Effectiveness of Terlipressin on Modulation of Portal Vein Pressure after Hepatic Resections in Non-Cirrhotic Patients. A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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Rezumat
Eficacitatea terlipresinei în modularea tensiunii venoase portale după rezeții hepatice la pacienți non-ciricți.
Bilanț sistematic și metaanaliză a unor teste clinice randomizate controlate


Metode: S-a efectuat cercetare sistematică a literaturii de specialitate în baze de date electronice conform PRISMA. Metaanaliza s-a efectuat pe modele cu efecte stabile și aleatorii.

Rezultate: S-au selectat trei studii clinice controlate randomizate (SCR) comparative, cu administrare de terlipresină și placebo, efectuate pe 284 dintr-un mix de 60 de studii, Pacienții din...
cohorta tratată cu placebo erau semnificativ mai tineri, cu 5 ani, comparativ cu cei din cohorta tratată cu terlipresină. Totuși, cohorta tratată cu terlipresină a prezentat spitalizare substanțial mai scurtă la terapie intensivă (ATI), comparativ cu cohorta tratată cu placebo.

Concluzii: Prima metaanaliză a demonstrat că pacienții din cohorta tratată cu terlipresină, deși semnificativ mai în vârstă, cu 5 ani, au prezentat o durată substanțial mai scurtă a spitalizării la ATI, comparativ cu cohorta tratată cu placebo. În plus, deși nesemnificativ statistic, doar 6% din pacienții tratați cu terlipresină au necesitat suport inotrop, comparativ cu 16,4% din cohorta tratată cu placebo.

Cuvinte cheie: tensiune venoasă portală, terlipresină, resecție hepatică majoră, hepatectomie majoră, studii clinice controlate randomizate

Abstract

Background-Objectives: It has been reported, that high posthepatectomy portal vein pressure (PVP) has deleterious effect on the liver parenchyma and causes posthepatectomy liver failure (PHLF) and increased 90-day mortality. Terlipressin, is widely used to mitigate the effects of portal hyper-tension. Randomised clinical trials (RCTs) demonstrated encouraging results of use of terlipressin for modulation of increased posthepatectomy PVP. The aim of the present study was to evaluate the effectiveness of the pharmacological modulation of the increased post-hepatectomy PVP after major hepatectomy.

Methods: Systematic literature searches of electronic databases in accordance with PRISMA was conducted. Meta-analysis was conducted using both fixed- and random-effects models.

Results: Three randomised controlled trials (RCTs) comparing terlipressin versus placebo including 284 patients of pooled 60 studies were selected. Placebo cohort patients were significantly younger by 5 years compared to terlipressin cohort. However, the terlipressin cohort demonstrated significantly shorter intensive care unit (ICU) stay compared to placebo cohort.

Conclusions: The first meta-analysis demonstrated that terlipressin cohort patients although significantly older by 5 years had significantly shorter ICU stay compared to placebo cohort. Furthermore, though statistically nonsignificant only 6% of terlipressin patients needed inotropic support compared to 16.4% of placebo cohort.

Key words: portal vein pressure, terlipressin, major liver resection, major hepatectomy, randomised controlled trials

Introduction

The deleterious effect of the acute portal hypertension first identified in the “small for size syndrome” after living donor liver transplantation (LDLT) (1). It is reported that maintaining PVP < 15 mmHg is a crucial factor for successful LDLT using small grafts (2). Ligation of splenic artery and portocaval shunt were successfully used to reduce the portal venous pressure after small for size LDLT syndrome (3,4).

Furthermore, it has been reported that increased PVP might be contributed crucially in the development of ascites and PHLF after major hepatectomy. High intravascular shear stress associated with acute portal hyper-perfusion together with compensatory decrease in hepatic arterial flow (hepatic arterial buffer response) were considered contributors of the above complications after major hepatic resections (5,6).

In 2013, first Allard et al reported that posthepatectomy PVP can be used as an
independent predictive factor for PHLF and 90-day mortality after major hepatectomy and recommended intraoperative modula-
tion if the PVP is greater than 20 mmHg (7). Recently, three RCTs investigated the
effectiveness of terlipressin for the manage-
ment of increased PVP after major hepatic resections (8-10).

The aim of the present study was to inves-
tigate the evolution of evidence over time in studies investigating the role of terlipressin for management of increased PVP after major hepatic resections.

Methods and Materials

This systematic review was conducted following the guidelines set out in the
Preferred Reporting in Systematic Review &
Meta-Analysis (PRISMA) checklist (11).

Literature Search

A systematic literature search of articles published from inception until March 2020 performed in Embase, MEDLINE (PubMed),
Cochrane library, and Google Scholar databases using free text and MeSH terms
(portal venous pressure, posthepatectomy
liver failure, 90-day mortality, portal venous
flow, terlipressin, placebo). A grey literature
search on www.clinicaltrials.gov was also performed. References cited in the retrieved
articles were manually checked for further analysis. Disagreements between authors
were resolved through discussion.

Study, Selection, and Inclusion and Exclusion
Criteria

RCTs comparing terlipressin versus placebo
after liver resections were included in this study. Abstracts, case reports, cases series
and editorials without original data were excluded.

Definitions

Major hepatectomy was defined any removal
of at least three segments (12). Posthepatec-
tomy liver failure was defined according (a)
the International study group of liver surgery
(ISGLS-18) (13), (b) the criteria peak of serum
bilirubin greater than 120 µmol/L (14), (c) the
“50-50 criteria” on postoperative day 5 (15),
d (d) Liver cancer Study group of Japan
(LCSGJ) (16).

Statistical Analysis

Cochrane’s criteria were used to assess the
methodological quality of all included RCTs. Two authors PG and RS stratified the risk of bias as low, unclear and high according to
Cochrane criteria. Any discrepancies resolved
by consensus (17).

The Review Manager 5.3 software
(Cochrane Collaboration, Oxford, England)
was used to conduct the statistical analysis. Heterogeneity was assessed using the $F$ test,
and cut-off values of 25%, 50%, and 75% were
considered of low, moderate, and high hetero-
geneity, respectively (18). In cases of $F$ value
less than 25% fixed-effects models were used.

The odds ratios (ORs) with 95% confidence
intervals were used to analyse dichotomous
variables. For the outcomes considered, the
reference categories were selected such that
OR<1 favoured Terlipressin cohort.

Continuous variables were combined based
on the mean difference (MD) and the stan-
dardised MD. The studies were then combined
using the Mantel–Haenszel. For studies that
did not report the means and variances of the
2 groups, these values were estimated from
the median, range, and the size of sample,
using the technique described by Hozo et al.
where possible (19).

In all analyses, the point estimate was
considered significant at p<0.05.

Sensitivity Analysis

In order to assess the impact of heterogeneity
on the robustness of the conclusions the results of both secondary and primary out-
comes were calculated using the random-
effects and fixed-effect models.
Results
Search Strategy and Included Study Characteristics

Three studies from a pool of 60 studies including 142 in terlipressin cohort and 142 patients in placebo cohort were selected \(^8\)\(^-\)\(^10\), (Fig. 1, Table \(\text{I}\)). Terlipressin cohort included 29% cirrhotic patients of Child-Pugh A&B and placebo cohort 22% Child-Pugh A&B patients, respectively \([\text{OR}=1.45(0.80, 2.64), \ p=0.22, \ I^2=6\%]\), (Table \(\text{I}\)).

Statistically Significant Results of the Meta-Analysis

Age

There was evidence that significantly younger patients by five years were included in the placebo cohort compared to terlipressin cohort \((\text{Mean difference (MD)}= \ 4.84 (3.70, 5.94), \ p<001, \ I^2=0\%\)\), (Table \(\text{I}\)).

Intraoperative Mean Arterial Pressure (MAP)

Intraoperative MAP was significantly lower in placebo cohort compared to terlipressin cohort \((\text{MD}=4.51(1.72, 7.30), \ p=0.002, \ I^2=0\%\)\).

ICU Stay

Terlipressin cohort demonstrated significantly shorter ICU stay compared to placebo cohort \([\text{MD}=-0.77 (-1.34, -0.19), \ p=0.009, \ I^2=60\%]\) (Table \(\text{I}\), Fig. \(\text{I}\)).
### Table 1. Study characteristics of included RCTs

<table>
<thead>
<tr>
<th>Author, country, year</th>
<th>Number of patients</th>
<th>Age</th>
<th>Gender</th>
<th>Cirrhotic patients</th>
<th>Indications</th>
<th>Surgical intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbas, Egypt, 2018</td>
<td>42-42</td>
<td>55.86±9.5</td>
<td>30-25</td>
<td>19-12 Child A&amp;B</td>
<td>NR</td>
<td>All Major resections</td>
</tr>
<tr>
<td>Mahdy, Egypt, 2019</td>
<td>25-25</td>
<td>58.7±5.9</td>
<td>10-12</td>
<td>NR</td>
<td>NR</td>
<td>R Hep/my: 6-5 L Hep/my: 7-9 Whipple’s op: 12-11</td>
</tr>
<tr>
<td>Pooled estimates</td>
<td>142-142</td>
<td>MD=4.84</td>
<td>OR=1.10</td>
<td>MD=0.09-0.18, 0.36</td>
<td>OR=1.45(0.80, 2.64)</td>
<td>p&lt;.001 p=0.70 p=0.22 NA NA</td>
</tr>
</tbody>
</table>


### Table 2. Outcome of interests

<table>
<thead>
<tr>
<th>Outcome of Interest</th>
<th>Number of studies and patients</th>
<th>Statistical method, estimated effect, 95% CI</th>
<th>p-value</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3,284</td>
<td>MD=4.84(3.70, 5.94)</td>
<td>&lt;001</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>3,284</td>
<td>OR=1.10(0.67, 1.82)</td>
<td>.70</td>
<td>0</td>
</tr>
<tr>
<td>Operative time</td>
<td>3,284</td>
<td>MD=0.09(-0.18, 0.36)</td>
<td>.51</td>
<td>17</td>
</tr>
<tr>
<td>Cirrhotic patients</td>
<td>2,234</td>
<td>OR=1.45(0.80, 2.64)</td>
<td>.22</td>
<td>6</td>
</tr>
<tr>
<td>EBL</td>
<td>2, 234</td>
<td>MD=-114.63(-931, 702)</td>
<td>.78</td>
<td>91</td>
</tr>
<tr>
<td>HR Baseline</td>
<td>2, 134</td>
<td>MD=-2.31(-5.19, 0.57)</td>
<td>.12</td>
<td>0</td>
</tr>
<tr>
<td>HR intraoperative</td>
<td>2, 234</td>
<td>MD=-3.35(-8.13, 1.43)</td>
<td>.17</td>
<td>0</td>
</tr>
<tr>
<td>MAP Baseline</td>
<td>2, 234</td>
<td>MD=-2.79(-6.49, 0.92)</td>
<td>.14</td>
<td>0</td>
</tr>
<tr>
<td>MAP intraoperative</td>
<td>2, 234</td>
<td>MD=-4.51(-1.72, 7.30)</td>
<td>.002</td>
<td>0</td>
</tr>
<tr>
<td>CVP Baseline</td>
<td>2, 234</td>
<td>MD=-0.60(-0.45, 1.65)</td>
<td>.26</td>
<td>0</td>
</tr>
<tr>
<td>CVP intraoperative</td>
<td>2, 234</td>
<td>MD=-1.14(-0.2, 2.31)</td>
<td>.39</td>
<td>75</td>
</tr>
<tr>
<td>CI Baseline</td>
<td>2, 234</td>
<td>MD=-0.18(-0.52, 0.15)</td>
<td>.29</td>
<td>65</td>
</tr>
<tr>
<td>CI intraoperative</td>
<td>2, 234</td>
<td>MD=-0.03(-0.2, 0.14)</td>
<td>.78</td>
<td>66</td>
</tr>
<tr>
<td>SVV Baseline</td>
<td>2, 234</td>
<td>MD=-1.15(-2.30, 0.01)</td>
<td>.05</td>
<td>0</td>
</tr>
<tr>
<td>SVV intraoperative</td>
<td>2, 234</td>
<td>MD=-0.05(-0.68, 0.78)</td>
<td>.89</td>
<td>0</td>
</tr>
<tr>
<td>TB Preop</td>
<td>2, 234</td>
<td>MD=-1.96(-4.91, 1.00)</td>
<td>.19</td>
<td>0</td>
</tr>
<tr>
<td>TB POD 1</td>
<td>2, 234</td>
<td>MD=-2.52(-7.22, 2.19)</td>
<td>.72</td>
<td>19</td>
</tr>
<tr>
<td>ASAT Preop</td>
<td>2, 234</td>
<td>MD=-0.87(-5.64, 3.90)</td>
<td>.79</td>
<td>0</td>
</tr>
<tr>
<td>ASAT POD 1</td>
<td>2, 234</td>
<td>MD=-6.53(-41.11, 54.19)</td>
<td>.60</td>
<td>0</td>
</tr>
<tr>
<td>ALT Preop</td>
<td>2, 234</td>
<td>MD=-2.21(-6.08, 10.50)</td>
<td>.69</td>
<td>0</td>
</tr>
<tr>
<td>INR Preop</td>
<td>2, 234</td>
<td>MD=-0.03(-0.07, 0.01)</td>
<td>.16</td>
<td>47</td>
</tr>
<tr>
<td>INR POD 1</td>
<td>2, 234</td>
<td>MD=-0.05(-1.34, -0.19)</td>
<td>.11</td>
<td>0</td>
</tr>
<tr>
<td>ICU stay</td>
<td>2, 234</td>
<td>MD=-0.77(-1.34, -0.19)</td>
<td>.009</td>
<td>60</td>
</tr>
<tr>
<td>Need of inotropic support</td>
<td>2, 134</td>
<td>MD=0.32(0.10, 1.07)</td>
<td>.06</td>
<td>0</td>
</tr>
</tbody>
</table>

MD: mean difference, OR: odds ratio, CI: confidence intervals, EBL: estimated blood losses, HR: heart rate, MAP: mean arterial pressure, CVP: central venous pressure, CI: cardiac index, SVV: stroke volume variation, TB: total bilirubin, ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, ICU: intensive care unit, red highlighted significant results
Statistically Nonsignificant results of the Meta-Analysis

There was evidence that fewer patients in terlipressin cohort (6%; 4/67 patients) needed inotropic support compared to placebo cohort (16.4% 11/67), [OR=0.32(0.10, 1.07), p=0.06, I²=0%]. Of note, the result was marginally statistically nonsignificant.

There was evidence of nonsignificant differences in gender, number of cirrhotic patients, operative time, estimated blood losses, heart rate, MAP, central venous pressure, cardiac index, stroke volume variation, systemic vascular resistance, liver function and clotting profile tests between the two cohorts (Table 2).

Risk of Bias of Included RCTs

The overall quality of RCTs was moderate. None of them blinded the outcome assessors. Therefore, detection bias might have influenced the results (Table 3).

Discussion

The results of the first conducted meta-analysis of RCTs comparing terlipressin versus placebo following major hepatectomy mainly in non-cirrhotic livers demonstrated that although significantly older patients by five years were included in the terlipressin cohort the ICU stay was significantly shorter compared to placebo. Further analysis demonstrated that terlipressin did not affect adversely the haemodynamics parameters such as MAP, CVP, CI, SVV (Table 2). In addition, the need for inotropic support was lower in terlipressin cohort without to reach significant levels compared to placebo cohort (Table 2).

Another point that need to be stressed although the difference was statistically nonsignificant more cirrhotic patients were included in the terlipressin cohort (29%; 34/117) compared to placebo cohort (22%; 26/117) 9,10. Therefore, more cirrhotic patients and significantly older total sample are suggestive of selection bias against the terlipressin cohort; however it is demonstrated significantly shorter ICU stay.

The risk of bias analysis of RCTs demonstrated low risk in the domains of sequence generation and allocation concealment. None of the included RCTs blinded the outcome assessors. Therefore, detection bias might have influenced the results (Table 3).

Limitations

Up to authors best knowledge this the first meta-analysis. However, the results of the present study should be interpreted in the context of its limitations. The total sample of

![Figure 2](image-url)
Table 3. Risk of bias of RCTs

<table>
<thead>
<tr>
<th>Author</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Incomplete Outcome data</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbas</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Kohler</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Mahdy</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

the included RCTs were heterogenous and conducted in single centres. Therefore, national, institutional, selection and underpowered sample bias might have influenced the results.

Conclusions

Terlipressin demonstrated promising results by effectively modulated the increased PVP after major hepatic resections in non-cirrhotic patients. Although, significantly older patients by five years included in terlipressin cohort the ICU stay was significantly shorter compared to placebo cohort. Therefore, further investigation of terlipressin with multicentre RCT might shed further light on the topic.

Conflict of Interest

All named authors hereby declare that they have no conflict of interest to disclose.

Acknowledgements and Sources of Support:

None.

Ethical Approval

This study does not contain any studies with human participants or animals performed by any of the authors.

References