Peer Review File

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Reviewer A

The present article presents a review plus meta-analysis on the effects of local and remote ischemic preconditioning on transaminases at postoperative day 1 (primary endpoint) as well as several secondary endpoints (total bilirubin, blood loss, surgical time, hospital stay) in patients undergoing hepatectomy. Overall, both local and remote ischemic preconditioning significantly reduced transaminases and local ischemic preconditioning also reduced blood loss. All other endpoints remained neutral.

The information in this paper is valuable, but the paper requires thorough revision and improvement:

Unfortunately, the analyzed studies were not stratified for the mode of anesthesia (volatile vs. propofol) which may interfere with remote ischemic conditioning (Acta Anesthesiol Scand 56, 2012, 30-8; Lancet 382, 2013, 597-664).

The paper/discussion must be more critical throughout – the decrease in transaminases is nice, but a laboratory surrogate, and no improvement in clinical outcome was reported.

The language is poor throughout, and professional language editing is mandatory.

Specific issues:

l. 68: please add AJP 280, 2001, H198-207 to refs. 13-18

l. 76: please replace refs. 20-22 by JACC 65, 2015, 177-95 and Pflueger's Arch 469, 2017, 159-81

l. 241: please add Lancet 382, 2013, 597-604 and JACC 71, 2018, 252-4

Comment 1

Unfortunately, the analyzed studies were not stratified for the mode of anesthesia (volatile vs. propofol) which may interfere with remote ischemic conditioning (Acta Anesthesiol Scand 56, 2012, 30-8; Lancet 382, 2013, 597-664).

Reply 1

Thanks for your constructive suggestions.

We highly agree with your point that the mode of anesthesia may interplay with the efficacy of remote ischemic preconditioning (RIPC). Many studies supported that volatile but not propofol was a positive influencing factor in RIPC for myocardial protection. [1-5]. Similar results were confirmed in kidney protection during cardiac surgery [6-8]. Thus, anesthesia may be a confounding factor in the role of RIPC in cardiac surgery.

However, no studies have indicated that the anesthesia model can interact with the efficacy of LIPC or RIPC in hepatectomy. We found that the use of volatile or propofol in liver resection remains controversial, with some studies indicating no significant difference in liver protection [9-10], while others confirmed the superiority of propofol over sevoflurane in liver surgery [11-12]. Therefore, whether anesthesia is an interfering factor in liver protection remains an

important issue.

Unfortunately, only 8 trials included in our study provided specific details on anesthesia administration, while others did not provide this information. Due to a lack of sufficient data, subgroup analysis of anesthetic methods was not conducted in our study in order to reduce the instability and unreliability of the results. Nevertheless, 5 eligible studies indicated the beneficial impact of RIPC on liver function, all of which utilized propofol (Table1,2,3,4). Therefore, in propofol anesthesia, RIPC may exert protective effect on liver function in patients undergoing hepatectomy, which highlights the complexity of differential organ protective effects under different anesthesia methods.

Furthermore, other important aspects regarding RIPC research are lack of evidence regarding the site, duration and timing of RIPC. These questions need to be addressed by future studies [13].

Reference:

[1] Zangrillo A, Musu M, Greco T, et al. Additive effect on survival of anaesthetic cardiac protection and remote ischemic preconditioning in cardiac surgery: A Bayesian Network Meta-Analysis of Randomized Trials. PLoS One. 2015;10(7):e0134264. doi: 10.1371/journal.pone.0134264.

[2] Kottenberg E, Thielmann M, Bergmann L, et al. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. Acta Anaesthesiol Scand. 2012;56(1):30-8.

[3] Pierce B, Bole I, Patel V, et al. Clinical Outcomes of Remote Ischemic Preconditioning Prior to Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc.2017;20:6(2).

[4] Xie J, Zhang X, Xu J, et al. Effect of remote ischemic preconditioning on outcomes in adult cardiac surgery: a systematic review and meta-analysis of randomized controlled studies. Anesth Analg. 2018;127:30–38.

[5]Meybohm P, Bein B, Brosteanu O, et al. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. N Engl J Med. 2015;373(15):1397-407.

[6] Zarbock A, Schmidt C, Van Aken H, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA. 2015;313:2133–2141.

[7] Zhou H, Yang L, Wang G, et al. Remote ischemic preconditioning prevents postoperative acute kidney injury after open total aortic arch replacement: a double-blind, randomized, sham-controlled trial. Anesth Analg. 2019;129:287–293.

[8] Zarbock A, Kellum JA, Van Aken H, et al. Long-term effects of remote ischemic preconditioning on kidney function in high-risk cardiac surgery patients: follow-up results from the RenalRIP trial. Anesthesiology. 2017;126:787–798.

[9] Song JC, Sun YM, Yang LQ, Zhang MZ, Lu ZJ, Yu WF. A comparison of liver function after hepatectomy with inflow occlusion between sevoflurane and propofol anesthesia. Anesth Analg. 2010 Oct; 111 (4):1036–41.

[10] Slankamenac K, Breitenstein S, Beck-Schimmer B, et al. Does pharmacological conditioning with the volatile anaesthetic sevoflurane offer protection in liver surgery? HPB (Oxford). 2012;14(12):854–62.

[11] Matsumi J, Sato T. Protective effect of propofol compared with sevoflurane on liver

function after hepatectomy with Pringle maneuver: A randomized clinical trial. PLoS One. 2023, doi: 10.1371/journal.pone.0290327.

[12] Laviolle B, Basquin C, Aguillon D, et al. Effect of anesthesia with propofol compared with desflurane on free radical production and liver function after partial hepatectomy. Fundam Clin Pharmacol 2012 Dec; 26(6): 735–42.

[13] Peters, J. Remote ischaemic preconditioning of the heart: remote questions, remote importance, or remote preconditions? BASIC RES CARDIOL. 2011; 106 (4): 507-9. doi: 10.1007/s00395-011-0187-7

Table 1:

AST(IU/L)	**No-preconditioning**			**RIPC**			
ID	**Sample**	**Mean**	**SD**	**Sample**	**Mean**	**SD**	**Anesthesia**
Kong E et al (2023)	27	525.5	71.5	28	442.7	78.4	**Propofol**
Zou BY et al (2021)	20	310.2	12.3	20	196.8	26.4	**Propofol**
Wu Y et al (2014)	10	530.0	266.0	10	214.0	77.0	**Propofol**
Cao YS et al (2021)	30	220.5	15.2	30	126.5	8.1	**Propofol**
Li X et al (2015)	30	359.5	45.4	30	260.4	64.0	**Propofol**
Liu X et al (2019)	67	390.0	139.0	69	437.0	176.0	**Volatile**

Table 2:

AST(IU/L)	**No-preconditioning**			**LIPC**			
ID	**Sample**	**Mean**	**SD**	**Sample**	**Mean**	**SD**	**Anesthesia**
Arkadopoulos N et al(2009)	43	498	255	41	288	140	**Volatile**
Choukèr A et al (2005)	19	408.4	322.5	14	237.2	155.1	**Volatile**

Table 3:

ALT(IU/L)	**No-preconditioning**			**LIPC**			
ID	**Sample**	**Mean**	**SD**	**Sample**	**Mean**	**SD**	**Anesthesia**
Kong E et al (2023)	27	459.4	67.01	25	322.2	52.7	**Propofol**
Zou BY et al (2021)	20	156.9	11.63	20	162.8	14.4	**Propofol**
Wu Y et al (2014)	10	530.0	266.00	10	214.0	77.0	**Propofol**
Cao YS et al (2021)	30	240.2	9.82	30	120.1	1.3	**Propofol**
Li X et al (2015)	30	375.2	52.90	30	278.2	47.6	**Propofol**
Liu X et al (2019)	67	390.0	409.00	69	440.0	518.0	**Volatile**

Table 4:

ALT(IU/L)	**No-preconditioning**			**LIPC**			
ID	**Sample**	**Mean**	**SD**	**Sample**	**Mean**	**SD**	**Anesthesia**
Scatton O et al (2011)	41	518.8	69.0	43	546.0	69.0	**Volatile**

Choukèr A et al (2005)	19	549.8	749.1	14	254.6	135.3	**Volatile**

Changes in the text

We have added the suggestion content to the manuscript in Discussion part. (See page 13; line 241-250 in clean revision or page 16 line 301-310 in marked version)

Comment 2

The paper/discussion must be more critical throughout – the decrease in transaminases is nice, but a laboratory surrogate, and no improvement in clinical outcome was reported.

Reply 2

We are grateful for your attention to outcomes, especially your emphasis on the importance of focusing on clinical outcomes. In this meta-analysis, we chose to compare short-term liver function and surgery-related outcomes for the following reasons:

1. Feasibility: the selected indicators are routine tests in clinical practice. Thus, these indicators are easily accessible. Additionally, in most randomized clinicals trials [1-5], postoperative aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were regarded as the primary outcomes. Selecting these indicators are beneficial for enhancing the feasibility, consistency, and rationality of this study.
2. Guidance for clinical practice: the degree of liver ischemia-reperfusion injury is closely related to changes in liver function indicators. Studies have shown that postoperative transaminase levels are independent predictors of postoperative morbidity and mortality, and transaminase levels generally reach peak within 24 hours after surgery [6]. Therefore, we collected AST, ALT, and TBIL levels on the first day or at their peak levels after surgery. Moreover, laboratory indicators such as AST and ALT are commonly used as primary outcomes in clinical trials; however, they may not provide a comprehensive assessment of short-term recovery and clinical outcomes following liver surgery. Therefore, lacking sensitive and specific indicators reflecting liver function remains a significant concern in clinical studies, which needs to attract enough attention in future investigations.

Furthermore, under your guidance, we have focused on the significance of postoperative complications. We believe that this improvement contributes to more comprehensive refinement for our study. Unfortunately, both global and local inconsistencies were found in our study, which hindered further analysis.

Reference:

[1] Clavien PA, Selzner M, Rüdiger HA, et al. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. Ann Surg. 2003;238(6):843-50; discussion 851-2.

[2] Rakić M, Patrlj L, Amić F, et al. Comparison of hepatoprotective effect from ischemia-reperfusion injury of remote ischemic preconditioning of the liver vs local ischemic preconditioning of the liver during human liver resections. Int J Surg. 2018;54(PtA):248-253.

[3] Beck-Schimmer B, Breitenstein S, Urech S, et al. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. Ann Surg. 2008 Dec;248(6):909-18.

[4] Meurisse N, Mertens M, Fieuws S, et al. Effect of a Combined Drug Approach on the

Severity of Ischemia-Reperfusion Injury During Liver Transplant: A Randomized Clinical Trial. JAMA Netw Open.2023;6(2):e230819.
[5] Scatton O, Zalinski S, Jegou D, et al. Randomized clinical trial of ischaemic preconditioning in major liver resection with intermittent Pringle manoeuvre. Br J Surg. 2011;98(9):1236-43.
[6] Olthof PB, Huiskens J, Schulte NR, et al. Postoperative peak transaminases correlate with morbidity and mortality after liver resection. HPB (Oxford). 2016;18(11):915-921.

Changes in the test

We have added the suggestion content to the manuscript in Discussion (limitations) part. (see Page 13-14, line 256-260 in clean version or Page 17,line 326-330 in marked version)

Comment 3

The language is poor throughout, and professional language editing is mandatory.

Reply 3

Thanks for your criticism.

The Review 2 also pointed this weakness. We tried our best to improve the manuscript and made some changes to the manuscript. And, we asked an English editing company for the linguistic retouching. These changes will not influence the content and framework of the paper.

We appreciate for your earnest work and hope these corrections will meet with your approval.

Changes in the test

We did not list the changes here but marked in red in the revised version of manuscript.

Comment 4:

l. 68: please add AJP 280, 2001, H198-207 to refs. 13-18
l. 76: please replace refs. 20-22 by JACC 65, 2015, 177-95 and Pflueger's Arch 469, 2017, 159-81
l. 241: please add Lancet 382, 2013, 597-604 and JACC 71, 2018, 252-4

Reply 4:

We sincerely appreciate these suggestions.

We have checked the literature carefully and added the references into the Backgroud and Discussion part in the revised manuscript according the advice above.

Changes in the test

We have included **AJP 280, 2001, H198-207** in the references. (See page 16, line 312-313;[16] in clean version)

JACC 65, 2015, 177-95 and Pflueger's Arch 469, 2017, 159-81 were added to references (See page 16-17, line 321-324; [20],[21] in clean version)

(); Lancet 382, 2013, 597-604 and JACC 71, 2018, 252-4 were added to the references (See page 18, line 351-356; [33],[34] in clean version)

Reviewer B

English editing is required.

Comment 1

English editing is required.

Reply 1

We feel great thanks for your professional work on this review.

The Review 1 also pointed this weakness. We tried our best to improve the manuscript and made some changes to the manuscript. And, we asked an English Editing Company for the linguistic retouching. These changes will not influence the content and framework of the paper.

We appreciate for your earnest work and hope these corrections will meet with your approval. Changes in the text: see the revised manuscript.

Changes in the test

We did not list the changes here but marked in red in the revised version of manuscript.