NOVEL THERAPEUTIC OPTIONS IN THE TREATMENT OF ACUTE PANCREATITIS

Ph.D. Thesis Booklet

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1. Introduction

1.1. Overview of the topic

1.1.1. What is the topic?

The investigations focused on the evaluation of different therapeutic options in the treatment of acute pancreatitis.

1.1.2. What is the problem to solve?

There is no disease-specific medication for acute pancreatitis, which targets pathophysiological pathways. Therefore, prompt and effective therapy is needed.

1.1.3. What is the importance of the topic?

Only a few supportive therapies are recommended in the current guidelines for acute pancreatitis or post-ERCP pancreatitis, which consist of early nutrition, pain relief, and fluid management. The currently applied therapies are not evidence-based, and the effectiveness is far from optimal.

1.1.4. What would be the impact of our research results?

We evaluated a possible specific and preventive therapy that are little known in western countries. Based on our statistical analyses, both ulinastatin and nafamostat can be used effectively in the treatment of disease, thus supporting better patient outcomes. In addition, we highlight the potential misuse of PPI in the treatment of acute pancreatitis, thereby improving patient safety and reducing health care costs.

2. Objectives

2.1. Study I. – Investigating the effects of ulinastatin-somatostatin analogue combination therapy in acute pancreatitis

There are several clinical trials in the literature that report on the effectiveness of ulinastatin combination therapy in acute pancreatitis, showing promising results. We aimed to conduct a systematic review and meta-analysis to summarize the available data on therapy.

2.2. Study II. – Investigating the effects of proton pump inhibitors in acute pancreatitis

Previous studies had contradictory findings on the impact of PPIs on the prognosis of patients with AP, our aim was to investigate the associations between PPIs in AP and various clinical outcomes in a systematic review and meta-analysis.

2.3. Study III. – Investigating the effects of nafamostat in the prevention of post-ERCP pancreatitis

A former network meta-analysis showed no beneficial effect of nafamostat, however, several trials have been published since. Therefore, our objective was to investigate the current evidence for nafamostat in the prevention of PEP in a systematic review and meta-analysis.

3. Methods

3.1. Search and selection strategy

The recommendations of the Cochrane Collaboration and the statements of Preferred Reporting Items for Systematic Reviews and Meta-analyses were followed in reporting the findings of these systematic reviews and meta-analyses. We registered the review protocol in the International Prospective Register of Systematic Reviews database (registration number: Study I.: CRD42021282614; Study II.: CRD42022303136; and Study III.: CRD42022367988). We used the PICO (Patient/Population, Intervention, Comparison and Outcomes) framework to formulate the research question, and to define eligibility criteria:

The systematic searches were performed in six databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE, Scilit, Scopus, Web of Science). The reference lists of the identified eligible studies were screened for further reports.

3.2. Selection and data collection

The systematic search results were exported to the EndNote X9 citation manager (Clarivate Analytics, Philadelphia, PA, USA). The selection process were done by two independent authors. A third author made the final decision in case of disagreements.

The available data were extracted from the eligible articles to Microsoft Excel (Microsoft, Office 365, Redmond, WA, USA).

3.3. Statistics

Only outcomes reported in at least three studies were considered for including in the meta-analysis. The pooled results were reported as ORs (odds ratios) for binary outcomes calculated with the Mantel–Haenszel method, and as mean differences (MDs) for continuous outcomes and the corresponding 95% confidence intervals (CI). For binary outcomes, ORs were used for the effect measure, while for continuous outcomes, MDs with corresponding standard deviations (SDs) were used. Random models were used for pooling in the case of both outcome types.

3.4. Risk of bias assessment and certainty of evidence assessment

Two authors independently evaluated the risk of bias for each included study and a third author resolved disagreements. The revised Cochrane Risk-of-Bias tool, while disagreements were resolved by consensus. The domains evaluate the bias arising from the randomization process, deviations from the intended intervention, missing data, the measurement of the outcome, and the selection of the reported results. Cohort studies were evaluated by Risk Of Bias in Non-randomized Studies-of Intervention tool.

The framework Grading of Recommendations, Assessment, Development and Evaluations and the corresponding tool were used to evaluate each outcome for the certainty of evidence.

4. Results

4.1. Study I. – Investigating the effects of ulinastatin-somatostatin analogue combination therapy in acute pancreatitis

Our pooled results revealed decreased complication rates in the intervention. With combination therapy, the rates of ARDS [OR 0.27; 95% CI 0.13–0.60] and AKI [OR 0.29; 95% CI 0.09–0.97] were reduced by approximately 70%, while MODS could be prevented in around 60% of cases [OR 0.39; 95% CI 0.20–0.75]. Reduction of shock incidence was not statistically significant [OR 0.46; 95% CI 0.20–1.07]. (Figure 1.)

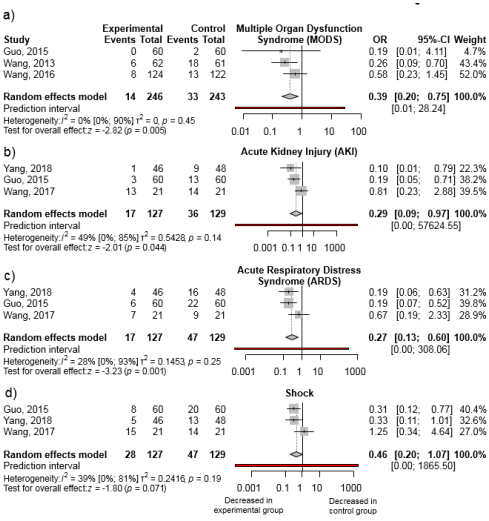

Figure 1. Ulinastatin in combination with somatostatin analogue decreases rates of: a) MODS, b) AKI, and c) ARDS, but not of d) shock, compared to somatostatin analogue monotherapy when administered besides standard of care in acute pancreatitis

Analysis of pooled data from four trials, including 583 patients, shows a trend for a decreased mortality rate with combination therapy [OR 0.55; 95% CI 0.29–1.07]; however, the result was not statistically significant.

In the intervention group, length of hospital stay was shortened by 9.43 days [95% CI (-12.55)–(-6.31)].

4.2. Study II. – Investigating the effects of proton pump inhibitors in acute pancreatitis

The analysis of the pooled results from three studies including 746 patients, showed that in the intervention group the rate of pseudocyst development decreased by 61% compared to the control group [OR 0.39; 95%CI 0.18–0.87] (Figure 2.).

The incidence of ARDS incidence was reported in three studies (746 patients), and there was no significant difference between the two groups in this concern [OR 0.56; 95% CI 0.04–8.59]. Regarding GI bleeding, our pooled results from four studies, including 27,963 patients, revealed a higher probability of occurrence in PPI administration cases [OR 1.81; 95 % CI 1.41–2.33].

The pooled results from three trials (690 patients), including all severity forms of AP, did not show statistically significant differences between the groups regarding the length of hospital stay [MD − 3.47; 95% CI (− 12.32)–5.39].

We were able to perform a meta-analysis for mortality at seven days after diagnosis. In three studies, including 10,607 patients, there were no significant differences

between the experimental and control groups [OR 0.77; 95%CI 0.05–0.10.65; I2=63%].

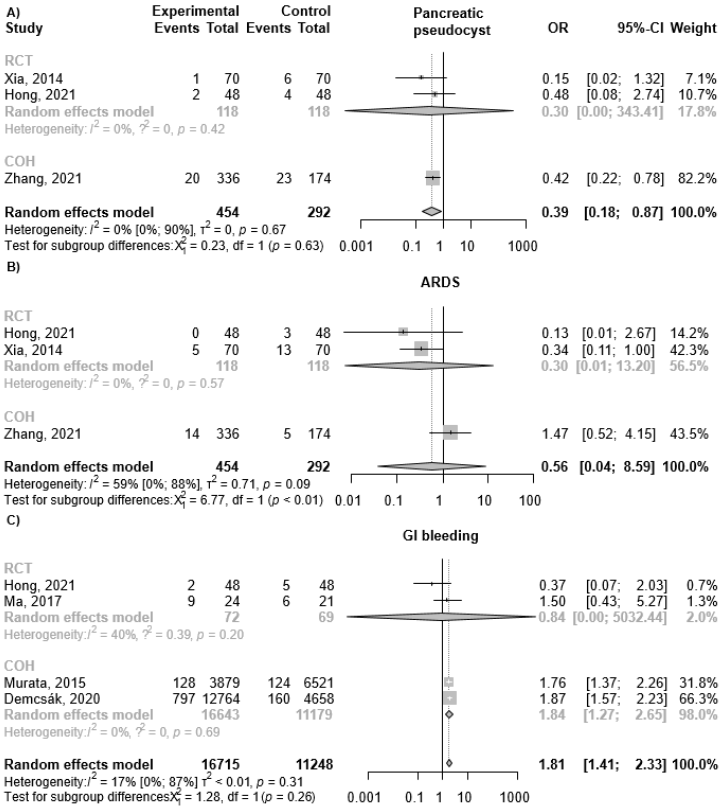

Figure 2. The addition of proton pump inhibitor treatment to standard of care in acute pancreatitis was associated with: (A) Decreased pancreatic pseudocyst development rate; (B) No significant difference regarding development of ARDS; (C) Increased odds of GI bleeding.

8.3. Study III. – Investigating the effects of nafamostat in the prevention of post-ERCP pancreatitis

Seven studies reported on PEP using 20 mg and 50 mg of nafamostat. The overall incidence of PEP was lower in both nafamostat groups compared to standard of care [20 mg: OR: 0.50, 95% CI 0.30–0.82; and 50 mg: OR: 0.48, 95% CI: 0.24–0.96] (Figure 3.).

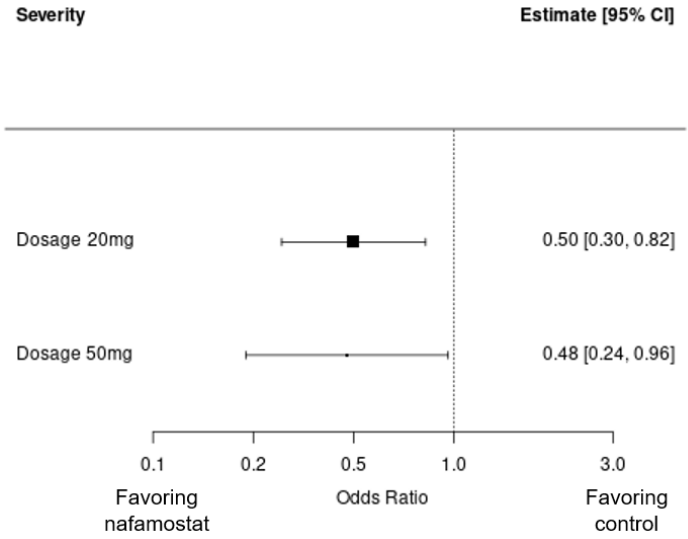

Figure 3. Multilevel model results on the overall effect of nafamostat therapy in the prevention of post-ERCP pancreatitis (PEP).

However, in the subgroup analysis, we found statistically a significant prevention of mild PEP only in the 20 mg subgroup [OR: 0.49, 95% CI: 0.31–0.77]. We found no statistical differences in other severity groups (mild, moderate, and severe) investigating 20 mg and 50 mg doses of nafamostat compared to standard of care.

5. Conclusions

Our study investigated the rational use of different pharmacologic agents (ulinastatin, nafamostat and PPIs) in acute pancreatitis. Ulinastatin combined with somatostatin analogue significantly decreased complication rates (ARDS, AKI, MODS) in AP in comparison with somatostatin analogue monotherapy. In addition, combination therapy is associated with earlier relief of symptoms and shorter hospital stay.

Our meta-analysis pointed out that even though PPI use in AP treatment reduced the rates of pancreatic pseudocyst formation, it did not show significant effects on other outcomes.

Nafamostat can reduce the overall incidence of PEP compared to placebo and should be considered for use in low-risk patients with mild PEP

6. Bibliography of the candidate's publications

6.1 Publications related to the thesis

Horvath IL, Bunduc S, Fehervari P, Vancsa S, Nagy R, Garmaa G, et al. The combination of ulinastatin and somatostatin reduces complication rates in acute pancreatitis: a systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2022;12(1):17979.

D1, IF: 4.6

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D1, IF: 3.8

Horvath IL, Kleiner D, Nagy R, Fehervari P, Hanko B, Hegyi P, et al. Nafamostat Reduces the Incidence of post-ERCP Pancreatitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Clin Pharmacol Ther. 2024;115(2):206-12.

D1, IF: 6.3*

6.2 Publications not related to the thesis

Kleiner D, **Horvath IL**, Bunduc S, Gergo D, Lugosi K, Fehervari P, et al. Nabiximols is Efficient as Add-On Treatment for Patients with Multiple Sclerosis Spasticity Refractory to Standard Treatment: A Systematic Review and Meta-Analysis of Randomised Clinical Trials. Curr Neuropharmacol. 2023;21(12):2505-15.

Q1, IF: 4.8

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D1, IF: 3.8*

* Based on the 2023 Journal Citation Reports