrhage, portal triad clamping, hepatectomy, vascular control

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Introduction

Haemorrhage has historically represented one of the major risks in liver resection and the amount of blood lost is proportionally linked to operative morbidity and mortality.1–3 Moreover, blood transfusion is associated with increased tumour recurrence after hepatectomy for both hepatocellular cancer and colorectal metastases.4–6 This effect seems to be present with both autologous and allogeneic blood products.7 In the 1970s, major liver resection was associated with operative mortality rates of > 20% and a significant proportion of these deaths resulted from intraoperative haemorrhage.8 Over the last three decades, there have been significant improvements in the results of liver resection. Operative mortality is < 5% in most modern series9–12 and > 90% of all hepatectomies are performed without transfusion.13–15 These improvements reflect better understanding of liver anatomy,16 improved surgical techniques (including the maintenance of low central venous pressure),17,18 more sophisticated equipment, advances in perioperative care and superior methods of anaesthesia.19 Portal triad clamping (PTC) has traditionally been the preferred method of vascular control, but, more recently, other means of vascular control during hepatic resection have been described. These include selective hepatic vascular exclusion (SHVE),20 total hepatic vascular exclusion (THVE)21,22 and hepatic vascular exclusion with caval flow preservation.23,24 Specialized techniques for liver mobilization, such as the hanging manoeuvre, combined with the various types of vascular control have also been reported.25

Although both intermittent and continuous PTC have been widely used, ≤ 60 min of continuous clamping has been shown to be safe under normothermic conditions, provided there is no pre-existing parenchymal liver disease rendering the organ more susceptible to ischaemia.26,27 More recently, it has been suggested that intermittent PTC can be detrimental to outcome through damage to the liver parenchyma during multiple reperfusion episodes, associated with bleeding during reperfusion and a longer operating time.28 Ischaemic preconditioning consists of a short period (e.g. 10 min) of clamping, followed by reperfusion (often...
10 min) applied prior to the prolonged clamping.14 Although the possible benefit of preconditioning was first seen in models of coronary occlusion,29 a recent meta-analysis failed to show any benefit of the technique in liver resection.30 The aim of this systematic review and meta-analysis was to review the efficacy and safety of PTC compared with other forms of vascular control in patients undergoing liver resection.

Materials and methods

Literature search

A systematic literature search was independently conducted by two authors (AJR and VWTL). The following electronic databases were searched: MEDLINE (1950–2011); EMBASE (1974–2011); the Cochrane Controlled Trials Register, and the Science Citation Index. Combinations of medical subject headings (MeSH), as well as keywords, were used, including the following terms: ‘inflow occlusion’; ‘hepatic vascular exclusion’; ‘vascular occlusion’; ‘portal triad occlusion’; ‘Pringle manoeuvre’; ‘hepatectomy’; ‘liver resection’; ‘hepatic vascular exclusion’; ‘hepatectomy’, and ‘liver surgery’. The literature search was not restricted by language or year of publication, but was restricted to human trials. The last search was performed on 14 October 2011. All the relevant articles identified were manually searched and independent experts were contacted in order to retrieve other relevant articles.

Study selection and primary endpoints

Only randomized controlled trials (RCTs) were included in the review. Studies comparing intermittent or continuous PTC with other means of vascular control in liver resection with or without ischaemic preconditioning were included. Studies describing paediatric liver resections, procedures related to transplantation or laparoscopic liver resection were excluded, as were animal trials. Studies comparing continuous with intermittent PTC were excluded.

The primary endpoints analysed were in-hospital mortality and number of patients receiving a blood transfusion. The secondary endpoints analysed were intraoperative blood loss, postoperative liver failure, total number of complications and operative time. Total number of complications was a composite endpoint that referred to incidences of myocardial infarction, chest infection, pulmonary embolus, bile leak and intra-abdominal collections. Studies with insufficient data relating to the defined primary or secondary outcomes were excluded. The reporting was conducted in accordance with the PRISMA criteria.31 Two reviewers independently performed study selection (AJR and VWTL) and disagreements were resolved by discussion with the third author (JML).

The methodological quality of studies was assessed to establish whether each study fulfilled the following criteria: use of adequate sequence generation; allocation concealment; use of blinding; addressing of incomplete data, and freedom from selective reporting and other biases.

Statistical analysis

Meta-analyses were performed using RevMan 5.0 (Review Manager Version 5.0; Cochrane Collaboration, Oxford, UK). Primary outcomes were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs) derived by the mean difference (MD) method with a random-effects model.32 The Mantel–Haenszel (M–H) method was used for dichotomous outcomes and the inverse variance method was used for continuous outcomes. Heterogeneity was assessed using Cochran’s Q statistic and an I² statistic, where values of ≤ 25% were considered to indicate low heterogeneity and values of ≥ 75% were taken to indicate high heterogeneity.33 Forest plots were constructed and P-values of < 0.05 were considered to indicate statistical significance. Funnel plots were constructed to assess for potential publication bias.

Results

Description of studies

Ten studies34–43 met the predefined criteria for inclusion in the meta-analysis; these are summarized in Table 1. The search strategy is shown in Fig. 1. The studies originated from China, France, Hong Kong, Germany, Greece and Italy. Outcomes for a total of 820 patients reported in the RCTs were available for meta-analysis. These included 409 and 411 patients undergoing hepatectomy with PTC and SHVE, respectively. The mean ± standard error of the mean (SEM) of the mean ages was 52.3 ± 3.3 years in the PTC group and 51.4 ± 3.3 years in the SHVE group. Methods of PTC and the control SHVE technique with which they were compared varied substantially across the studies analysed (Table 2). Methods of SHVE ranged from no vascular control at all, to complete vascular isolation of the liver achieved using both infra- and suprahepatic inferior vena cava clamping or clamping of all hepatic veins. The PTC technique was also variably continuous or intermittent with or without ischaemic preconditioning.

Study quality

Statistically significant heterogeneity was observed in analyses of blood loss (I² = 92%), operative times (I² = 84%), postoperative stays (I² = 94%) and transfusion requirements (I² = 80%), but not in analyses of mortality (I² = 0%), postoperative liver failure (I² = 0%) or incidences of postoperative complications (I² = 29%). Given the small number of studies reporting data appropriate for analysis, funnel plot analysis could only be used to explore bias44,45 in mortality (Fig. 2a), transfusion requirements (Fig. 2b) and incidences of postoperative complications (Fig. 2c). No significant funnel plot asymmetry was observed in these analyses. A risk for bias diagram is shown in Fig. 3. Only two studies reported the method of randomization.38,40

Mortality

There were six deaths in the PTC group and five in the SHVE group. Data were available in all 10 studies analysed and there was
no difference in the risk for death between the two groups (OR 1.15, 95% CI 0.38–3.50) (Fig. 4a).

**Transfusion**

Data on the number of patients receiving blood transfusions were available for nine RCTs relating to 780 patients (Fig. 4b). There was no difference in the number of patients receiving blood transfusion between the PTC and SHVE groups (OR 1.01, 95% CI 0.42–2.42).

**Secondary endpoints**

There was no difference between the PTC and SHVE groups in the incidence of operative blood loss (MD 57.92, 95% CI –180.77 to 296.61) (Fig. 5a), operative time (MD 0.04, 95% CI – 18.15 to 18.22) (Fig. 5b), total postoperative complications (OR 0.93, 95% CI 0.64–1.37) (Fig. 5c), postoperative stay (MD – 0.54, 95% CI – 4.89 to 3.81) (Fig. 5d) or postoperative liver failure (OR 0.86, 95% CI 0.28–2.66) (Fig. 5e).

**Discussion**

This systematic review addressed the question of whether PTC is superior to other methods of vascular control in liver resection. The main outcome measures were in-hospital mortality and the number of patients requiring transfusion. The meta-analysis of
RCTs showed no significant differences between the methods in the main or secondary endpoints analysed. Blood loss, along with extent of resection and presence of cirrhosis, is one of the major determinants of outcome after liver resection. Loss of > 600 ml of blood has been associated with rising morbidity and mortality. The proportional relationship among blood loss, transfusion requirement and mortality is mirrored in other surgical procedures. Therefore, manoeuvres to limit blood loss might be expected to improve outcomes. The results of liver resection have improved over time, coincidently with reductions in intraoperative blood loss and requirements for transfusion. Portal triad clamping was the earliest method reported to limit haemorrhage during liver resection and has been described as effective. Nevertheless, there is still concern that the routine use of PTC may in fact be detrimental, particularly in cases with significant pre-existing parenchymal liver damage. Although it is well tolerated in the majority of patients, PTC may lead to significant increases in mean arterial pressure and systemic vascular resistance with a decrease in cardiac index. Portal triad clamping has also been linked with splanchnic congestion and bacterial translocation from the gut. The main advantage of PTC is that it is simple and applicable in many situations, although it should be avoided in the resection of lesions involving the hepatic veins or inferior vena cava and in patients with right heart failure and pulmonary hypertension. A number of techniques to limit the physiological impact of PTC have been described. These include the intermittent application of PTC and ischaemic preconditioning. Intermittent PTC has been associated with higher blood loss than continuous PTC, but a reduced incidence of postoperative liver failure, particularly in the presence of cirrhosis. Ischaemic preconditioning involves a short period of liver ischaemia prior to transection with PTC in place. The technique is believed to augment the liver’s tolerance to prolonged ischaemia. Although ischaemic preconditioning has been widely studied with contradictory results, a meta-analysis has not shown the technique to make significant differences in mortality, blood loss or liver failure, although significant improvements in length of intensive care unit and hospital stay have been demonstrated. There was considerable variation in the precise form of PTC used in the studies included in this analysis. Continuous and intermittent PTC and ischaemic preconditioning were each variously used.

The techniques compared with PTC in the studies included in this meta-analysis were variable, ranging from no vascular control to THVE. Generally, the more complete the vascular isolation of the liver, the better the control of haemorrhage, but greater ischaemic insult to the organ causes greater congestion of the viscera and cardiac stress. Total hepatic vascular exclusion involves total inflow and outflow occlusion of the liver, and can be combined with aortic clamping and hypothermic perfusion of the liver. The major problem with THVE is that it results in an unpredictable fall in cardiac output that may cause the patient to become unable to tolerate the procedure. This technique is therefore commonly reserved for resection involving the inferior vena cava or hepatic veins and can be used to facilitate the reconstruction of these structures. Hemiepatic vascular clamping (HHVC) is a lesser form of vascular isolation that can be combined with clamping the hepatic veins ipsilateral to the resection and was popularized by Makuuchi. It is theoretically advantageous because it avoids ischaemia to the future liver remnant and splanchnic congestion and possibly affords greater haemodynamic stability. The major disadvantage of HHVC concerns the risk for bleeding from the perfused remnant during resection. The technique may be contra-indicated for tumours.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Details of PTC</th>
<th>Details of SHVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhelghi et al.</td>
<td>NS</td>
<td>PTC combined with infra- and suprahepatic IVC clamp –</td>
</tr>
<tr>
<td>Capussotti et al.</td>
<td>Intermittent: 15 min PTC and 5 min release; no IP</td>
<td>Extrapolachymal control of HA and PV ipsilateral to</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>NS</td>
<td>PTC combined with infrahepatic IVC clamp – MTHVE</td>
</tr>
<tr>
<td>Chouker et al.</td>
<td>Continuous; no IP</td>
<td>NVC</td>
</tr>
<tr>
<td>Liang et al.</td>
<td>Intermittent: 20 min PTC and 5 min release; no IP</td>
<td>Extrapolachymal control of HA and PV ipsilateral to</td>
</tr>
<tr>
<td>Man et al.</td>
<td>Intermittent: 20 min PTC and 5 min release to maximum of 120 min; no IP</td>
<td>NVC; extent of extraparenychmal control of HA and PV not stated</td>
</tr>
<tr>
<td>Man et al.</td>
<td>Intermittent: 20 min PTC and 5 min release to maximum of 120 min; no IP</td>
<td>NVC; extent of extraparenychmal control of HA and PV not stated</td>
</tr>
<tr>
<td>Fu et al.</td>
<td>Continuous if &lt; 30 min then intermittent: 15 min PTC and 5 min release; no IP</td>
<td>Extrapolachymal control of HA and PV ipsilateral to resection</td>
</tr>
<tr>
<td>Smyrnios et al.</td>
<td>Continuous; IP used in last 20 patients</td>
<td>PTC combined with clamping of all hepatic veins – THVE</td>
</tr>
<tr>
<td>Smyrnios et al.</td>
<td>Continuous; no IP</td>
<td>PTC combined with clamping of all hepatic veins – THVE</td>
</tr>
</tbody>
</table>

HA, hepatic artery; HVE, hepatic vascular exclusion; IP, ischaemic preconditioning; IVC, inferior vena cava; MTHVE, modified technique of hepatic vascular exclusion; NS, not stated; NVC, no vascular control; PV, portal vein; THVE, total hepatic vascular exclusion.
approaching the hilum or where there are dense adhesions. Methods of segmental vascular occlusion have been described and may be useful for small peripheral tumours in cirrhotic livers, but were not used in the studies analysed. The variety of techniques of both PTC and SHVE are likely to contribute to the significant heterogeneity observed in this meta-analysis.

Many patients undergoing resection for colorectal metastasis and hepatocellular carcinoma have liver damage induced by preoperative chemotherapy and cirrhosis, respectively. The more complete vascular isolation of the liver may reduce blood loss during transection, but also increases the ischaemic insult to the organ. Although the liver is relatively resistant to periods of warm ischaemia, it is vulnerable to anoxic conditions and may be more severely vulnerable if it has been chronically damaged by either cirrhosis or chemotherapy. It may be that PTC induces only partial ischaemia of the liver as a result of hepatic back-perfusion from the inferior vena cava and venous anastomoses between the human splanchnic and systemic circulations. Reperfusion injury can lead to further parenchymal damage from Kupffer cell activation, the production of free radicals, neutrophil activation and micro-circulatory disturbances.

Figure 2 Outcomes in portal triad clamping and selective hepatic vascular exclusion for (a) postoperative mortality, (b) number of patients requiring transfusion and (c) the incidence of postoperative complications. SE, standard error; OR, odds ratio

Figure 3 Summary of risk for bias: authors’ judgements about each risk for bias item for each study included

Belghiti et al. (1996)
Capussotti et al. (2006)
Chen et al. (2006)
Chouker et al. (2004)
Fu et al. (2010)
Liang et al. (2009)
Man et al. (1997)
Man et al. (2003)
Smyrniotis et al. (WJS) (2003)
Smyrniotis et al. (JACS) (2003)
risk associated with excessive haemorrhage and the liver ischaemia induced in order to prevent it. The lack of difference between PTC and the methods of vascular control used in the studies reviewed here may reflect the relative counterbalancing effect of these two imperatives in each study protocol.

Despite the inclusion of newly available data from recent and relatively large RCTs,\textsuperscript{39,40} the results of this meta-analysis are broadly consistent with those of previous meta-analyses\textsuperscript{77,78} and the Cochrane review\textsuperscript{30} of the topic. Although the analysis includes only RCTs, they are of variable quality and provide little information about potential sources of bias. Moreover, the number of trials in the analysis is small and each contributes a small number of patients. Meta-analysis is primarily a tool for overcoming the problem of the reduced statistical power afforded by studies with small sample sizes.\textsuperscript{79} The failure of the current meta-analysis to detect a difference in outcomes between the PTC and SHVE groups naturally raises the question of whether this reflects a lack of power or a false negative result arising from other causes. Significant heterogeneity was observed in the meta-analytic statistical measures. This heterogeneity may be attributable to differences in the patients (such as in numbers with benign lesions or underlying liver disease), methods of transection of the liver parenchyma, outcome assessment and quality of reporting. Most significantly, the techniques of both PTC and the control method with which it was compared in each RCT were variable. This heterogeneity may obscure an important treatment effect. In order to initiate a change in practice, it is imperative that further RCTs not only address \textit{a priori} the question of power, but also reflect contemporary liver surgery in the design of their experimental and control arms.

\textbf{Conflicts of interest}

None declared.

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\textbf{Figure 4} Forest plots illustrating the meta-analysis of outcomes in patients undergoing liver resection with portal triad clamping (PTC) or selective hepatic vascular exclusion (SHVE) for (a) postoperative mortality and (b) number of patients requiring transfusion. M–H, Mantel-Haenszel test; 95% CI, 95% confidence interval.
**Figure 5** Forest plots illustrating the meta-analysis of outcomes in patients undergoing liver resection with portal triad clamping (PTC) or selective hepatic vascular exclusion (SHVE) for (a) intraoperative blood loss, (b) operative time, (c) total postoperative complications, (d) postoperative stay and (e) postoperative liver failure. M–H, Mantel–Haenszel test; 95% CI, 95% confidence interval.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PTC Mean SD</th>
<th>SHVE Mean SD</th>
<th>Total Mean SD</th>
<th>Mean difference IV, Random, 95% CI</th>
<th>Mean difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belghiti et al. (1996)</td>
<td>989 1,250</td>
<td>24 1,195</td>
<td>1,105 28</td>
<td>9.6% -206.00 (-852.23, 440.23)</td>
<td></td>
</tr>
<tr>
<td>Liang et al. (2009)</td>
<td>570 286</td>
<td>40 649</td>
<td>279 40</td>
<td>29.4% -79.00 (-202.82, 44.82)</td>
<td></td>
</tr>
<tr>
<td>Fu et al. (2010)</td>
<td>339 205</td>
<td>60 354</td>
<td>240 60</td>
<td>30.9% -15.00 (-94.87, 64.87)</td>
<td></td>
</tr>
<tr>
<td>Chen et al. (2006)</td>
<td>770 320</td>
<td>58 420</td>
<td>250 60</td>
<td>30.1% 350.00 (246.16, 453.84)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>182</strong></td>
<td></td>
<td></td>
<td><strong>57.92 (-180.77, 296.61)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $t^2 = 46396.09; X^2 = 38.48; d.f. = 3 (P < 0.00001); I^2 = 92$

(a) Test for overall effect: $Z = 0.48 (P = 0.63)$

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PTC Mean SD</th>
<th>SHVE Mean SD</th>
<th>Total Mean SD</th>
<th>Mean difference IV, Random, 95% CI</th>
<th>Mean difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belghiti et al. (1996)</td>
<td>301 103</td>
<td>24 366</td>
<td>106 24</td>
<td>6.7% -65.00 (-124.13, -5.87)</td>
<td></td>
</tr>
<tr>
<td>Chouker et al. (2004)</td>
<td>257 51</td>
<td>19 272</td>
<td>46 15</td>
<td>13.4% -15.00 (-47.68, 17.68)</td>
<td></td>
</tr>
<tr>
<td>Smyrniotis et al. (JACS) (2003)</td>
<td>145 30</td>
<td>20 195</td>
<td>40 20</td>
<td>17.6% -10.00 (-31.91, 11.91)</td>
<td></td>
</tr>
<tr>
<td>Chen et al. (2006)</td>
<td>125 11</td>
<td>58 133</td>
<td>12 60</td>
<td>23.3% -8.00 (-12.15, -3.85)</td>
<td></td>
</tr>
<tr>
<td>Fu et al. (2010)</td>
<td>134 45</td>
<td>60 114</td>
<td>37 60</td>
<td>20.4% 20.00 (5.26, 34.74)</td>
<td></td>
</tr>
<tr>
<td>Liang et al. (2009)</td>
<td>236 49</td>
<td>40 204</td>
<td>38 40</td>
<td>18.7% 32.00 (12.78, 51.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>221</strong></td>
<td></td>
<td></td>
<td><strong>0.04 (-18.15, 18.22)</strong></td>
<td></td>
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</table>

Heterogeneity: $t^2 = 365.48; X^2 = 31.81; d.f. = 5 (P < 0.00001); I^2 = 84$

(b) Test for overall effect: $Z = 0.00 (P = 1.00)$
References


24. Li AJ, Pan ZY, Zhou WP, Fu SY, Yang Y, Huang G et al. (2008) Compari-
sion of two methods of selective hepatic vascular exclusion for liver resec-

tectomy. Hepatogastroenterology 56:442–446.


