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Efficacy and adverse effects of insulin versus plasmapheresis in patients with hypertriglyceridemia-3-induced acute pancreatitis: a systematic review and meta-analysis

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Abstract

Background Hypertriglyceridemia is a common cause of acute pancreatitis (AP). This literature review compared the effectiveness and adverse events of insulin therapy, with or without heparin, and plasmapheresis, in reducing triglyceride levels in patients with hypertriglyceridemia-induced AP.

Methods Systematic reviews, meta-analyses, evidence syntheses, editorials, commentaries, protocols, abstracts, theses and preprints were excluded. Review Manager was used to conduct the meta-analysis. The literature search yielded 2765 articles, but only 5 were included in the systematic review and meta-analysis and the total number of participants in the review was 269.

Results From this study's analysis, insulin ± heparin was more successful in reducing triglyceride levels than plasmapheresis (standardized mean difference -0.37, 95% confidence interval [CI] 0.99 to 0.25; P=0.25). Insulin ± heparin therapy had a lower mortality rate than plasmapheresis (risk ratio [RR] 0.70, 95%CI 0.25-1.95). Hypotension, hypoglycemia, and acute renal failure were less common in the plasmapheresis therapy group than in insulin ± heparin therapy (RR 1.13, 95%CI 0.46-2.81, RR 3.90, 95%CI 0.45-33.78, and RR 0.48, 95%CI 0.02-13.98 for hypotension, hypoglycemia, and acute renal failure, respectively).

Conclusions This study found no significant difference in mortality between insulin ± heparin therapy and plasmapheresis used for the reduction in triglyceride levels. It is notable that no substantial differences were observed in the most common side-effects encountered during these therapies, thus indicating non-inferiority.

Keywords Insulin, plasmapheresis, acute pancreatitis, hypertriglyceridemia

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Conflict of Interest: None

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Introduction

Acute pancreatitis (AP) is a severe disease that can represent an important challenge for physicians, especially gastroenterologists and surgeons; it has an incidence of 4.6-100/100,000 persons in Europe [1]. In the United States of America, the hospitalization rate for AP increased from 65.4 to 81.9/100,000 persons between 2001 and 2014 [2]. AP has been shown to have a high incidence and was the fifth-ranked cause of in-hospital fatalities, as well as a significant contributor towards hospitalization expenses [3]. Hypertriglyceridemia ranks third among all known causes of AP, after excessive alcohol consumption and gallstone disease [4]. Patients with noticeably elevated chylomicron levels often seek emergency

care because of symptoms resembling AP, including persistent abdominal discomfort, nausea and vomiting. Those with triglyceride concentrations exceeding 500-1000 mg/dL face a significant risk of developing AP, while individuals experiencing hyperchylomicronemia syndrome exhibit triglyceride levels exceeding 2000 mg/dL [5].

Currently, the initial conservative approach for management involves pain control with opioid analgesics and intravenous fluids. Insulin therapy has traditionally been the cornerstone of inpatient care, and has been extensively studied. However, over the past few decades, plasmapheresis has emerged as an increasingly common therapeutic option for hyperlipidemic pancreatitis [6].

In AP patients with hypertriglyceridemia, insulin therapy, with or without heparin, and plasmapheresis have been proposed and employed as potential treatment strategies in selected individuals [7]. The effectiveness and outcome benefits of the therapy are still debatable and the available literature is severely limited [8-11]. There is also a paucity of data regarding the adverse events these interventions may cause in patients with hypertriglyceridemia-induced pancreatitis requiring acute treatment.

The objectives of the current systematic review and meta-analysis were to: (a) compare the effectiveness of insulin ± heparin vs. plasmapheresis in managing patients with hypertriglyceridemia; (b) compare triglyceride reduction levels due to insulin ± heparin therapy vs. plasmapheresis therapy; and (c) investigate adverse events due to insulin ± heparin therapy vs. plasmapheresis therapy.

The PICO model was used to organize the research question in: patients diagnosed with hypertriglyceridemia-induced AP. Intervention included insulin ± heparin therapy vs. plasmapheresis (control). The primary outcome was the reduction in triglyceride level while the secondary outcome was the comparison of the adverse events between the 2 groups.

Materials and methods

Search strategy

A current systematic review and meta-analysis were carried out following the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [12]. A systematic search for articles was conducted in various databases (PubMed, EMBASE, Web of Science, Scopus, Science Direct, and Google Scholar) for articles published until 30th September 2022. Since only electronic databases were searched and grey literature was not taken into consideration, the reference lists of selected publications were scanned to find further studies.

To conduct an electronic database search, a search string was developed for PubMed, then slightly adjusted for use in the other databases. The search string used was as follows:

[(insulin) OR (heparin)] AND [(plasmapheresis) OR (plasma exchange)] AND [(hypertriglycerid*) OR (triglycerid*)].

Inclusion criteria

For inclusion in this systematic review, studies had to be written in English and published between January 2000 and September 2022. In the process of determining whether to incorporate an article into this systematic review and meta-analysis, factors such as the study's population, publication date, and objectives were taken into account. The following prerequisites had to be met for the inclusion of a research paper in this review: (a) original studies, including case-control studies, randomized controlled trials, and both retrospective and prospective cohort studies; (b) studies employing a comparative methodology that compared insulin-treated hypertriglyceridemia patients with those who received plasmapheresis treatment. Consequently, studies lacking either an intervention group (insulin ± heparin treatment) or a control group (plasmapheresis) were excluded from consideration and analysis; and (c) studies in which one of the investigated intervention outcomes was the reduction of triglyceride levels in the patients.

Exclusion criteria

Systematic reviews, literature reviews, letters to the editor, conference papers, and other non-original works were not taken into consideration. Studies that failed to discuss how intervention and control affected triglyceride levels were excluded, as were journal publications without peer review and articles without full text.

Assessment of methodological quality

Quality assessments were performed on the studies that satisfied the requirements for inclusion. The quality of every study was evaluated using the Effective Public Health Practice Project (EPHPP) quality assessment instrument. The EPHPP has been recommended for the assessment of the quality of public health interventions, particularly those that use particular experimental designs [13,14]. Comparing the EPHPP to the Cochrane Collaboration Risk of Bias, it has also been said that the EPHPP has greater inter-rater reliability [15]. Selection bias,

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confounders, study design, participant blinding, data collection methods, and withdrawals and dropouts were the 6 assessment criteria of a study's methodological quality that were scored as either weak, moderate or strong, to reach an overall quality rating, also graded as strong, moderate or weak (Table 1). We assigned an overall score of "weak" when there were 2 or more "weak" ratings, "moderate" for a single "weak" rating, and "strong" when no "weak" ratings were present. Systematic Reviews and Meta-Analyses typically involve publications that are already available on the internet and contain de-identified patient data. Consequently, Institutional Review Board approval was waived in accordance with international publication standards.

Data extraction

Data from the studies that met the inclusion criteria were entered into a prepared Excel spreadsheet. The data extracted included: author's name, year of publication, study region, study design, age and sex of participants, and triglyceride levels before and after therapy.

Statistical analysis

Data collected was analyzed using Review Manager 5.3 software. Comparison of continuous and dichotomous variables was done using the standardized mean difference (SMD) with the 95% confidence interval (CI) and the risk ratio (RR). P-value and I^2 statistics were used to evaluate the heterogeneity among the included studies. Evidence of heterogeneity was defined as a P-value of less than 0.10. I^2 values of more than 70% were regarded as the definitive indicator of study heterogeneity, whereas values between 50% and 70% were regarded as substantial heterogeneity.

Results

Search results

The search of articles in e-databases yielded 2832 articles: 175 articles from PubMed, 146 from Scopus, 335 studies from EMBASE, 1124 articles from Science Direct, and 1052 articles from Google Scholar. After screening the reference lists, an additional 21 articles were identified, increasing the total to 2853 articles. Following the removal of 1233 duplicate articles, we proceeded to review the abstracts and titles of the remaining 1620 publications. Of these, 1442 were rejected during the screening process. Only 5 of the remaining 178 papers matched the requirements for inclusion in this systematic review and meta-analysis after being read in their entirety. The data selection process is provided in Fig. 1. According to the EPHPP quality assessment tool, 2 studies had a moderate overall rating [8,16], 2 studies had a strong overall rating [9,10], while 1 study had a weak overall rating [11] (Table 1).

Characteristics of the included studies

The studies are presented in Table 2. The sample size of these studies ranged from 22-89, with a total of 269 participants. Of these, 145 patients were treated with insulin ± heparin while 124 were treated with plasmapheresis. All these participants were adults aged ≥18 years. Among these studies, 1 was a case-control study, 3 were retrospective studies and 1 was a randomized controlled trial. The characteristics of the included studies are summarized in Table 2.

Results of individual studies

Araz et al, 2022 [8]

Patients in the plasmapheresis group experienced a significant reduction in triglyceride levels, by 88.7%, while those in the insulin ± heparin group showed a reduction of 79.9% by the end of the treatment period. It is important to note that, while 2 deaths occurred among individuals who received plasmapheresis treatment, there was no direct link between the treatment and mortality.

The incidence of respiratory failure and hypotension throughout the hospital stay did not differ between the 2 groups: 3 (16%) in the plasmapheresis group and 1 (5%) patient in the insulin ± heparin group. Acute renal failure (0 vs. 4 [21.1%] for insulin ± heparin vs. plasmapheresis) and disturbed mental state (1 [3%] vs. 7 [37%] for insulin ± heparin

Table 1 Effective Public Health Practice Project quality assessment scores

	Assessment item						
Study, year [ref.]	Selection bias	Study designs	Confounders	Blinding	Data collection method	Withdrawals and dropouts	Overall rating score
Araz *et al*, 2022 [8]	S	M	S	W	M	M	Moderate
Gubensek *et al*, 2022 [9]	S	S	S	M	S	S	Strong
Jin *et al*, 2018 [10]	M	M	S	M	M	S	Strong
Yu *et al*, 2020 [11]	M	M	W	M	W	M	Weak
Frankova *et al*, 2018 [16]	M	M	M	W	M	M	Moderate

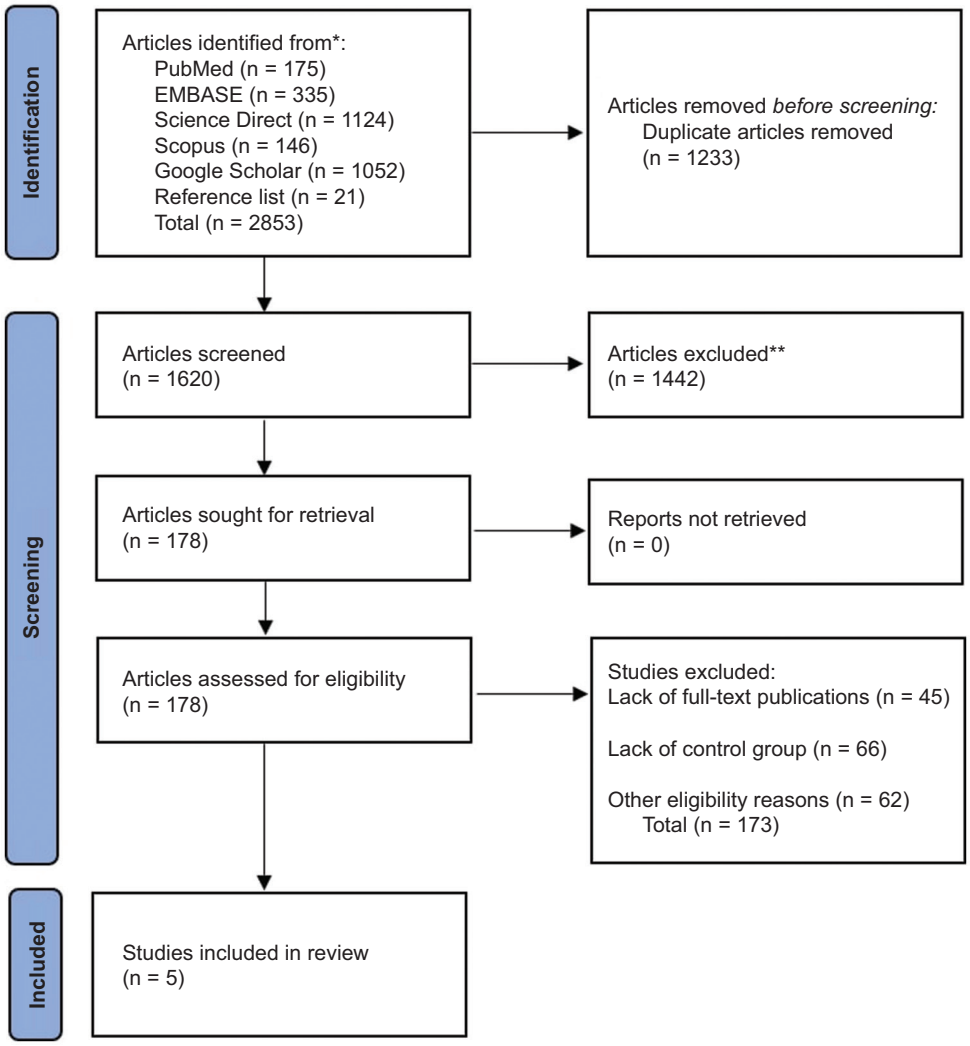

Figure 1 The PRISMA diagram details our search and selection process applied during the overview

vs. plasmapheresis] were also significantly more common in the plasmapheresis group.

Gubensek et al, 2022 [9]

Although there was a tendency for the plasmapheresis group to experience a greater reduction in triglycerides within 24 h of admission (67±17mg/dL in the plasma exchange group vs. 53±17mg/dL in the insulin group, P=0.07), the actual difference in treatment effectiveness was only marginal: mean difference of 6 mmol/L (95%CI 1-15 mmol/L) within 24 h, or 14% (95%CI 0-28%) of baseline triglycerides.

Regarding the side-effects of the 2 triglyceride-lowering therapies, there was 1 minor hypoglycemia in the insulin ± heparin group and 1 allergic response (urticaria and hypotension) in the plasmapheresis group, which occurred almost at the conclusion of the plasmapheresis procedure.

Jin et al, 2018 [10]

After the first plasmapheresis session, the triglyceride level was found to be lowered by 66.9±21.5%, and after the first day of insulin ± heparin therapy, it was found to be reduced by 75.0±14.6%. In total, 6 (21.4%) patients reported adverse effects related to plasmapheresis, including 1 case of deep venous thrombosis brought on by a central venous catheter, 2 cases of anaphylaxis, 2 cases of hypocalcemia, and 1 case of hypokalemia. Repeated measures ANOVA revealed that there was no significant difference between the 2 groups in the tendency to lower triglyceride levels.

Yu et al, 2020 [11]

Patients in the insulin ± heparin group had significantly lower 24-h triglyceride clearance rates than those in the

Table 2 Included studies

Study, year [ref.]	Study design	Study region	Sample size	Patient characteristics	Triglyceride levels at admission mean±SD (mmol/L)	Triglyceride levels after treatment mean±SD (mmol/L)
Araz *et al*, 2022 [8]	Cross-sectional	Turkey	Insulin±heparin group (n=29) plasmapheresis group (n=19)	Age ≥18 years, 47% male	Insulin±heparin group 21.9±17.5 plasmapheresis group 50.7±42.8	Insulin±heparin group 4.4±2 plasmapheresis group 5.7±2.3
Gubensek *et al*, 2022 [9]	RCT	Slovenia	Insulin±heparin group (n=11) plasmapheresis group (n=11)	Aged ≥18 years, 72% male	Insulin±heparin group 26±8 plasmapheresis group 31±9	Insulin±heparin group 12±3 plasmapheresis group 10±5
Jin *et al*, 2018 [10]	Retrospective	China	Insulin±heparin group (n=34) plasmapheresis group (n=28)	Aged ≥18 years, 48% male	Insulin±heparin group 39.4±23.8 plasmapheresis group 37.3±29.7	Insulin±heparin group 5.0±2.1 plasmapheresis group 5.7±2.4
Yu *et al*, 2020 [11]	Retrospective	China	Insulin±heparin group (n=46) plasmapheresis group (n=43)	Aged ≥18 years, 66% male	Insulin±heparin group 28.22 (23.58-38.90) plasmapheresis group 23.10 (16.62-47.11)	NA
Frankova *et al*, 2018 [16]	Retrospective		Insulin±heparin group (n=25) plasmapheresis group (n=23)	Mean age 45.9 years	Insulin±heparin group 36.7±16.6 plasmapheresis group 38.1±15.8	Insulin±heparin group 8.8±11.0 plasmapheresis group 6.7±4.9

SD, standard deviation; RCT, randomized controlled trial

plasmapheresis group (P<0.05). Patients in the insulin ± heparin group took longer than those in the plasmapheresis group to reach the target triglyceride level. The frequency of therapy-related problems was substantially greater in the plasmapheresis group (30.23%) than in the insulin ± heparin group (2.17%).

Frankova et al, 2018 [16]

At each evaluated time point, the triglyceride levels were significantly reduced by each treatment, but there was no difference between the groups at any of the time points. The researchers did not report any adverse event associated with insulin ± heparin therapy or plasmapheresis.

Statistical analysis of the measured outcomes

Reduction in triglyceride levels

The data used for this analysis came from Araz *et al* (2022) [8], Frankova *et al* (2018) [16], Gubensek *et al* (2022) [9], Jin *et al* (2018) [10] and Yu *et al* (2020) [11]. In assessing the outcome of mortality, the total number of people included was 269,145 in the insulin ± heparin group (first arm) and 124 in the plasmapheresis group (second arm) (Fig. 2).

A random-effects model was used, and the calculated standardized mean difference (SMD) was 0.37 (95%CI -0.99 to 0.25), with a P-value of 0.25. The included studies had high heterogeneity (P=0.008, I^2=75%). The overall results showed that, compared to plasmapheresis, insulin ± heparin therapy tends to have a positive impact on reducing triglyceride levels in patients with hypertriglyceridemia.

Mortality

The data used for this analysis came from Araz *et al* (2022) [8], Gubensek *et al* (2022) [9], Jin *et al* (2018) [10] and Yu *et al* (2020) [11]. For inpatient mortality, the total number of subjects was 221, 120 in the insulin ± heparin group and 101 in the plasmapheresis group. The death rates were 5% in the insulin ± heparin group vs. 7.92% in the plasmapheresis group.

A random-effects model was used, and the calculated RR was 0.70 (95%CI 0.25-1.95), with a P-value of 0.50. The included studies had low heterogeneity (P=0.50, I^2=0%). The overall results showed that insulin ± heparin therapy tends to have a positive impact on reducing the mortality rate in patients with hypertriglyceridemia compared to plasmapheresis therapy.

Hypotension events

The data used for this analysis came from Araz *et al* (2022) [8], Gubensek *et al* (2022) [9] and Jin *et al* (2018) [10]. In assessing this outcome, the total number of people included was 132, 74 in the insulin ± heparin group and 58 in the plasmapheresis group. The number of hypotension events was 18 in the insulin ± heparin group vs. 12 in the plasmapheresis group (Fig. 3).

A random-effects model was used, and the calculated RR was 1.13 (95%CI 0.46-2.81), with a P-value of 0.79. The included studies had low heterogeneity (P=0.33, I^2=11%). The overall results showed that plasmapheresis therapy is associated with a lower number of hypotension events in patients with hypertriglyceridemia compared to insulin ± heparin therapy.

Hypoglycemia

The data used for this analysis came from Gubensek *et al* (2022) [9] and Yu *et al* (2020) [11]. In assessing this outcome, the total number of people included was 108, 54 in the insulin ± heparin group and 54 in the plasmapheresis group. The number of hypoglycemia complications was 3 in the insulin ± heparin group vs. 0 in the plasmapheresis group (Fig. 4).

A random-effects model was used, and the calculated RR was 3.90 (95%CI 0.45-33.78), with a P-value of 0.22. The included studies had low heterogeneity (P=0.82, I^2=0%). The overall results showed that plasmapheresis therapy is associated with a lower risk of hypoglycemia complications in patients with hypertriglyceridemia compared to insulin ± heparin therapy.

Acute renal failure

The data used for this analysis came from Araz *et al* (2022) [8] and Jin *et al* (2018) [10]. In assessing this outcome, the total number of people included was 110, 63 in the insulin ± heparin group and 47 in the plasmapheresis group. The number of acute renal failure complications was 18 in the insulin ± heparin group vs. 12 in the plasmapheresis group (Fig. 5).

A random-effects model was used, and the calculated RR was 0.48 (95%CI 0.02-13.98), with a P-value of 0.67. The included studies had high heterogeneity (P=0.02 and I^2=81%). The overall results showed that insulin ± heparin therapy is associated with a lower risk of acute renal failure in patients with hypertriglyceridemia compared to plasmapheresis therapy.

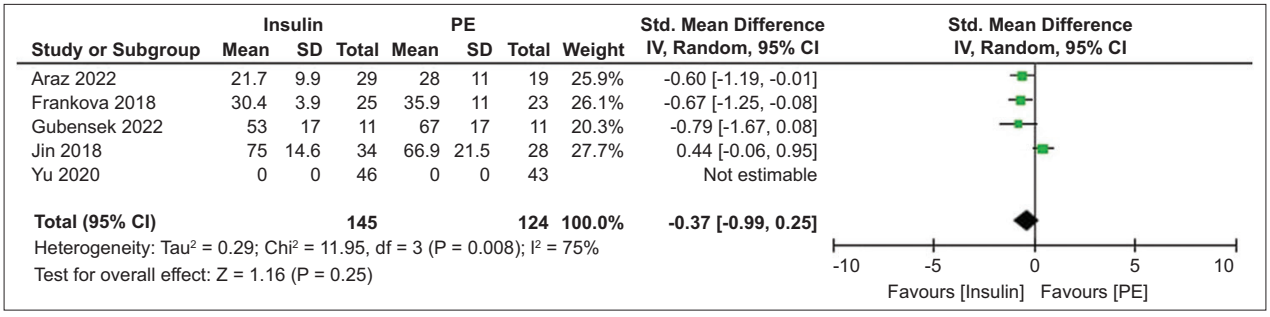

Figure 2 Forest plot depicting the standard mean difference in reduction of serum triglyceride levels between the insulin group and the plasma exchange group

Green squares and their corresponding lines are the PE and 95%CIs for each study. Black diamonds represent the pooled effect estimate
SE, standard error; IV, inverse variance; CI, confidence interval; DF, degree of freedom; PE, point estimates

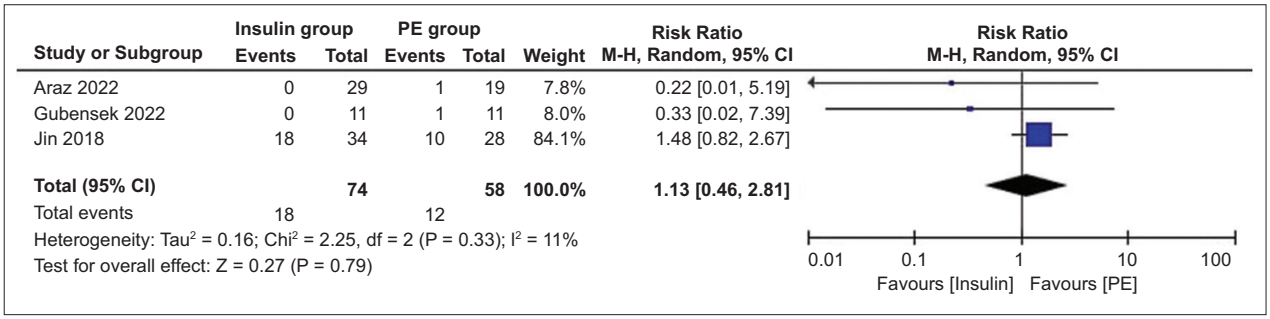

Figure 3 Forest plot comparing risk of hypotension in insulin and plasma exchange group

Blue squares and their corresponding lines are the PE and 95%CIs for each study. Black diamonds represent the pooled effect estimate
SE, standard error; IV, inverse variance; CI, confidence interval; DF, degree of freedom; PE, point estimates

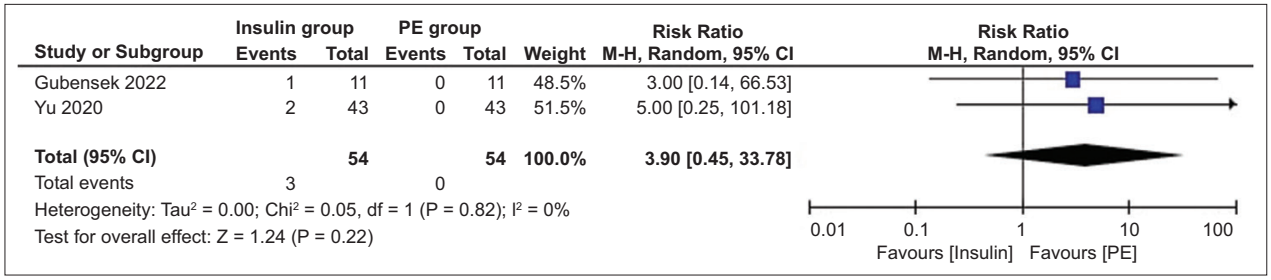

Figure 4 Forest plot comparing risk of hypoglycemia in insulin and plasma exchange group
Blue squares and their corresponding lines are the PE and 95%CIs for each study. Black diamonds represent the pooled effect estimate
SE, standard error; IV, inverse variance; CI, confidence interval; DF, degree of freedom; PE, point estimates

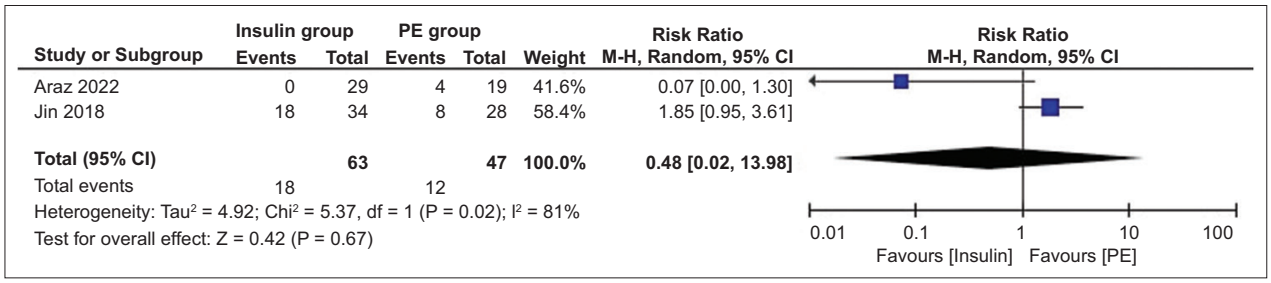

Figure 5 Forest plot comparing risk of acute renal failure in insulin and plasma exchange group
Blue squares and their corresponding lines are the PE and 95%CIs per each study. Black diamonds represent the pooled effect estimate
SE, standard error; IV, inverse variance; CI, confidence interval; DF, degree of freedom; PE, point estimates

Discussion

The goal of this review was to examine how well insulin ± heparin and plasmapheresis treatments reduced triglyceride levels in patients with hypertriglyceridemia-induced AP. Many studies, the majority of which were single-center studies, have reported the retrospective outcomes of their treatment approaches. However, a direct comparison of insulin ± heparin and plasmapheresis was the main focus of the present study. Consequently, only studies that compared the 2 therapeutic options were included. Further large-scale clinical trials may be warranted to increase the strength of such evidence. Substantial heterogeneity among the pooled studies was also observed (I^2=75%, P=0.008).

The safety of the therapies stands as a significantly important aspect for patients, physicians and medical professionals in the management of hypertriglyceridemia-induced AP. Safety outcomes associated with the 2 therapies, including death, were evaluated in this study. According to this systematic review, insulin ± heparin therapy, as opposed to plasmapheresis therapy, was related with a statistically insignificant reduction in mortality.

Adverse events were compared between insulin ± heparin therapy and plasmapheresis intervention using the results of 3 adverse events (hypertension, hypoglycemia and acute renal failure). From the analysis of this study, no statistically significant difference in hypotension events was reported between insulin ± heparin or plasmapheresis (RR 1.13, 95%CI 0.46-2.81; P=0.79). However, a high number of hypotension events were noticed in the insulin ± heparin group (n=18) compared to the plasmapheresis group (n=12).

With respect to hypoglycemia, this study found that insulin-treated patients have a high risk of developing hypoglycemia complications compared to patients treated with plasmapheresis (RR 3.98, 95%CI 0.45-33.78; P=0.22). Both the studies used to compare hypoglycemic events, reported an unambiguous preference towards plasmapheresis in terms of safety [9,11]. However, larger studies are required to achieve statistical significance. In these studies, no hypoglycemia complications were observed in patients treated with plasmapheresis, while insulin ± heparin therapy was linked with a few hypoglycemia complications.

Acute renal failure is another complication that was investigated in this study and compared between the 2 treatment groups. From the study analysis, patients from the plasma exchange therapy group had a high chance of developing acute renal failure compared to patients managed by insulin ± heparin therapy. However, the difference was statistically insignificant and contradictory between the 2 studies. Therefore, a conclusive comparison cannot yet be established.

Taking into consideration cost-effectiveness, convenience of administration and resource stewardship, insulin ± heparin therapy may be more favorable in the actual clinical context. Easier affordability with insulin ± heparin may further improve treatment rates for self-paying patients, leading to better follow-up rates. In addition, insulin ± heparin therapy involves a simpler setup than plasmapheresis, which requires costly equipment and greater operating and maintenance costs. Clinical decisions may also be influenced by the healthcare

setting and the availability of resources until more clear research on the superiority of a specific therapy is established. Given the limited availability of plasmapheresis in rural areas, insulin ± heparin therapy will invariably be favored over plasmapheresis for the treatment of such patients. To gain a deeper understanding of this illness, more randomized trials are required to establish concrete evidence.

There were numerous findings in this review that pointed in opposite directions. The analytical results did not show any significant difference in favor of either therapy in lowering triglyceride levels in patients with hypertriglyceridemia, when they were combined under a single observation. However, a number of issues along the way might have limited these results.

Firstly, the included studies had a substantial level of heterogeneity (75%), which is far above the maximum level permitted (50%). Second, this systematic review's findings are additionally constrained by the dearth of trials comparing the effectiveness of insulin ± heparin and plasmapheresis in decreasing triglyceride levels in patients with hypertriglyceridemia-induced AP. Finally, since the findings of this study found only small differences in the safety of the 2 classes of therapies, clinical decision-making may be driven by the reduction in triglyceride levels, given the similar safety profile of both groups.

All the studies included in the current systematic review and meta-analysis compared the efficacy of insulin ± heparin vs. plasma exchange in the reduction of triglyceride levels among patients with hypertriglyceridemia-induced AP. From the analysis of this study, there was no statistical difference between insulin ± heparin and plasma exchange in reducing triglyceride levels in patients with hypertriglyceridemia-induced AP. Furthermore, there was no significant difference in terms of safety between the 2 treatment options, indicating non-inferiority in terms of safety profile as well as the reduction in triglyceride levels. More studies with a larger sample size are needed to confirm these findings.

Summary Box

What is already known:

- Acute pancreatitis (AP) is a significant medical challenge with a rising incidence and substantial healthcare costs
- Hypertriglyceridemia is a leading cause of AP, but optimal treatment strategies remain debatable
- Insulin ± heparin therapy and plasmapheresis have been proposed as potential treatments, but limited literature exists on their comparative effectiveness and safety

What the new findings are:

- This systematic review and meta-analysis found insulin ± heparin therapy and plasmapheresis AP to be equally effective in reducing triglyceride levels in AP patients
- Considering cost-effectiveness, convenience, and resource availability, insulin ± heparin therapy may be preferred in clinical practice, especially in resource-limited settings for AP

References

1. Iannuzzi JP, King JA, Leong JH, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. *Gastroenterology* 2022;**162**:122-134.
2. Gapp J, Hall AG, Walters RW, Jahann D, Kassim T, Reddymasu S. Trends and outcomes of hospitalizations related to acute pancreatitis: epidemiology from 2001 to 2014 in the United States. *Pancreas* 2019;**48**:548-554.
3. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. *Lancet* 2015;**386**:85-96.
4. Yang AL, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis. *Pancreatology* 2020;**20**:795-800.
5. Francisco AR, Gonçalves I, Veiga F, Pedro MM, Pinto FJ, Brito D. Hypertriglyceridemia: is there a role for prophylactic apheresis? A case report. *J Bras Nefrol* 2016;**38**:366-369.
6. Yeh JH, Chen JH, Chiu HC. Plasmapheresis for hyperlipidemic pancreatitis. *J Clin Apher* 2003;**18**:181-185.
7. Gavva C, Sarode R, Agrawal D, Burner J. Therapeutic plasma exchange for hypertriglyceridemia induced pancreatitis: a rapid and practical approach. *Transfus Apher Sci* 2016;**54**:99-102.
8. Araz F, Bakiner OS, Bagir GS, Soydas B, Ozer B, Kozanoglu I. Continuous insulin therapy versus apheresis in patients with hypertriglyceridemia-associated pancreatitis. *Eur J Gastroenterol Hepatol* 2022;**34**:146-152.
9. Gubensek J, Andonova M, Jerman A, et al. Comparable triglyceride reduction with plasma exchange and insulin in acute pancreatitis – a randomized trial. *Front Med (Lausanne)* 2022;**9**:870067.
10. Jin M, Peng JM, Zhu HD, et al. Continuous intravenous infusion of insulin and heparin vs plasma exchange in hypertriglyceridemia-induced acute pancreatitis. *J Dig Dis* 2018;**19**:766-772.
11. Yu S, Yao D, Liang X, et al. Effects of different triglyceride lowering therapies in patients with hypertriglyceridemia induced acute pancreatitis. *Exp Ther Med* 2020;**19**:2427-2432.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.
13. Jackson N, Waters E; Guidelines for Systematic Reviews in Health Promotion and Public Health Taskforce. Criteria for the systematic review of health promotion and public health interventions. *Health Promot Int* 2005;**20**:367-374.
14. Deeks J, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;**7**:iii-x.
15. Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. *J Eval Clin Pract* 2012;**18**:12-18.
16. Frankova D, Olson KM, Whyms BJ, Guevara Hernandez MA, Franko J. The effect of intravenous insulin, apheresis and oral lipid-lowering agents on non-fasting hypertriglyceridemia and associated pancreatitis. *Postgrad Med* 2018;**130**:494-500.