PERIOPERATIVE MANAGEMENT AND CRITICAL CARE FOR PATIENTS WITH LIVER DYSFUNCTION

Ph.D. Thesis Booklet

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1 INTRODUCTION

1.1 What is the importance of our work

Liver dysfunction preceding surgical intervention, or acutely manifesting in the context of critical illness, is an exceptionally dangerous phenomenon due to the ‘circular causality’ of liver diseases: as the liver mediates many processes implicated in both recovery and further deterioration, disturbance of its many functions creates an unpredictable chain of complications for the patient, often resulting in even more severe liver injury, thus even worse complications. The practitioner must carefully manage this potentially life-threatening ‘downward spiral’ perioperatively and in the intensive care unit.

1.2 What is our research work

With study 1, we performed an interventional meta-analysis of randomized controlled trials based on the Enhanced Recovery After Surgery (ERAS) protocol on liver surgery, investigating the efficacy of preoperative high-dose glucocorticoid administration in reducing postoperative complications, which are thought to be the consequence of liver injury, at least partly. We compared

any type of high-dose glucocorticoid administration in major hepatic resections and liver transplantations and assessed whether there was a significant reduction in overall postoperative complications.

With study 2, we collected all relevant original research papers on the use of any hemoadsorption therapy for critically ill patients who developed an acute liver dysfunction within the context of critical illness and multiorgan dysfunction sequelae, as opposed to long-term deterioration of chronic liver diseases. This study investigated the effects of hemoadsorption therapy by contextualizing the clinical parameters observed before and after the therapy. As the intervention is novel, and the pathological entity is relatively rare, multifactorial, and deadly, no large-scale randomized controlled trials were published before our publication.

2 OBJECTIVES

2.1 Study 1

We aimed to summarize and contextualize the existing evidence, based on two hypotheses: (1) preoperative glucocorticoid administration can reduce the

complication rate following any type of liver surgery; (2) the effect of glucocorticoids on some complications will be different than on the overall complication rate. Our overall goal with this study was to provide clarification and a critical appraisal to policy-makers.

2.2 Study 2

We aimed to assess the effect of hemoadsorption therapy on critically ill patients with acute liver dysfunction associated with critical illness. We statistically analyzed clinical outcomes, the removal of total bilirubin, and the reduction in liver enzymes. Our overall goal with this study was to guide practitioners and researchers using hemoadsorption therapy for their patients by summarizing and contextualizing the current practice, literature, and any uncertainty in evidence quality and to inform the design of prospective clinical trials to answer specific, patient-related research questions.

3 METHODS

Both studies were conducted with full adherence to the Cochrane Handbook for Systematic Reviews of Interventions, and were protocolized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement. In order to ensure transparency, novelty, and the scientific integrity of our work, both of our studies were also prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO), with the following identifiers for the first and second study, respectively: CRD42021284559, CRD42022286213.

3.1 Search Strategy

Systematic searches were conducted for both studies, in three databases for Study 1: MEDLINE via PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, Scopus and Web of Science databases were searched for Study 2. Both systematic searches were repeated at a later date to ensure no other studies were published between the finalization of the manuscript and its submission for publication. No

filters or restrictions, such as language or date were used to maximize the reproducibility of our systematic search.

3.2 Eligibility Criteria

Eligibility criteria were defined using the PICO framework for both studies.

3.2.1 Study 1

(P): adult patients of either sex undergoing liver surgery, including open or laparoscopic hepatic resection or liver transplantation; intervention (I): preoperative administration of any type of high-dose glucocorticoids; control (C): placebo or non-administration; main outcome (O): overall postoperative complication rate, with the rates of distinct complications and safety outcomes such as length of hospital stay being secondary outcomes.

3.2.2 Study 2

(P): adult patients with acute liver dysfunction or failure associated with critical illness; intervention (I): treated with hemoadsorption using any technology or modality; control (C): if available, standard of care; outcome (O): mortality, bridge-to-transplantation, liver function parameters, critical illness parameters, safety outcomes.

3.3 Selection and data collection processes

In both studies, systematic selection of articles and the collection of data from included articles were performed by two groups of review authors, independent from each other. In both cases, the two groups of review authors compared their findings to ensure quality. Rate of inter-reviewer agreement was calculated using Cohen's kappa before finalizing both steps of the selection.

3.4 Quality assessment

In both studies, risk of bias and level of certainty of evidence were assessed for every outcome. All tools used were based on the Cochrane Handbook's recommendations. The following tools were used for the given study types: (1) RoB2 tool for randomized controlled trials; (2) Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) for non-randomized studies such as cohort studies and registry analyses; (3) Joanna-Briggs Institute's Critical Appraisal Tool (JBI) for case reports and case series. GRADE assessment was used to assess the level of certainty of evidence in all cases.

3.5 Data analysis

3.5.1 Study 1

Meta-analyses were performed for all outcomes presented in the study design section of the prospectively registered protocol, given that at least three included articles

presented data in a format that allowed for pooling. Data without measures of distribution, no specified units of measure, or inconsistent reporting were not eligible for pooling. If the reported outcome measures differed, estimations were made to convert medians with ranges into means with standard deviations, given that the reported data were of sufficient quality for the estimation. Adjustments and statistical models were used wherever appropriate for meta-analysis. To calculate and report the effect size estimation, odds ratio (OR) with 95% confidence interval (CI) were used for dichotomous outcomes; mean differences (MD) with 95% CI were used for continuous outcomes. Statistical heterogeneity was assessed in all cases using Cochrane Q and I^2 tests.

3.5.2 Study 2

Meta-analysis was performed for all outcomes for which at least three studies of comparable types (cohorts or cases) reported data. Before-after differences were calculated and compared for continuous outcomes using the classical inverse variance method and Hartung-Knapp adjustment. Where a measure of distribution was not

provided, we made observations by inputting −0.5 to 0.9 to correlation models to see if our estimations were sound. Upon validating our mathematical model, we published our estimations using a correlation of 0.8, meaning that we assumed the variables were highly correlated; therefore, we underestimated the effect size.

4 RESULTS

4.1 Study 1

11 studies included in this meta-analysis investigated 964 patients in total, with 477 and 487 patients with no significant between-group heterogeneity in glucocorticoid (treatment) and comparator (placebo or non-administration with standard of care) groups, respectively.

Out of the eleven eligible studies in our analysis, nine (n = 836) reported the overall rate of postoperative complications as an outcome. This outcome did not differentiate between major and minor complications or varying pathomechanisms. In this pooled analysis, 418 patients received preoperative glucocorticoids in the intervention group, while 419 patients in the control group

were given either saline, a placebo, or nothing. The intervention group showed a trend toward a lower overall postoperative complication rate (OR: 0.71; 95% CI: 0.38–1.31, p = 0.23), although this finding was not statistically significant. Considerable heterogeneity was observed, as defined by the Cochrane Handbook [I^2 = 54% (2%; 78%), p = 0.03].

4.2 Study 2

The selection process identified 30 eligible studies published between 2011 and 2022, with an additional 3 studies included from a subsequent systematic search. These studies collectively documented the use of hemoadsorption in 323 patients. Among the studies, 19 were case reports, 7 were case series (totaling 84 patients), 3 were observational studies (130 patients), and 1 was a registry analysis (109 patients). All patients who had liver dysfunction associated with acute critical illness were treated with hemoadsorption techniques: CytoSorb (23 datasets, 232 patients), Coupled Plasma Filtration Adsorption (4 datasets, 88 patients), oXiris (2 datasets, 2

patients), and a combination of CytoSorb and oXiris (1 dataset, 1 patient).

The primary outcomes assessed in this study were mortality, the rate of bridging to transplantation, and the duration of ICU stay. Due to the scarcity of well-documented original research data in the literature, none of these outcomes could be meta-analyzed as initially intended. Observational cohort studies reported an in-hospital mortality rate of 38% (50 out of 130 patients), while case reports and series indicated a mortality rate of 23% (19 out of 82 patients). The registry analysis documented a total in-hospital mortality rate of 59.6% (65 cases), with 10 deaths occurring at the end of hemoadsorption therapy (9.2%), 60 deaths during the ICU stay (55%), and 5 more during the post-ICU hospitalization period. This was the only study to report on the length of ICU stay, providing a median duration of 14.0 days (IQR: 7.0–23.0). None of the studies in the analysis provided data on the success rate or any other descriptive outcomes regarding bridging to liver transplantation.

Among the outcomes, only six laboratory parameters were suitable for meta-analysis. Data from 160 patients demonstrated a significant post-treatment reduction in total bilirubin levels, with a mean difference of −4.79 mg/dL (95% CI: −6.25 to −3.33, p = 0.002). In the case series involving 38 patients, there was a non-significant decrease in serum creatinine, with a mean difference of −0.38 mg/dL (95% CI: −1.27 to 0.5, p = 0.20). Additional analyses could be conducted only with individual patient data derived from case reports. Pre- and post-treatment values for each laboratory parameter were aggregated from these case reports and illustrated in box plots. The change in each parameter for individual patients was represented by lines connecting dots that reflect pre- and post-treatment values. These analyses revealed a significant reduction in AST levels (Wilcoxon p = 0.03) and in the need for vasopressors (Wilcoxon p = 0.03) after treatment. Analyses of ALT, C-reactive protein (CRP), creatinine, and total bilirubin levels post-treatment showed non-significant trends toward reduction.

5 CONCLUSIONS

5.1 Study 1

Preoperative administration of high-dose glucocorticoids do not reduce overall postoperative complication rate significantly. Although several included articles found significant improvements in laboratory outcomes, these data could not be meta-analyzed due to poor reporting.

5.2 Study 2

We found that hemoadsorption therapy for critically ill patients with acute liver dysfunction significantly improves bilirubin levels, need for vasopressors, and liver enzymes. These findings support the use of hemoadsorption as an adjuvant therapy in this patient population.

6 BIBLIOGRAPHY OF THE CANDITATE'S PUBLICATIONS

Publications related to the thesis

Hemoadsorption Therapy for Critically Ill Patients with Acute Liver Dysfunction: A Meta-Analysis and Systematic Review

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