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Meta-analysis

Meta-Analysis of Re-perfusion Injury and Ischaemic Conditioning in Limb Surgery

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ABSTRACT

Background: Pneumatic tourniquet commonly used for orthopedic surgery is associated with morbidity related to ischemia-reperfusion injury. Ischaemia conditioning (IC) had shown beneficial effects to attenuate these outcomes. This study aimed to systematically review the evidence of IC effect on outcomes of the patient undergoing orthopedic surgery.

Subjects and Method: This was a systematic review and Meta-Analysis conducted through the online database search from PubMed, Central, Clinicaltrials.gov, and Scopus with topics related to IC and all possible orthopedic surgical interventions. Articles were searched with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocols used keywords "Ischemic conditioning," "Reperfusion injury," "Orthopaedic surgery." The data were extracted from the eligible study within inclusion and exclusion criteria. Two independent reviewers collected the study characteristics. Each study was examined for the risk of bias. The pooled data were analyzed using RevMan 5.3 in Standardized Mean Difference (SMD) as a summary measure with 95% Confidence Interval (CI).

Results: Out of 12 eligible studies collected for qualitative analysis, eight studies with the same outcomes were analyzed for quantitative analysis. A random-effect model was used for analysis with high heterogeneity. The pooled SMD data for IC compared to control for postoperative pain were -0.50 (95% CI= -0.95 to 0.06; p<0.001). Outcome measures for hemodynamic stability, systemic inflammation, and end-organ injury were pooled with MD= 4.81 (95% CI= 3.19 to 6.44); SMD= -1.33 (95% CI= -2.06 to -0.60); SMD= 0.15 (95% CI= -0.14 to 0.71); respectively.

Conclusion: Ischaemic conditioning significantly reduces postoperative pain, inflammation response and maintains hemodynamic stability. A better study design with a higher population number is needed for further study.

Keywords: ischaemic conditioning, reperfusion injury, orthopedic surgery, Meta-Analysis

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BACKGROUND

Pneumatic tourniquets are regularly used during orthopedic surgery to maintain bloodless fields, minimalize blood loss, and aid vital structures identification. However, their use is associated with potentially serious morbidity and mortality related to ischemia-reperfusion injury (Wakai et al., 2001). The ischemia-reperfusion injury occurs when tissue is exposed to a certain duration of ischemia followed by replenishment (Zhou et al., 2018). This event pro-

duces both local and systemic inflammatory responses (Halladin et al., 2014; Leurcharusmee et al., 2018).

In humans, muscle atrophy following intraoperative tourniquet produces early postoperative deficits in quadriceps muscle strength and further impaired total knee arthroplasty rehabilitation (Leurcharusmee et al., 2018). There is a possible metabolic acidosis, hyperkalemia, myoglobinemia, myoglobinuria, and renal failure following systemic metabolic dysfunction after reperfusion (Wakai et al., 2001).

Ischemic conditioning refers to strategic endogenous organ protective mechanisms, all based on rendering the organ tolerance to acute ischemia-reperfusion injury by a single or multiple brief cycles of ischemia and reperfusion. The flexibility in the timing of the ischemia conditioning stimulus has enabled its application in a wide variety of clinical settings (Hausenloy and Yellon, 2016). Ischemic preconditioning (IPC) is an implementation of ischemia conditioning before prolonged ischemic insult. Remote ischemic preconditioning (RIPC) is an IPC performed in one tissue to protect other distant tissue from subsequent prolonged ischemia (Leurcharusmee et al., 2018; Ouyang et al., 2020; Pilcher et al., 2012; Sukkar et al., 2016). Other settings like ischemic postconditioning (IPostC) or blood flow restricted (BFR) exercise was presented in many clinical trials with the same basic principle (Hausenloy and Yellon, 2016; van der Velde et al., 2013; Žargi et al., 2018).

There were many variations of ischemia conditioning intervention effect across clinical settings (Halladin et al., 2014; Leurcharusmee et al., 2018; Sukkar et al., 2016). This study aimed to systematically review the evidence of ischemia conditioning's effect on clinical outcomes and pathophysiological process related to an ischemia-reperfusion injury on the patient undergoing orthopedic surgery.

SUBJECTS AND METHOD

1. Study Design

This systematic review and meta-analysis study was carried out by two independent reviewers at Medline through an online database such as PubMed, Central, Scopus, and clinicaltrials.gov to find a related paper published from 1970 until 2020. We started the search from August 12th, 2020, for seven days and repeated the search a week before the study was submitted for possible new related papers.

The search strategy was based on topic IC and possible orthopedic surgery that using tourniquet procedure. Keywords and their relative terms were generated from the PubMed and MesH database. Additional data were obtained from Google Scholar search and manual search from bibliographies of the relevant studies.

2. Inclusion Criteria

The inclusion criteria for this study were all randomized controlled studies evaluating ischemia condition (IC) on orthopedic surgery, which the trials must include the tourniquet procedure during the surgery. We included all types of IC interventions.

3. Exclusion Criteria

The exclusion criteria were studies that lack a control group, quasi-experimental, observational, and articles that did not use English.

4. Operational Definition of Variables

Ischemic reperfusion (IR) injury is defined as cellular damage after reperfusion of previously viable ischemic tissue. The tourniquet is a common procedure in lower extremity surgery with IR injury as its complication (Halladin et al., 2014). The primary endpoint for this meta-analysis is postoperative pain related to IR injury. Visual Analog Scale (VAS) as an outcome measure

for pain was chosen. We chose outcomes from 48 hours after tourniquet release.

We analyzed the effect on systemic circulation and remote organ damage for the secondary outcome, based on (Leurcharusmee et al., 2018) and (Halladin et al., 2014). The outcome domains were selected based on the pathophysiological process of IR injury. Hemodynamic stability, metabolic stability, inflammation response, and lung damage were selected with outcome measures mean arterial pressure (MAP), lactate serum, potassium serum, interleukin-6 (IL-6), and partial pressure of oxygen (PaO2), respectively. The analysis was carried out with the same time point as much as possible to avoid heterogeneity. We defined the outcomes in line with the authors' definition in primary articles.

The risk of bias within the study included was calculated using the revised Risk of Bias (RoB) 2.0 assessment tools designed by The Cochrane Handbook for Systematic Reviews of Interventions. Six domains of bias were evaluated: randomization process, deviation from intended intervention, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias (Higgins and Cochrane Collaboration, 2020).

5. Data Analysis

This systematic review and Meta-Analysis was constructed using a checklist provided by PRISMA protocols (Moher et al., 2009). The data were analyzed using a forest plot produced by Revman 5.4 statistical software.

Heterogeneity was assessed from I2 statistics with a value >50% considered to represent substantial heterogeneity. If substantial heterogeneity occurred within the analysis, we used the random-effect model for the meta-analysis (Borenstein, 2009; Higgins and Cochrane Collaboration, 2020).

Data measured the same way between trials were recorded as Mean Difference (MD) with 95% confidence interval (CI) for continuous outcomes. Standardized Mean Difference (SMD) was used when different measures were applied.

Subgroup analysis was carried out based on a predefined group to analyze the heterogeneity. This group was selected based on factors that possibly affect the primary outcome. These included the quality of the study, participants' characteristics, characteristics of IC, and anesthetic intervention (Halladin et al., 2014; Sukkar et al., 2016). If the subgroup analysis were not eligible, the heterogeneity was explored by excluding the study with proper scientific reasons (Higgins and Cochrane Collaboration, 2020).

Publication bias was examined with a funnel plot. The publication bias was performed in groups or subgroups of meta-analysis with homogenous data (Borenstein, 2009).

RESULTS

A. Search Results

The study selection was conducted based on a flowchart from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocols (Moher et al., 2009). Author PU and BY identify the relevant trial by reading the title and abstract available from the search protocol results. Duplicate articles were removed. Full-text of relevant trials was gathered based on inclusion and exclusion criteria. We identified a total of 565 records through the electronic search. We exclude 18 records with the same title. After scanning, 398 irrelevant references were excluded. By screening 149 abstracts, we collected 21 full-text articles that were assessed for eligibility later. The final selection for the trial was included after finalized discussion with other authors.

Reasons for exclusion of the study were stated.

Nine studies were excluded with reasons after the assessment. Following the algorithm for study selection, 12 studies were left for the final review. Only eight studies presented with the outcome mentioned above measure were included in the quantitative synthesis. All the studies that qualified for the inclusion criteria were published from years 2006 until 2018. The details of the search result were outlined in PRISMA flow chart seen in Figure 1.

B. Study Characteristics

As demonstrated in Table 1, a total of 393 participants were included in this review. All the studies were lower extremities orthopedic surgery. There were six studies with means of age under 60 years (Koca et al., 2011; Lin et al., 2010; Orban et al., 2006; Van et al., 2008; Žargi et al., 2016, 2018), four studies' participants were over 60 years (Memtsoudis et al., 2014, 2010; Murphy et al., 2010; Oh et al., 2017), and two studies with no information (Sullivan et al., 2009; van der Velde et al., 2013).

Two studies were using BFR exercise protocol for IC (Žargi et al., 2016, 2018). Only one study was using IPostC in this review (van der Velde et al., 2013). The remainder were IPC with three studies reported using no cycle on its conditioning procedure (Memtsoudis et al., 2014, 2010; Orban et al., 2006), and six studies reported using three cycles of ischemia and reperfusion (Koca et al., 2011; Lin et al., 2010; Murphy et al., 2010; Oh et al., 2017; Sullivan et al., 2009; Van et al., 2008). Some anesthetic interventions like propofol, dexmedetomidine, ketamine, sevoflurane, and halothane were related to reducing the IR injury effect (Leurcharusmee et al., 2018). In this study, five studies mentioned one or more of the anesthetics mentioned above intervention (Memtsoudis et al., 2014; Oh et al., 2017; Orban et al., 2006; Sullivan et al., 2009; van der Velde et al., 2013).

C. Assessment of Methodological Quality

The risk of bias assessment in the individual study was shown in Figure 2. One study used a quasi-randomization process, and no allocation concealment was stated to assess the high risk in a bias of the randomization process (Žargi et al., 2018). There were no deviations from the intended intervention on all studies included in this review. Two studies were at high risk of bias due to missing outcome data (van der Velde et al., 2013; Žargi et al., 2018). One study was assessed with a high risk of bias due to selecting reported results (van der Velde et al., 2013).

In summary, 33.3% of the included studies were at low risk of bias. There were 41.7% of the included studies in this review which have some concern risk of bias. And 25% of the rest were categorized high risk of bias. The risk of bias summary is shown in Figure 3.

D. Primary Outcome Measures

Three studies reported only the p-value of the selected outcomes measures (Memtsoudis et al., 2014, 2010; van der Velde et al., 2013). Further contact with the original author was made to gather additional data, but we accomplished no response.

1. Post Operative Pain

Figure 4 showed the pooled point estimate for this domain of SMD= -0.50 (95% CI= -0.95 to -0.06), and it was statistically significant (p= 0.032) with no heterogeneity were present (I^2= 0%).

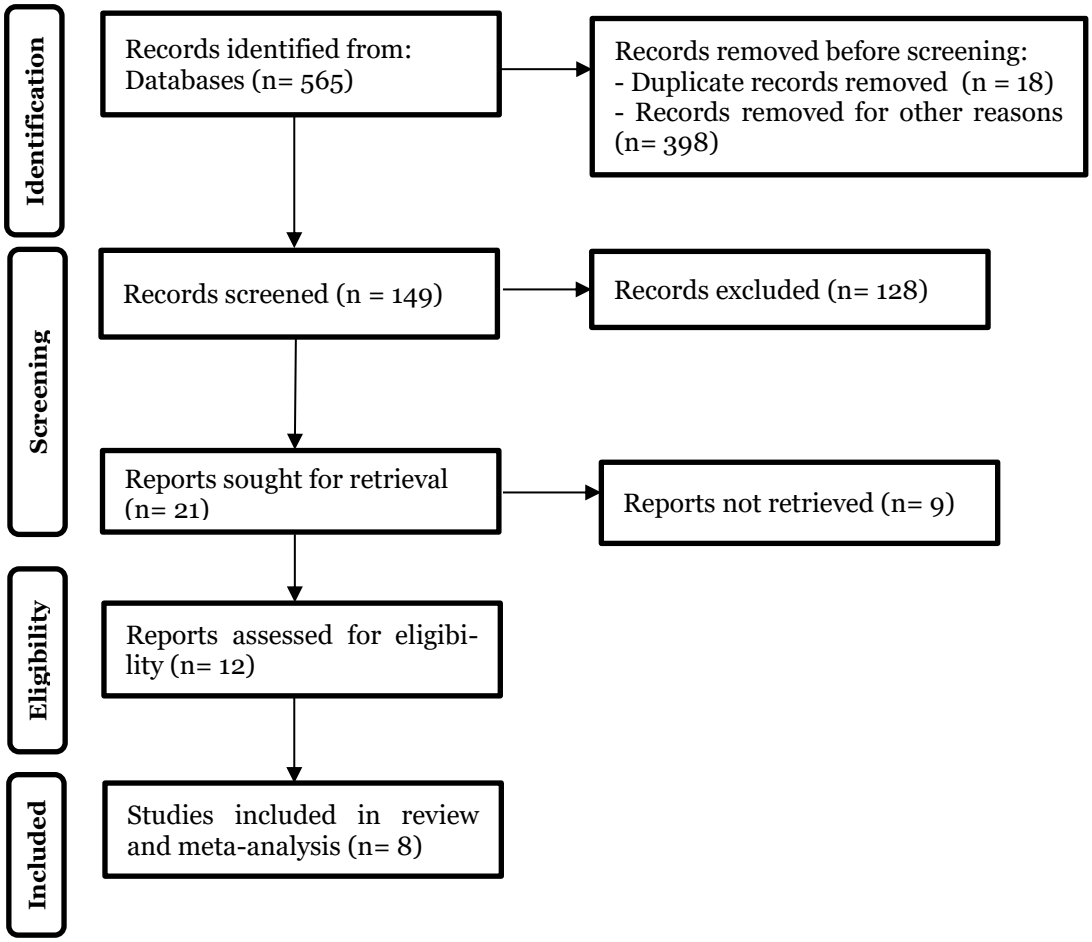


Figure 1. PRISMA Flow Diagram

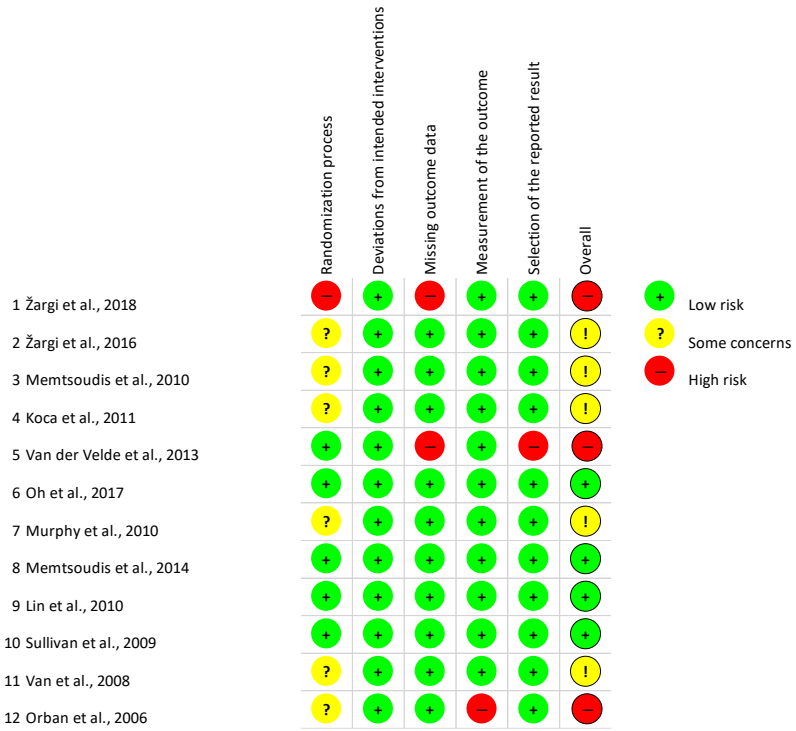


Figure 2. Risk of Bias in Individual Study

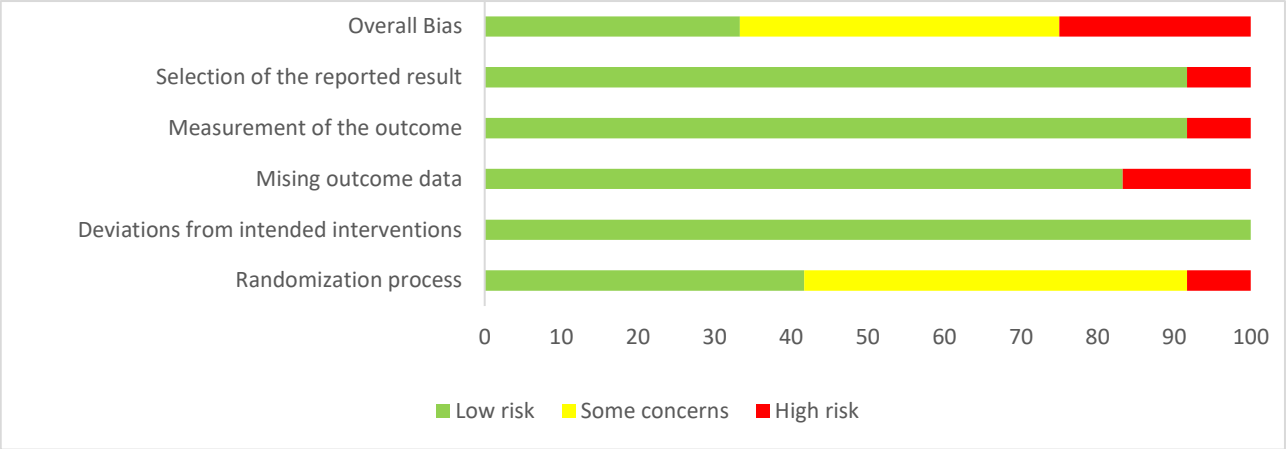


Figure 3. Summary of Risk of Bias Assessment

2. Secondary Outcome Measures

a. Hemodynamic Stability

Figure 5 showed a statistically significant difference of IC versus control on preventing acute hypotension during IR injury MD= 4.27 (95% CI= 2.72 to 5.83; p< 0.001) with mild heterogeneity (I2= 43%). By excluding the high risk of bias, the study failed to explain the heterogeneity.

Subgroup analysis was made based on the study with IPC only, ASA 1-2, age under 60, and anesthetic intervention characteristics compared with other IC conditioning protocols. The analysis found no clinically significant difference on the IPC group (MD= -1.58; 95% CI= -6.94 to 3.78; p= 0.563; I2= 0%). Furthermore, the hemodynamic stabilizing effect was statistically significant on the other IC protocol (SD= 4.81; 95% CI= 3.19 to 6.44; p< 0.001; I^2= 0%).

b. Metabolic Stability

Figure 6 showed that the IC did not attenuate the rise of serum lactate level on the IR injury (SMD= -0.06; 95% CI= -0.31 to 0.20; p= 0.664; I2= 76%). The exclusion of skewed data, time, and ASA status couldn't explain the heterogeneity. Subgroup analysis by grouping the time sample were measured, found no significantly statistical difference in both 1 hour group (SMD= 0.01; 95% CI= -0.26 to 0.28; p= 0.933; I2= 0%) and under 1 hour group (SMD= -0.10; 95% CI= -0.50 to 0.31; p= 0.641; I2= 88%). Figure 7 showed the pooled point estimate from 3 studies (Orban et al., 2006; van der Velde et al., 2013; Van et al., 2008), which found no statistically significant difference on IC for attenuating hyperkalemia due to IR injury (MD= -0.11; 95% CI= -0.34 to 0.13; p= 0.372; I2= 34%).

c. Inflammation Response

Figure 8 showed that IL-6 in the IC group was not significantly different from the control group (SMD= -0.82; 95% CI= -2.06 to 0.41; p= 0.192; I2= 91%). However, Figure 9 showed that exclusion of study with skewed data demonstrated significantly different effects (SMD= -1.33; 95% CI= -2.06 to -0.60; p= 0.001) despite having better but still substantial heterogeneity (I^2= 55%). Study with a high risk of bias, anesthetic intervention, or type of IC protocol could not explain the heterogeneity. However, the effect favors the IC group on attenuating the inflammation response during IR injury.

Table 1. Characteristics of included study

No.	Author (Year)	Population	Surgery	IC Protocols			Control	Anesthesia	Outcomes Domain
				Ischaemic Cycle	Average Ischaemic Time	Cuff Pressure			
1.	Žargi et al. (2018)	N=20, Mean age 34.5 years, ACL history >6 months, no prev. knee surgery	Arthroscopic single-bundle ACL reconstruction	BFR Exercise Protocol*	71 minutes	300 mmHg	Sham BFR Intervention	Spinal	Muscle strength and endurance
2.	Žargi et al. (2016)	N=20, Mean age 33.5 years, ACL history >6 months, no previous knee surgery	Arthroscopic ACL reconstruction with ipsilateral hamstring auto-graphs	BFR Exercise Protocol*	72 minutes	300 mmHg	Sham BFR Intervention	Spinal	Muscle strength and postoperative muscle atrophy
3.	Memtsoudis et al. (2010)	N=34, BMI>30, ASA II & III, Mean age 66.5 years	Primary uni-lateral total knee arthroplasty	IPC/ 5' inflation/ 5' reperfusion/ no cycle	55 minutes	250 mmHg	Full tourniquet without preconditioning	Spinal and Epidural	Inflammatory response, lung injury, post-operative compli-cation, pain, length of hospital stay
4.	Koca et al. (2011)	N=45, man, ASA I, Mean age 22 years	Knee arthroscopy with partial meniscectomy, chondral debridment, plica release, and irrigation	IPC/ 5' inflation/ 5' reperfusion/ 3 cycle	88 minutes	350 mmHg	Full tourniquet without preconditioning	Spinal	Oxidative stress, antioxidant enzyme, antioxidant effect
5.	van der Velde et al. (2013)	N=16, ASA I & II	Bimalleolar ankle fracture repair	IPostC/ 3' reperfusion/ 30" inflation/ 3 cycle	66 minutes	300 mmHg	Full tourniquet without staggered release	General anesthesia with propofol, fentanyl, & sevoflurane	Metabolic & hemodynamic stability
6.	Oh et al. (2017)	N=72, Mean age 70.25 years	Total knee replacement	RIPC/ 5' inflation/ 5' reperfusion/ 3 cycle	110 minutes	300 mmHg	Full tourniquet without preconditioning	General anesthesia with thiopental	Cerebral oxygenation, lung injury, inflammatory

								sodium and sevoflurane	response, muscle damage
7.	Murphy et al. (2010)	N=20, Mean age 68.5 years	Primary elective knee arthroplasty	IPC/ 5' inflation/ 5' reperfusion/ 3 cycle	78 minutes	+ 100 mmHg from patient's systolic blood pressure	Full tourniquet without preconditioning	Spinal	Protective gene expressions, inflammatory response
8.	Memtsoudis et al. (2014)	N=60, ASA I, II & III, Age > 65 years	Primary total knee arthroplasty	IPC/ 5' inflation/ 5' reperfusion/ no cycle	51 minutes	250 mmHg	Full tourniquet without preconditioning	Spinal and epidural and propofol	Postoperative pain, inflammatory response, systemic coagulation, length of hospital stay, healing speed
9.	Lin et al. (2010)	N=30, ASA I & II, Mean age 42.5 years	Unilateral lower extremity surgery	IPC/ 5' inflation/ 5' reperfusion/ 3 cycle	75.5 minutes	480 mmHg	Full tourniquet without preconditioning	Spinal and epidural	Oxidative stress, lung injury, inflammatory response
10.	Sullivan et al. (2009)	N= 25, ASA I, Age >25	ACL repair	IPC/ 5' inflation/ 5' reperfusion/ 3 cycle	64 minutes	350 mmHg	Full tourniquet without preconditioning	General anesthesia with propofol, remifentanil, & sevoflurane	Changes in lymphocyte population and function
11.	Van et al. (2008)	N=20, ASA I & II, Mean age 41.5 years	Elective knee surgery	IPC/ 5' inflation/ 5' reperfusion/ 3 cycle	80 minutes	300 mmHg	Full tourniquet without preconditioning	Spinal and epidural	Hemodynamic, respiratory, and metabolic stability
12.	Orban et al. (2006)	N=31, ASA I, Mean age 30 years	Knee ligamentoplasty	IPC/ 5' inflation/ 10' reperfusion/ no cycle	86.3 minutes	350 mmHg	Full tourniquet without preconditioning	Spinal and fentanyl	Postoperative pain, muscle strength, muscle damage

IC: Ischaemic Conditioning; IPC: Ischaemic Preconditioning; RIPC: Remote Ischaemic Preconditioning; IPostC: Ischaemic Postconditioning; BFR: intermitten blood flow restriction similar to IPC protocol combined with low load resistance exercise some periods before surgery (Žargi et al., 2018); ASA: American Society of Anesthesiologist Physical Score.

d. Lung Damage

Figure 10 showed that IC did not affect the increase of PaO2 related to IR injury (SMD= 0.15; 95% CI= -0.14 to 0.71, p= 0.601). No evidence of heterogeneity was present (I^2= 0%).

e. Publication Bias

The funnel plot method was not be done due to a lack of homogeneity between studies on this review (Borenstein, 2009).

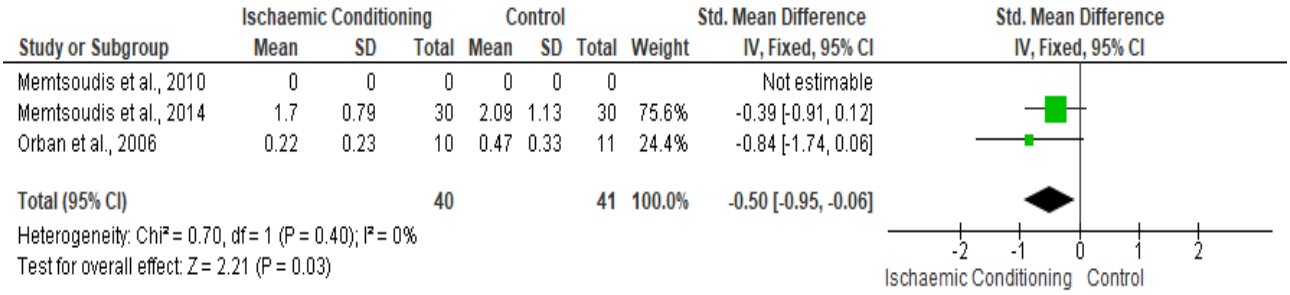


Figure 4. Forest Plot of Comparison: Postoperative Pain

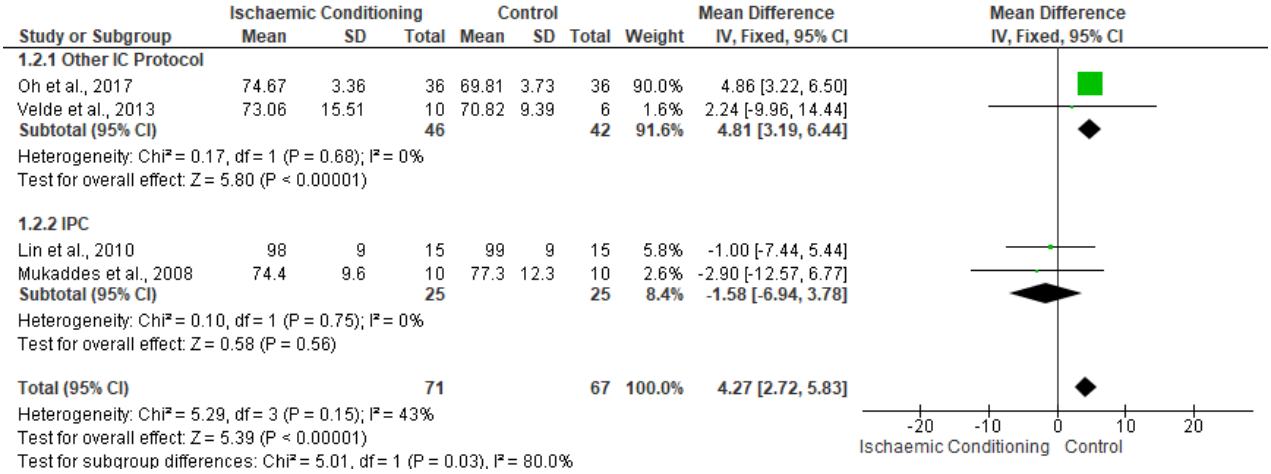


Figure 5. Forest Plot of Comparison: Mean Arterial Pressure

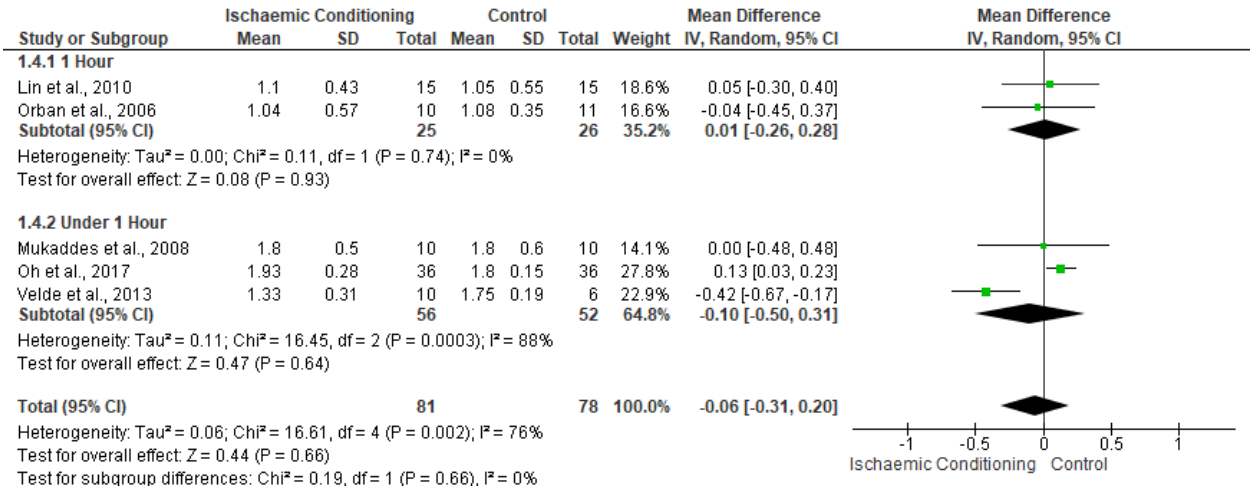


Figure 6. Forest Plot of Comparison: Serum Lactate Level

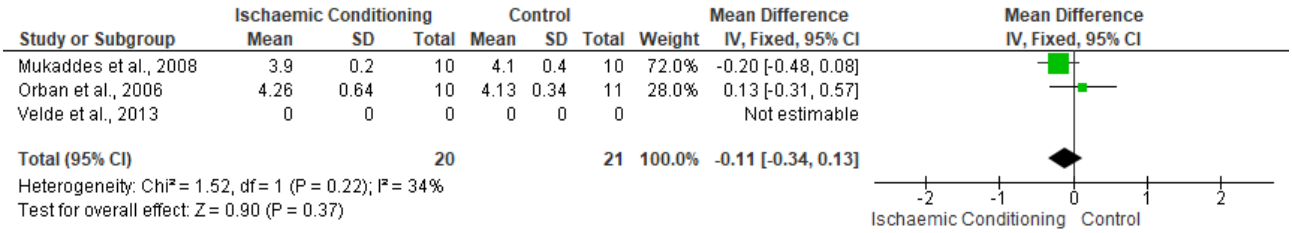
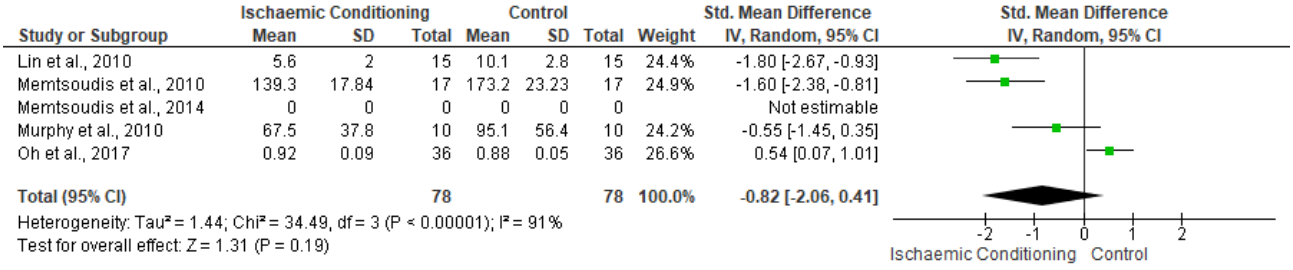
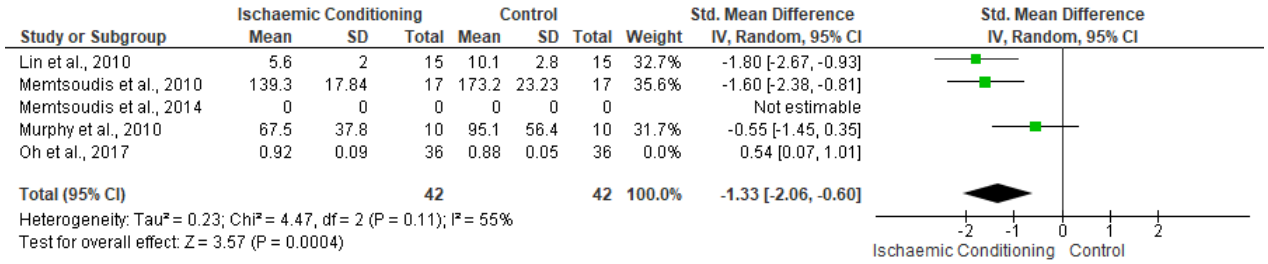


Figure 7. Forest Plot of Comparison: Serum Potassium Level





Figures 8 and 9. Forest Plot of Comparison: Serum Interleukin- 6, Before And After Exclusion of Skewed Data

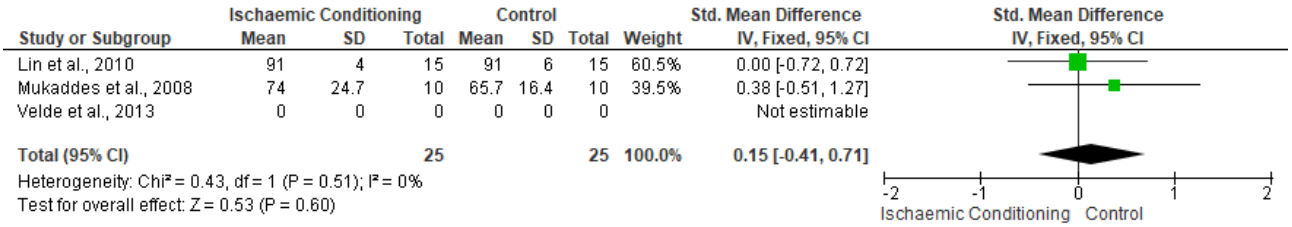


Figure 10. Forest Plot of Comparison Outcome: Partial Pressure Of oxygen (PaO2)

DISCUSSION

IC significantly reduced postoperative pain related to tourniquet usage in orthopedic surgery due to IR injury. Moreover, IC significantly reduced the risk of acute hypotension, providing hemodynamic stability. However, this effect was limited to study using RIPC and IPostC protocol. The IC has significantly reduced the increase of IL-6, albeit substantial heterogeneity was present. There was no significant difference in IC effect on metabolic stability or end-organ injury.

To our knowledge, this is the first meta-analysis describing the effect of IC on tourniquet-related IR injury in orthopedic surgery. Our study results differed from the previous study (Sukkar et al., 2016), which performed a meta-analysis of IC effect on clinical outcomes of 11,619 participants

undergoing invasive procedures. It found that IC doesn't affect all-cause of mortality. However, the study didn't include the population from orthopedic surgery. It also showed the need for further RCT research of IC in the orthopedic field, focusing on clinical outcomes with a bigger population.

In our meta-analysis, on average, the IC could attenuate IL-6 in IR injury. However, this result should be interpreted with caution because the true differences in effects between studies might be due to uncharacterized or unexplained underlying factors. There were possibilities that the average effect could be different on the individual study level. The prediction interval was used to calculate this problem. But the calculation wasn't be done as some studies included weren't at low risk of bias (Riley et al., n.d.).

Some concepts could be postulated to explain why the IC didn't significantly affect this review. The study population with coronary or peripheral artery disease could be subject to chronic ischemia and reperfusion (i.e., claudication and angina), which repeatedly generates signals of IC. It was plausible to assume the threshold of the protective signaling pathway had been achieved. Thus, IC didn't give additional protection (Ouyang et al., 2020). Anesthesia techniques like spinal anesthesia could interfere with the neural pathway mechanism of RIPC.

Some anesthesia agents were also proven to have an antioxidative effect that might hinder or conceal the effect of IC (Leurcharusmee et al., 2018). Lastly, the lack of effective IC duration and protocol (Gurusamy et al., 2008). It should be a consideration for designing a better study in the future.

There were some limitations to this meta-analysis. First, some studies couldn't be analyzed due to incomplete reporting. This problem, followed by a small study population on this review, was prone to random error. Smaller studies are subject to greater sampling variation and hence are less precise (Higgins and Cochrane Collaboration, 2020). Second, most of the surrogate endpoints in the included study were reported using multiple time points. Considering, it comes from the same population, there was a correlation between data. A typical approach for meta-analysis would ignore the correlation between the time-specific effect sizes. Understanding the pattern of each treatment arm and measuring the pooled effect between arms could bring new insight into the effect of IC on IR injury (Trikalinos and Olkin, 2012).

In conclusion, this systematic review and meta-analysis demonstrated that ischemia conditioning significantly reduces postoperative pain, inflammation response and maintains hemodynamic stability in ischemia-reperfusion injury conditioned orthopedic surgery. This study shows some promising effects to lower the risk of comorbidity of the patient in orthopedic surgery while maintaining simplicity and cost-effectiveness. Further research was needed and should be focused on the bigger population and clinical outcomes.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. PU reviewed the manuscript. PU and BY were responsible for screening the literature, abstracted data and did statistical analysis. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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REFERENCE

Borenstein M (2009). Introduction to meta-analysis. John Wiley & Sons, Chichester. U.K.

Gurusamy KS, Kumar Y, Sharma D, Davidson BR (2008). Ischaemic preconditioning for liver transplantation. Cochrane Database Syst Rev. 1: CD-006315. https://doi.org/10.1002/146-51858.

Halladin NL, Zahle FV, Rosenberg J, Gogenur I (2014). Interventions to reduce tourniquet related ischaemic damage in orthopaedic surgery: a qualitative systematic review of randomised trials. Anaesthesia. 69: 1033–1050. https://doi.org/10.1111/anae.12664.

Hausenloy DJ, Yellon DM (2016). Ischaemic conditioning and reperfusion injury. Nat Rev Cardiol. 13(4): 193–209. https://doi.org/10.1038/nrcardio.2016.5.

Higgins JPT (2020). Cochrane Collaboration (Eds.). Cochrane handbook for systematic reviews of interventions, Second edition. ed, Cochrane book series. Wiley-Blackwell, Hoboken, NJ.

Koca K, Yurttas Y, Cayci T, Bilgic S, Kaldirim U, Durusu M, Cekli Y, et al. (2011). The role of preconditioning and n-acetylcysteine on oxidative stress resulting from tourniquet-induced ischemia-reperfusion in arthroscopic knee surgery. J Trauma Inj Infect Crit Care 70(3): 717–723. https://doi.org/10.1097/TA.0b013e3181f30fb0

Leurcharusmee P, Sawaddiruk P, Punjasawadwong Y, Chattipakorn N, Chattipakorn SC (2018). The possible pathophysiological outcomes and mechanisms of tourniquet-induced ischemia-reperfusion injury during total knee arthroplasty. Oxid Med Cell Longev. 2018: 8087598. https://doi.org/10.1155/2018/8087598.

Lin L, Wang L, Wang W, Jin Lie-lie, Zhao X, Zheng L, Jin Li-da, et al. (2010). Ischemic preconditioning attenuates pulmonary dysfunction after unilateral thigh tourniquet–induced ischemia–reperfusion. Anest Analg. 111(2): 539–543. https://doi.org/10.1213/ane.0b013e3181e368d2.

Memtsoudis SG, Stundner O, Yoo D, Gonzalez DVA, Boettner F, Bombardieri AM, Jules-Elysee K, et al. (2014). Does limb preconditioning reduce pain after total knee arthroplasty? a randomized, double-blind study. Clin Orthop Relat Res. 472(5): 1467–1474. https://doi.org/10.1007/s11999-013-3106-4.

Memtsoudis SG, Valle AGD, Jules-Elysse K, Poultsides L, Reid S, Starcher B, Ma Y, et al. (2010). Perioperative inflammatory response in total knee arthroplasty patients. Reg Anesth. Pain Med. 35(5): 412-6. https://doi.org/10.1097/aap.0b013e3181e82e8e.

Moher D, Liberati A, Tetzlaff J, Altman DG (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. PLoS Med. 6(7): e1000097. https://doi.org/10.1371/journal. pmed.1000097.

Murphy T, Walsh PM, Doran PP, Mulhall KJ (2010). Transcriptional responses in the adaptation to ischaemia-reper-

fusion injury: a study of the effect of ischaemic preconditioning in total knee arthroplasty patients. J Transl Med. 8: 46. https://doi.org/10.1186-/1479-5876-8-46.

Oh CS, Kim SH, Lee J, Rhee KY (2017). Impact of remote ischaemic preconditioning on cerebral oxygenation during total knee arthroplasty. Int J Med Sci. 14(2): 115–122. https://doi.-org-/10.7150/ijms.17227.

Orban JC, Levraut J, Gindre S, Deroche D, Schlatterer B, Ichai C, Grimaud D (2006). Effects of acetylcysteine and ischaemic preconditioning on muscular function and postoperative pain after orthopaedic surgery using a pneumatic tourniquet. Eur J Anaesthesiol. 23, 1025–1030. https://doi.-org/10.1017/S026502150600086X.

Ouyang H, Zhou M, Xu J (2020). Effect of remote ischemic preconditioning on patients undergoing elective major vascular surgery: a systematic review and meta-analysis. Ann Vasc Surg. 62: 452–462. https://doi.org/10.1016/j.-avsg.2019.05.035.

Pilcher JM, Young P, Weatherall M (2012). A systematic review and meta-analysis of the cardioprotective effects of remote ischaemic preconditioning in open cardiac surgery. J R Soc Med 105(10): 436–445. https://doi.org/-10.1258/jrsm.2012.120049.

Riley RD, Higgins JP, Deeks JJ (2011). Research Methods and Reporting. BMJ. 342: d549. doi: 10.1136/bmj.-d549

Sukkar L, Hong D, Geot Wong M (2016). Effects of ischaemic conditioning on major clinical outcomes in people undergoing invasive procedures: systematic review and meta-analysis. BMJ. 355. https://doi.org/10.1136/-bmj.i5599.

Sullivan PJ, Sweeney KJ, Hirpara KM, Malone CB, Curtin W, Kerin MJ (2009). Cyclical ischaemic preconditioning modulates the adaptive immune response in human limb ischaemia-reperfusion injury. Br J Surg. 96(4): 381-90. https://doi.org/-10.1002/bjs.6554.

Trikalinos TA, Olkin I (2012). Meta-analysis of effect sizes reported at multiple time points: A multivariate approach. Clin Trials. 9(5): 610–620. https://-doi.org/10.1177/17407745124532-18.

van der Velde J, Serfontein L, Iohom G (2013). Reducing the potential for tourniquet-associated reperfusion injury: Eur. J. Emerg. Med. 20, 391–396. https://doi.org/10.1097¬/MEJ.-0b013e3283591668

Van M, Olguner Ç, Koca U, Şişman AR, Muratli K, Karci A, Mavioğlu Ö, et al. (2008). Ischaemic preconditioning attenuates haemodynamic response and lipid peroxidation in lower-extremity surgery with unilateral pneumatic tourniquet application: A clinical pilot study. Adv Ther. 25, 355–366. https://doi.org/10.1007/s1-2325-008-0037-7.

Wakai AC, Winter DT, Street J, Redmond PH (2001). Pneumatic tourniquets in extremity surgery. Am Acad Orthop Surg. 9(5): 345–351. https://doi.org/-10.5435/00124635-200109000-000-08.

Žargi T, Drobnic M, Koder J (2016). The effects of preconditioning with ischemic exercise on quadriceps femoris muscle atrophy following anterior cruciate ligament reconstruction a quasi-randomized controlled trial. Eur J Phys Rehabil Med. 52(3): 310–320.

Žargi T, Drobnič M, Stražar K, Kacin A (2018). Short–term preconditioning

with blood flow restricted exercise preserves quadriceps muscle endurance in patients after anterior cruciate ligament reconstruction. Front. Physiol. 9: 1150. https://doi.org/10.-3389/fphys.-2018.01150.

Zhou TR, Prather EE, Garrison D, Zuo L (2018). Interplay between ROS and antioxidants during ischemia-reperfusion injuries in cardiac and skeletal muscle. Int J Mol Sci. 19(2): 1–20. https://doi.org/10.3390/ijms1902041 7.