Inhalation anesthesia and hepatoprotection in patients undergoing right hepatectomy for living donor liver transplantation

Anestesia inalatória e hepatoproteção em pacientes submetidos a hepatectomia direita para transplante hepático intervivos

Flávio Takaoka¹, Paulo Celso Bosco Massarollo², Sérgio Mies³, Alexandre Teruya⁴

ABSTRACT

Objective: To verify if inhalation anesthesia administered during right lobe hepatectomy for living donor transplantation, as performed at Hospital Israelita Albert Einstein, could attenuate postoperative liver dysfunction in these patients. Methods: We retrospectively reviewed perioperative data of 56 patients who underwent right lobe hepatectomy for living donor transplantation. Patients were separated into two groups: one group received inhalation anesthesia, and another received total intravenous anesthesia. Results: Standard liver function tests: prothrombin time, platelet count, ALT/AST were not statistically different in patients who received inhalation anesthesia compared to total intravenous anesthesia in the early postoperative period. Conclusion: Hepatoprotective properties of inhalation anesthesia could not be demonstrated in this retrospective study when compared to intravenous anesthesia in patients submitted to right lobe hepatectomy. Increased safety of this procedure for the donor is mandatory. Therefore, strategies resulting in preservation of liver function, like preconditioning, deserve further studies.

Keywords: Inhalation anesthesia; Intravenous anesthesia; Liver transplantation

INTRODUCTION

Advances in our understanding of mechanisms underlying ischemia-reperfusion (IR) injury to the liver led to a number of experimental and clinical studies that showed liver protection by ischemic preconditioning (IPC)⁴⁻⁶. IPC has been demonstrated to improve liver function after hepatic surgery⁴⁻⁶. It has been also demonstrated that commonly used inhalation anesthetics – isoflurane, sevoflurane, halothane and enflurane – share many IPC-induced characteristics⁴⁻⁶. Additionally, anesthetic

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preconditioning (APC) may present a safer way of eliciting protection during liver resection as there is no need to induce organ ischemia.

Transient liver dysfunction is observed in most living donor liver transplantation (LDLT) patients submitted to right lobe hepatectomy (RLH) in the early postoperative days; however, they usually recover uneventfully\textsuperscript{(8)}. Despite proven benefits during hepatic surgery, IPC has not yet been performed during hepatectomy for LVLT. Safety of RLH for LDLT has been recently questioned\textsuperscript{(9,10)}. These articles reported the incidence of serious morbidity and mortality for the living donor with closing or temporary suspension of a few LDLT programs.

To our knowledge there are no studies investigating a clinical benefit of APC during hepatectomy. We hypothesized that APC may attenuate postoperative liver dysfunction in patients submitted to RLH for LDLT in our institution.

METHODS

We retrospectively reviewed perioperative data of 56 patients submitted to RLH for LDLT, at Hospital Israelita Albert Einstein, from January 2002 to March 2004. Patients were separated into two groups: those receiving inhalation anesthesia and those submitted to total intravenous anesthesia (TIVA) during hepatectomy. Anesthesia technique was chosen depending upon the individual preference of 4 attending anesthesiologists of the transplant team. In the Inhalation Anesthesia group, patients received inspired isoflurane concentration ranging from 0.3 to 1.5\% (0.7 to 1.5 MAC) associated with fentanyl, cisatracurium and nitrous oxide. In the TIVA group, patients received propofol, remifentanil, fentanyl, nitrous oxide and cisatracurium. Hepatic pedicle clamping was not part of the surgical technique in both groups of patients. No patient in these groups received autologous blood transfusion perioperatively.

Data collection

Demographic data such as age, sex and weight were retrieved. Preoperative (PRE) and postoperative day 1 (POD1) standard liver function tests results (prothrombin time [INR], platelet count and AST/ALT) were retrieved.

Statistical analysis

The chi-square test was used to compare discrete variables and unpaired t test for continuous variables.

All liver function parameters were subjected to a logarithmic transformation to ensure a normal distribution. A two-factor repeated-measures analysis of variance was used to evaluate differences over time and between groups for all liver function parameters. Data analysis was performed using SPSS\textsuperscript{®}, a statistical software for Windows. A two-sided significance level of 0.05 was considered.

RESULTS

The results are shown on tables 1 and 2 and on figures 1, 2, 3 and 4, according to liver function parameters – Inhalation Anesthesia versus TIVA. Group comparison at preoperative (PRE) and postoperative day 1 (POD1). For INR: group effect, p = 0.291, group-time interaction, p = 0.439; for AST: group effect, p = 0.572, group-time interaction, p = 0.695; for ALT: group effect, p = 0.608, group-time interaction, p = 0.633.

Table 1. Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Inhalation (n=20)</th>
<th>TIVA (=36)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – mean±SD</td>
<td>32±9</td>
<td>30±9</td>
<td>0.607</td>
</tr>
<tr>
<td>Weight (kg) – mean±SD</td>
<td>74±10</td>
<td>73±12</td>
<td>0.622</td>
</tr>
<tr>
<td>Sex – n (%) male/female</td>
<td>14/6</td>
<td>23/13</td>
<td>0.644</td>
</tr>
</tbody>
</table>

*: differences were assessed by unpaired t test or chi-square test; p<0.05, significant

Table 2. Liver function parameters (mean ± SD) at pre and postoperative day 1 (POD1)

<table>
<thead>
<tr>
<th>Group</th>
<th>Ht% INR%</th>
<th>AST U/l</th>
<th>ALT U/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pré</td>
<td>POD1</td>
<td>Pré POD1</td>
<td>Pré POD1</td>
</tr>
<tr>
<td>Inhalation</td>
<td>44 ±4</td>
<td>35 ±5</td>
<td>1.08 ±0.2</td>
</tr>
<tr>
<td>TIVA</td>
<td>44 ±6</td>
<td>38 ±6</td>
<td>1.11 ±0.1</td>
</tr>
</tbody>
</table>

Figure 1. Inhalation x TIVA comparison
DISCUSSION

Murry et al.\(^{(11)}\) was first described IPC in coronary ischemia-reperfusion in dogs. It comprises brief periods of IR rendering an organ - heart, liver, brain or kidney - more tolerant to subsequent IR insults\(^{(12-15)}\).

Aiming at organ protection without ischemia and using common inhalation anesthetics has generated enormous interest in the literature. Immediate availability of the pharmacological agent, along with the possibility of an effective clinical use for this protective mechanism resulted in more than 150 publications, most experimental, in the literature. Despite theoretical benefits in major surgical procedures affecting major organs, as liver, brain, heart and kidney, most studies investigated the cardioprotective effects of APC during heart surgery\(^{(16-17)}\).

The incidence of serious morbidity and mortality in previously healthy donors during LDLT can be reduced.\(^{18}\) Temporary liver dysfunction that accompanies RLH in the majority of patients may be associated with serious morbidity, such as bleeding and encephalopathy. Therefore, postoperative amelioration of liver function may result in an improved patient outcome.

Organ ischemia is frequently induced during surgery due to hypoxia, hypotension or decreased blood flow. During hepatectomy, a number of surgical maneuvers can be responsible for multiple episodes of low hepatic blood flow and ischemia. Vascular pedicle maneuvers, direct hepatic tissue trauma, outflow obstruction during hepatic vein dissection and decreased portal flow during intestinal compression are the main causes of IR during hepatectomy, in addition to surgical bleeding, systemic hypoxia and hypotension.

Another interesting issue to be investigated is the effect of APC administered in deceased or living donors on graft function postoperatively. Theoretically, APC provides protection against reperfusion injury, so it is reasonable to expect improved graft function following transplant.

Since it is a retrospective study, results must be interpreted carefully. Modalities of inhalation anesthetic administration are still under discussion\(^{(19)}\). Some authors suggested that a 1MAC concentration must be administered in a defined timeline similar to IPC in order to achieve a protective effect\(^{(20)}\). However, a recent study demonstrated that cardioprotective effects were more evident when administered throughout surgery\(^{(17)}\). In our study, a large variation in the fractional inspired and expired concentration of isoflurane was observed during surgery and among different patients but a 1.5MAC was the higher limit for most patients. This may have limited the influence of APC on liver function postoperatively.
Another potential confounding effect in our study is remifentanil preconditioning mediated through opioid receptors (OR). In a recent experimental study\(^\text{(21)}\), systemic administration of remifentanil, an ultrashort-acting \(\mu\)-OR agonist, provided cardioprotection during a defined ischemia and reperfusion period. Remifentanil and fentanyl were administered to all patients in our study.

**CONCLUSION**

In our retrospective study we could not demonstrate a statistically significant effect on standard liver function tests in patients who received inhalation anesthesia as compared to total intravenous anesthesia during RLH for LDLT. Safety of this procedure for the donor is mandatory and strategies that result in preservation of liver function will certainly affect morbidity. Additional prospective controlled studies are required to confirm a beneficial effect of APC on liver function and patient outcome, both in donors and recipients following LDLT.

**REFERENCES**