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**Meta-Analysis**

# Is there a role for ischaemic pre-conditioning in orthopaedic and trauma surgery? A systematic review and meta-analysis of randomised controlled trials

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## ABSTRACT

Surgical procedures using a tourniquet submit tissues to ischaemia and reperfusion on restoring blood flow. Ischaemia-reperfusion may lead to local or remote tissue damage resulting in pain and complications. We aimed to evaluate the effectiveness of ischaemic preconditioning with a tourniquet in preventing pain, disability, adverse events, inflammation and facilitating recovery and discharge in patients receiving orthopaedic and trauma surgery. We conducted a systematic review of randomised controlled trials investigating ischaemic preconditioning in patients undergoing trauma and orthopaedic surgery. We searched The Cochrane Library, Medline and Embase until January 2021. Where possible continuous data were pooled and meta-analysis performed. Ten RCTs met inclusion criteria, eight of which underwent meta-analysis. Three studies reported lower acute post-operative pain or morphine consumption in patients randomised to IPC. We found weak evidence for shorter length of stay in the intervention group (MD-0.54 days; 95%CI-1.11, 0.03; p=0.0615). Malondialdehyde levels were lower in patients randomised to IPC at two hours following tourniquet deflation (MD -1.39 nmol/ml; 95%CI-2.23, -0.55; p=0.0012). We found no between group differences in Tumour Necrosis Factor-α, Lactate or Interleukin-6. The mechanism behind IPC may be related to reduced lipid peroxidation rather than reduced inflammation. There is evidence IPC reduces post-operative pain following knee surgery that merits further study.

**Keywords:** Ischaemic, Preconditioning, RCT, Reperfusion, Tourniquet, Surgery

## INTRODUCTION

In the United Kingdom, about 25% of all surgical interventions are for the treatment of orthopaedic conditions and trauma, in total about 1.2 million procedures annually in 2013-14.[1] The commonest elective procedures are: arthroscopic anterior cruciate ligament reconstruction, arthroscopic meniscal repair of the knee, arthroscopic partial meniscectomy of the knee, arthroscopic rotator cuff repair, arthroscopic subacromial decompression, carpal tunnel decompression, lumbar spinal decompression, lumbar spine fusion, total hip replacement and total knee replacement.[2] The trauma types with most hospital admissions and consultant episodes vary with patient age. Overall, hip, ankle and distal radius fractures are associated with the greatest surgical burden on the NHS in England.[3] Both acute and chronic pain are common after elective orthopaedic and trauma surgery.[4,5] In an Australian cohort of people with orthopaedic trauma surgery recruited in 2017-2018, 56% of patients reported severe acute post-surgical pain and in 65%, persistent pain was reported at three months after

surgery.[4] In 1998, a UK study found that surgery was the cause of chronic pain in 22.5% of patients attending pain clinics.[6] Approximately 10% of patients following hip replacement and 20% following knee replacement report moderate to severe pain in the long-term.[7] A direct link between acute post-surgical pain and chronic post-surgical pain has been described after diverse surgeries.[8] In some elective orthopaedic conditions, this association is less clear, probably due to the confounding associations with pre-operative pain, different associations with pain at rest and on movement and the extensive use of peri- and post-operative analgesia targeting problematic post-operative pain.[4,9-12] An operation itself is an important risk factor for chronic pain and factors relating to the operation and recovery may indicate possible interventions.[13,14] An example of a widely used technique in orthopaedic surgery that might impact on acute and chronic pain is the use of a tourniquet. A tourniquet is frequently used to provide a bloodless field during orthopaedic surgery.[15]

### *Ischaemia and ischaemia-reperfusion*

Tourniquet use may cause tissue injury locally through direct compression on underlying tissue and distally through molecular reactions to ischaemia. Tourniquet deflation restores tissue perfusion and interrupts ischaemic injury pathways but may lead to further injury to both the ischaemic tissue and remote organs via ischaemia-reperfusion phenomenon (Figure 1).[16,17]

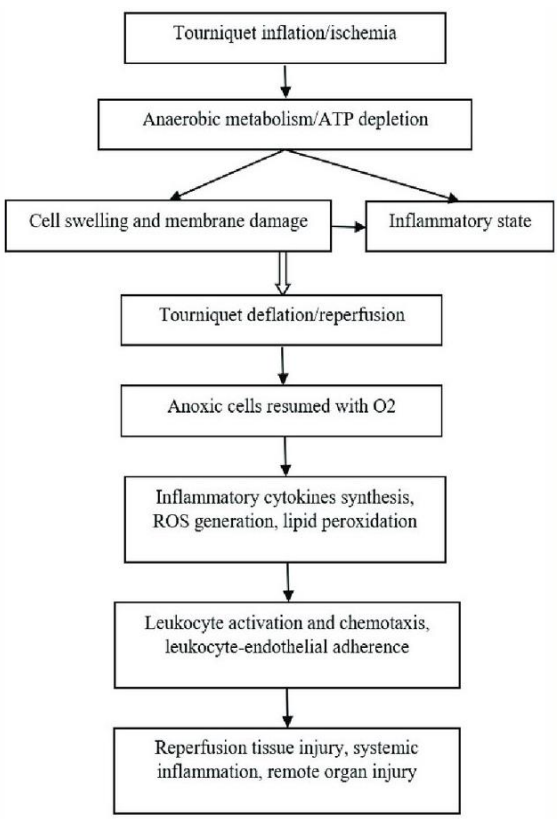


**Figure 1: Flow diagram of tourniquet associated ischaemia-reperfusion injury.**

Ischaemia-reperfusion mechanisms have been intensively studied, highlighting complex pathophysiological mechanisms and attenuating interventions. Ischaemia results in intracellular ATP depletion, ion disturbance, acidosis, cytosolic calcium accumulation, and eventually cellular damage.[18] Production of reactive oxygen species is stimulated and a proinflammatory state is promoted. These effects result in increased cellular vulnerability to subsequent reperfusion. Reoxygenation results in endothelial cell dysfunction, neutrophil recruitment, pro-inflammatory mediator release (tumour necrosis factor alpha and inteurleukin-1 beta), excessive oxidative stress (disproportionate reactive oxygen species production to antioxidant capacity), and cellular injury though oxidation of lipids, proteins and DNA.[16,18-20] Malondialdehyde is a product of lipid peroxidation, a process initiated by reactive oxygen species.[21] Malondialdehyde is a useful marker of ischaemia-reperfusion injury.[22]

### *Ischaemic pre-conditioning*

Ischaemic pre-conditioning (IPC) is a procedure involving a brief period of controlled ischaemia which stimulates a systemic adaptive protection from ischaemia-reperfusion injury following a subsequent prolonged ischaemic stress.[23] The protective effect may occur in tissue not exposed to the transient mild ischaemia, termed remote ischaemic preconditioning (RIPC). The mechanism through which IPC confers its protective effects is poorly understood, with no single established pathway. A neurogenic mechanism through the autonomic nervous system is thought to be implicated.[24] Ischaemia-reperfusion protection detected in animal models following transfer of serum from an IPC exposed donor to an IPC naïve recipient suggests a humoral mechanism, probably a combination of neurogenic, humoral and systemic components generate IPC related protection.[25,26]

### *IPC/RIPC in the orthopaedic setting*

The impact of ischaemia-reperfusion is both local and remote. Irreversible injury to local tissue may result in postoperative pain, neurological dysfunction and functional deficit necessitating prolonged inpatient stay and rehabilitation. Systemic responses associated with ischaemia-reperfusion injury can result in remote organ injury. End organ failure and death has been associated following massive ischaemic insults associated with major trauma, sepsis and myocardial infarction, but rarely observed following tourniquet-induced ischaemia-reperfusion. The benefits of IPC are therefore likely to be related to the local manifestations of ischaemia-reperfusion. The effects of IPC in orthopaedics have most commonly been investigated in arthroplasty and arthroscopic surgery to the knee, procedures where tourniquet use remains common practice. One potential model for IPC in orthopaedics is a short regime of intermittent air-tourniquet ischaemia to the operative limb or non-operative limb (RIPC) during induction, positioning and draping prior to prolonged ischaemia

during the procedure. Serum markers of the effects of IPC related protection can be broadly categorised into those related to oxidative stress, lipid peroxidation or inflammation. Previous trials have used a wide variety of outcomes to measure inflammation and ischaemia-reperfusion injury.

### *Aim*

In this systematic review we aim to evaluate the effectiveness of IPC with a tourniquet in preventing pain, disability, adverse events and inflammation, and facilitating recovery and discharge after orthopaedic and trauma surgery.

## METHODS

### *Eligibility criteria*

Eligible studies reflected the below criteria: People receiving an orthopaedic procedure, Ischaemic pre-conditioning intervention, Comparator of untreated, sham or attentional control, Primary outcomes of pain, disability, adverse events, length of hospital stay. Secondary outcomes relating to pathophysiological mechanisms and evaluation in a randomised controlled trial (RCT).

### *Data sources and search strategy*

The review was registered with PROSPERO prospective register of systematic reviews (CRD42021250452) and conducted in line with PRISMA guidelines. The search strategy targeted RCTs comparing IPC intervention with no IPC in trauma and orthopaedic procedures (Table 1).

The search was performed in Medline, Embase and The Cochrane Library and supplemented by manually screening relevant study reference lists and through the 'cited references' Web of Science function on 27 January 2021. Two clinical trial registries (clinicaltrials.gov and ICTRP) were searched for ongoing RCTs on 10 March 2021.

**Table 1: Search strategy as applied in Medline.**

| Sr. no. | Search strategy applied in Medline |
|---|---|
| **1** | (Isch?em* adj2 (precondit* or pre-condit* or "pre condit*").mp. (mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms) |
| **2** | Ischemic Preconditioning.mp. or Ischemic Preconditioning/ |
| **3** | IPC.ti,ab,kw. |
| **4** | Ischaemic preconditioning.tw. |
| **5** | 1 or 2 or 3 or 4 |
| **6** | (Randomized controlled trial or controlled clinical trial). pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab |
| **7** | Exp animals/ not humans.sh. |
| **8** | 6 not 7 |
| **9** | 5 and 8 |
| **10** | Exp Arthroscopy/ or arthroscopic.mp. or exp Anterior Cruciate Ligament Reconstruction/ or ACL reconstruction.mp. or ACLR.mp |
| **11** | (Exp Arthroscopy/ or arthroscopic.mp.) and (meniscus repair or meniscal repair or meniscal surgery).mp. and (exp Knee/ or exp Knee Joint/) |
| **12** | (Exp Meniscectomy/ or menisc*.mp.) and (exp Arthroscopy/ or arthroscopic.mp.) and (exp Knee/ or exp Knee Joint/) |
| **13** | (Exp Arthroscopy/ or arthroscop*.mp.) and exp Rotator Cuff/ |
| **14** | (Arthroscopy/ or arthroscop*.mp. or exp Decompression/ or subacromial.mp.) and (exp Shoulder/ or exp Shoulder Impingement Syndrome/ or subacromial impingement syndrome.mp.) |
| **15** | (Carpal tunnel surgery or carpal tunnel release).mp. or exp Decompression, Surgical/) and exp Carpal Tunnel Syndrome/ |
| **16** | (Exp Decompression, Surgical/ or lumbar decompression.mp. or spinal decompression.mp. or lumbar spinal decompression.mp.) and stenosis.mp. |
| **17** | (Exp Spinal Fusion/ or exp Lumbar Vertebrae/ or lumbar.mp.) and (exp Intervertebral Disc Degeneration/ or degenerative dis*.mp.) |
| **18** | Exp arthroplasty, replacement, hip/ |
| **19** | Exp arthroplasty, replacement, knee/ |
| **20** | Exp knee prosthesis/ |
| **21** | Exp hip prosthesis/ |

Continued.

| Sr. no. | Search strategy applied in Medline |
|---|---|
| **22** | Joint Prosthesis/ |
| **23** | (hip$ or knee$) adj10 (replace$ or arthroplast$ or prosthe$ or implant$).ti,ab. |
| **24** | 18 or 19 or 20 or 21 or 22 or 23 |
| **25** | trauma.mp. or "Wounds and Injuries"/ |
| **26** | fracture.tw. |
| **27** | (trauma* or fracture* or accident*). mp. |
| **28** | 25 or 26 or 27 |
| **29** | 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 24 or 28 |
| **30** | 5 and 29 |
| **31** | 9 and 30 |

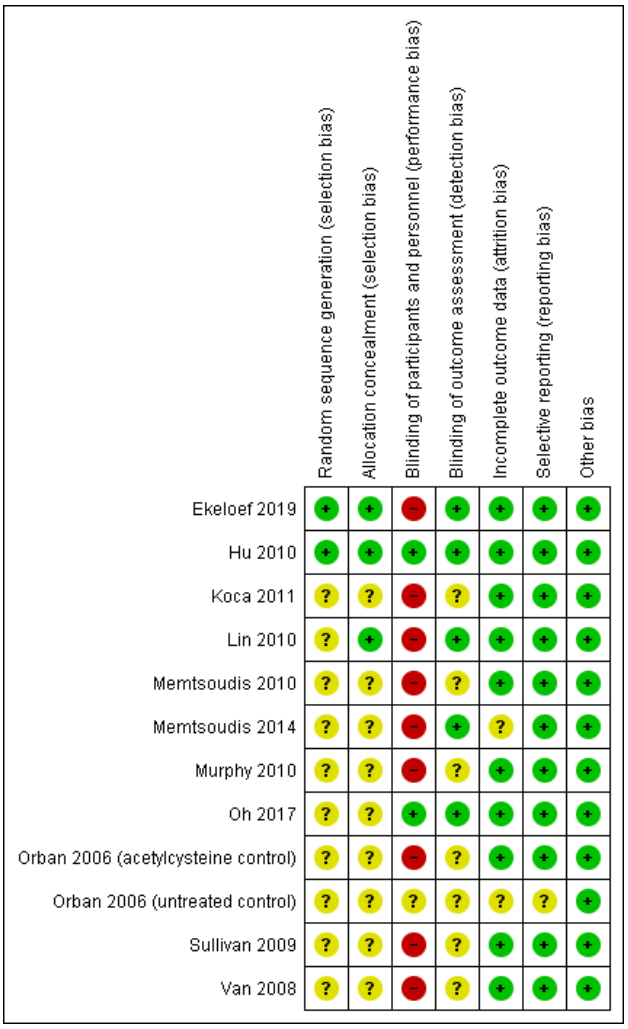


**Figure 2: Cochrane risk of bias table.**

### *Study selection and data extraction*

Identified studies were collated and stored using ENDNOTE X9 software. Articles were screened through review of title and abstract by two authors (SD and ADB). Reports with potential relevance were reviewed during a detailed screening process. Data extraction was performed by two authors separately (SD and ADB) on the final included studies and the data checked and stored in an excel database. Authors were contacted with a request to provide missing data.

### *Risk of bias assessment*

The Cochrane tool was used to assess the risk of bias specifically concerning: the randomisation process; deviations from intended interventions; missing outcome data (>20% considered high risk); outcome measurement and selection of the reported results.[27] RevMan software was used to store the individual author judgements and summarise the assessment (Figure 2).

### *Statistical analysis*

Continuous data was pooled and a meta-analysis was performed using mean and standard deviation with STATA version MP 16.1 (Stata Corp, Texas). Binary data reporting was insufficient for further analysis. Outcomes with multiple time points were analysed separately using a random effects model. Effect measures were presented as mean differences with 95% confidence intervals. Where the mean and standard deviation was not reported, it was calculated using established transformation equations.[28,29] Where separate studies reported the same outcome variable in different units, results were reported as a standardised mean difference, calculated using Hedge's G effect size measure.

## RESULTS

### *Study selection*

We identified 2054 articles and a further 46 articles through checking of study references and citation tracking in web of science leaving 2001 studies after removal of duplicates. The screening process led to exclusion of 1983 irrelevant articles (Figure 3). Eight studies failed to meet inclusion criteria and the remaining 10 RCTs were included in the analysis. Of these, seven studies reported data amenable to meta-analysis and the authors of one study provided sufficient data on request.[30-37] It was not possible to include two studies in the meta-analysis due to a lack of available data in published reports or following author request.[38,39]

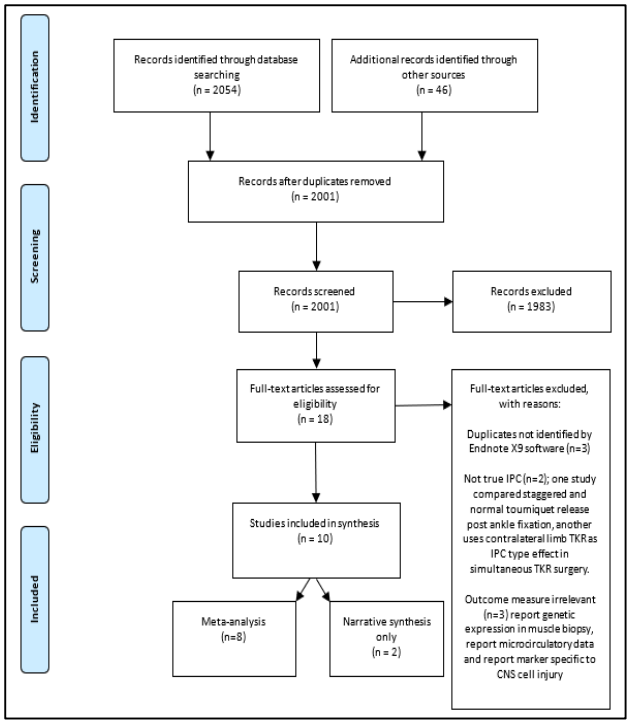


**Figure 3: PRISMA flow diagram of study selection.**

### *Study characteristics*

All were RCTs comparing ischaemic pre-conditioning (IPC) or remote ischaemic pre-conditioning (RIPC) with no IPC or N-acetylcysteine controls (Table 2).[30-41]

### *Risk of bias*

Risk of bias judgements are summarised in (Figure 2). With exception of two studies in which surgeons, anaesthetists and patients were blinded to the randomisation, there were concerns for risk of bias relating to blinding of participants and personnel.[35,42] However, this is not unusual in RCTs in the surgical setting. Otherwise, there were no specific issues that suggested high risk of bias but information in studies was limited, particularly in relation to randomisation and allocation concealment.

### *Pain*

Three RCTs reported a pain outcome, all using visual analogue scale (VAS) scoring. Raw VAS data was only available in one study, and meta-analysis was not possible. In a study including 34 patients receiving a total knee replacement, median pain scores at 6, 12 and 24 hours after surgery in patients receiving IPC were lower compared with untreated controls ($p<0.001$).[33,37] The authors' subsequent study with 60 patients receiving total knee replacement, found significantly lower pain scores at rest ($p=0.043$), and on exercise ($p=0.004$) in the IPC group.[33] This difference compared with controls was greatest at 24 and 48 hrs post-surgery with exercise. In a study of 31 knee ligamentoplasty patients randomised to IPC, acetylcysteine or control, no significant difference in pain scores measured up to 48 hours were noted between groups.[39] The mean morphine consumption over 48 hours was however significantly less ($p<0.05$) in the IPC (0.22, SD 0.23 mg/kg) and acetylcysteine groups (0.22, SD 0.31 mg/kg) compared with the control group (0.47, SD 0.33 mg/kg).[39]

### *Length of stay*

In total, three RCTs reported length of stay.[30,33,37] Additional to studies in people with total knee replacement, RIPC was compared with untreated controls in one study with 573 people receiving hip fracture surgery. Pooled data including 667 participants (Figure 4) showed weak evidence that the treatment group had a shorter length of stay (MD-0.54 days; 95% CI-1.11, 0.03; $p=0.0615$). There was no heterogeneity between studies ($I^2$ 0%).

### *Lactate*

Four RCTs including people with lower extremity surgery, total knee replacement or knee ligamentoplasty reported serum lactate, a marker of tissue hypoxia.[30,32-36,38-40] In three studies with 122 participants included in meta-analysis (Figure 5), IPC did not impact on lactate levels immediately post tourniquet deflation (SMD 0.14; 95%CI-0.21, 0.49; $p=0.4283$). One study not included in the meta-analysis noted that post-operative rate of increase in lactate up to six hours did not differ in groups randomised to IPC, acetylcysteine or untreated control.[39]

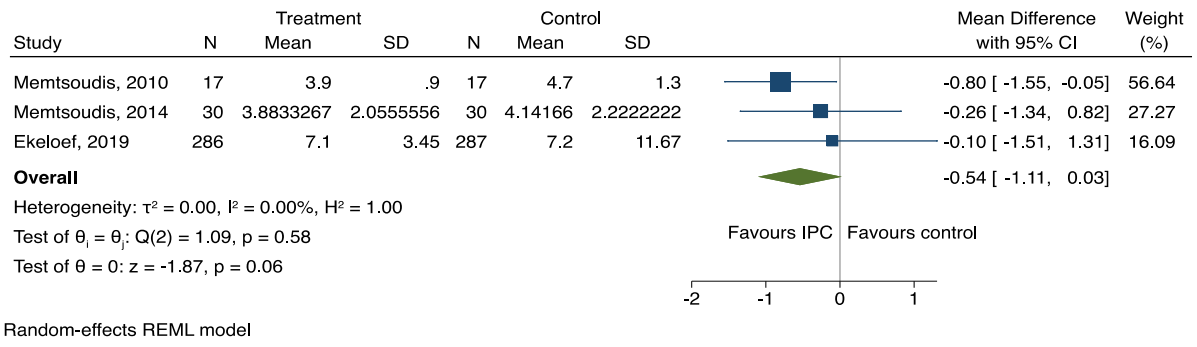


**Figure 4: Length of hospital stay.**

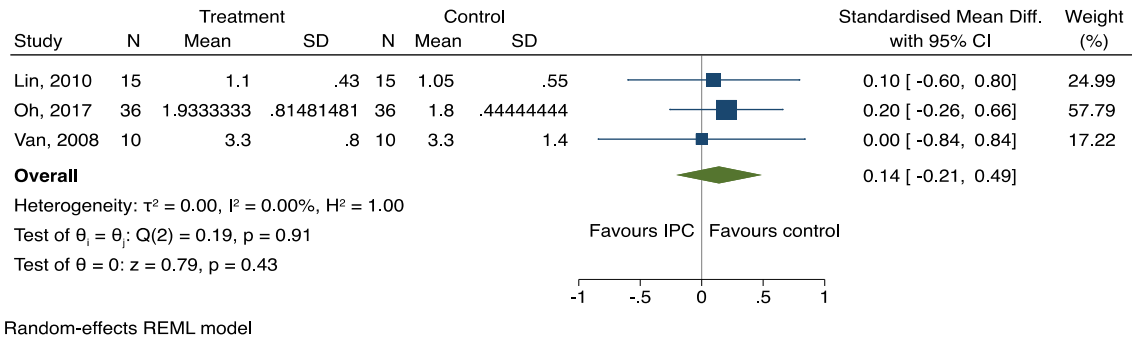


**Figure 5: Lactate immediately after tourniquet deflation.**

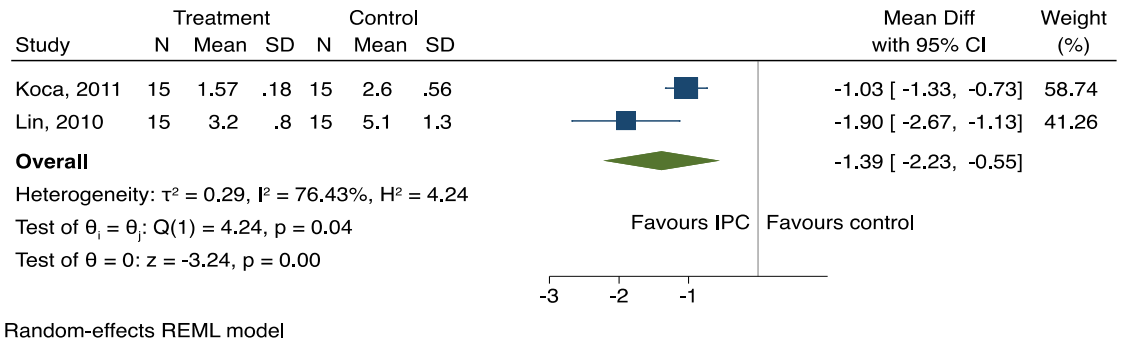


**Figure 6: Malondialdehyde two hours after tourniquet deflation.**

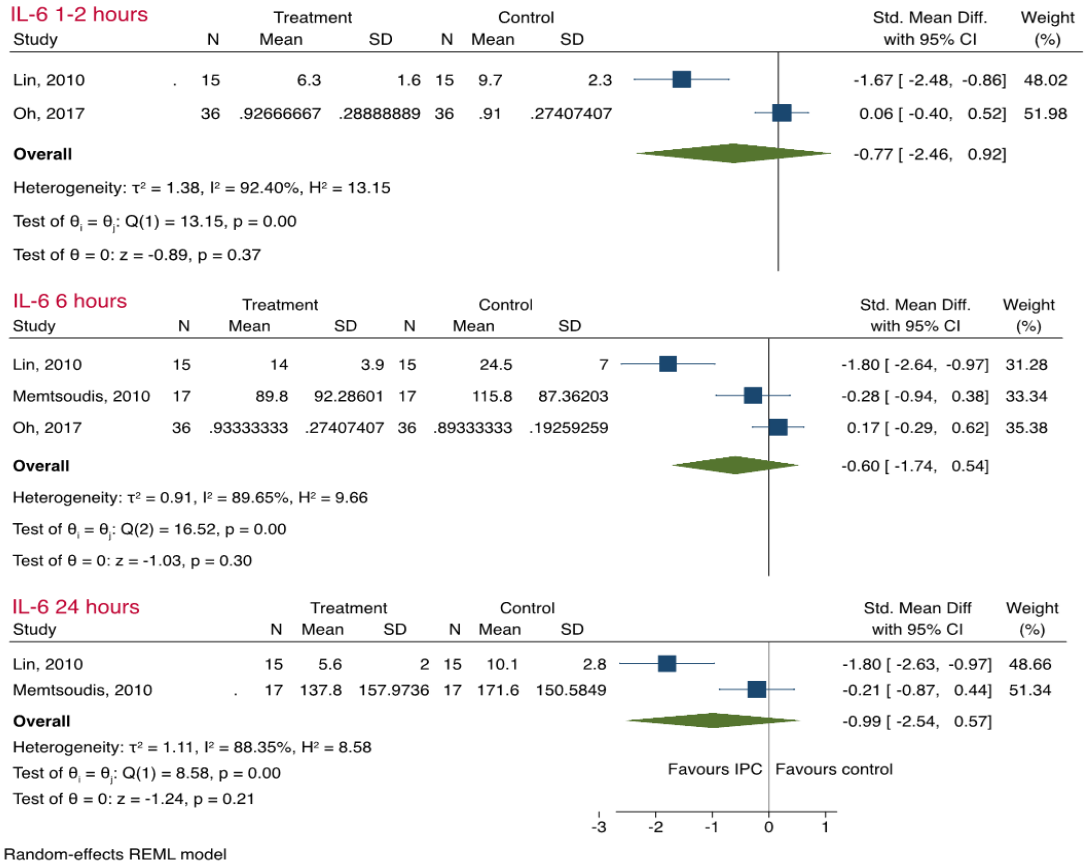


**Figure 7: Interleukin-6 standardised mean differences and confidence intervals over the first 24-hour data time points.**

### *Malondialdehyde*

Two RCTs including 60 people with knee arthroscopy or lower limb surgery reported malondialdehyde levels.[31,32] Meta-analysis shows the malondialdehyde levels were significantly lower at two hours following tourniquet deflation with IPC (MD -1.39 nmol/ml; 95% CI-2.23, -0.55; p=0.0012) (Figure 6). The $I^2$ value of 76.43%, suggested large heterogeneity between studies.

### *Interleukin-6*

Interleukin-6, a marker of acute inflammation, was measured in five RCTs including patients with total knee replacement or lower limb surgery with data available for meta-analysis in three RCTs including 136 participants.[32,33,35,37,43] At each time point (Figure 7), there was no difference in interleukin-6 levels between groups (1-2 hours SMD -0.77; 95% CI -2.46, 0.92; p=0.3717, 6 hours SMD -0.60; 95% CI -0.74, 0.54; p=0.3043 and 24 hours SMD-0.99; 95% CI-2.54, 0.57; p=0.2137). In two RCTs with no data suitable for meta-analysis, authors reported no difference in interleukin-6 between IPC and control groups.[33,34]

### *Tumour necrosis factor alpha (TNF-α)*

TNF-α, a marker of acute inflammation, was reported in two studies including 106 participants and there was no difference between groups randomised to IPC or control after tourniquet deflation (6 hours SMD 0.21; 95% CI -0.17, 0.59; p=0.2736 and 24 hours SMD 0.23; 95% CI -0.14, 0.61; p=0.2281).[35,37]

### *Trial registrations*

Searches of trial registries identified 171 trials registered between 2003 and 2020. No registered trials of IPC included patients receiving orthopaedic or trauma surgery.

## DISCUSSION

RCTs are feasible for the study of IPC in orthopaedic and trauma surgery. Acute post-surgical pain or morphine analgesia consumption was reduced in all three studies that reported an appropriate outcome. No studies reported a long-term pain outcome. While there was a suggestion in meta-analysis that length of stay was shorter for patients receiving IPC, there was no benefit in a study of 573 patients with hip fracture surgery.[30] The focus of most studies related to the mechanisms of IPC. Malondialdehyde levels were significantly lower in the treatment group at two hours after tourniquet deflation. Malondialdehyde is a toxic metabolite of lipid peroxidation, a process considered central to the ischaemia-reperfusion injury pathway. This finding supports IPC has a protective effect, dampening the lipid peroxidation process. It is likely this protective effect lasts longer than two hours. Lin 2010 recorded malondialdehyde levels up to 24 hours post tourniquet deflation, identifying significantly lower values in the IPC group with a peak difference at six hours.[32] In meta-analyses, similarities in levels of TNF-α and IL-6 after surgery provide no clear support for a role of acute inflammation in IPC. Our review has several strengths, it was registered a priori and conducted in line with PRISMA guidelines. Multiple reviewers conducted the search and data extraction ensuring accuracy in the analysis. All included studies were randomised trials minimising confounder and bias influence. This review also has limitations, it is limited by a small number of included studies and few patient outcomes, effectively narrowing the data for each outcome. Data was not available for meta-analysis for some specific outcomes and data time points. In event of missing data, the authors of the relevant studies were contacted, unfortunately not all missing data was retrieved. Blinding patients of this intervention is challenging to achieve. In two studies, an attempt was made to blind clinical personnel and patients to the intervention by concealing the cuff-inflator and cuff. However, most outcomes are biochemical in the first 24 to 48 hours post operatively and blinding would be unlikely to affect these results. Finally, the intervention is not standardized between studies. Differing protocols for IPC exist and may impact the magnitude of the resultant effect. The studies included in this review used IPC protocols ranging from three cycles of 5 minutes ischaemia and 5 minutes reperfusion using a pressure of 480 mmHg to one cycle of 5 minutes ischaemia and 5 minutes reperfusion using a pressure of 200 mmHg.[32,37] Due to low numbers of studies a subanalysis of the IPC protocol was not possible. Aktas et al reported significantly higher serum malondialdehyde, creatine kinase and lactate levels after the first knee replacement during simultaneous bilateral knee replacement procedures.[44] The authors concluded the tourniquet used in the first knee replacement created an IPC type effect for the second procedure, significantly reducing oxidative stress. Further study into the optimum IPC protocol is required. A meta-analysis of RIPC effects in cardiac patients found no difference in length of stay in hospital or the intensive care unit.[45] Length of hospital stay is to some extent dependent on the quality of clinical care. However, structural and process issues relating to the healthcare system and its delivery are the main determinants of length of hospital stay after trauma and emergency surgery.[46,47] Future research: Does IPC reduce long-term pain following TKR? A RCT and Does IPC reduce mortality after hip fracture? A RCT.

## CONCLUSION

Minimising ischaemia-reperfusion injury post orthopaedic and trauma surgery could produce important benefits to patients, particularly in reducing post-operative pain. We found significantly lower serum malondialdehyde following IPC, suggesting that IPC confers a protective effect reducing lipid peroxidation, a key process in ischaemia-reperfusion injury. IPC reduces post-operative pain following knee surgery which concurs with published findings in relation to non-Orthopaedic surgery. This

review found no significant difference in TNF- α, IL-6 or lactate. The benefits and mechanisms related to IPC remain unclear, however the findings demonstrating lower malondialdehyde levels with IPC suggests that the mechanism of action is likely to be protection from ischaemia-reperfusion injury.

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*Ethical approval: Not required*

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