INTRODUCTION:

Ischaemic preconditioning (IPC) is a phenomenon whereby a tissue becomes more tolerant to a period of prolonged ischaemia when it is first subjected to short bursts of ischaemia and reperfusion. It has been most comprehensively studied in cardiothoracic surgery where it has been shown to limit myocardial injury in both animal and human studies. However, its application to orthopaedic surgery remains limited to date.

In this study, we report on a clinical trial of ischaemic preconditioning in total knee arthroplasty patients and show the potential of this technique in an orthopaedic setting. We demonstrate the ability of ischaemic preconditioning to reduce the post-operative systemic inflammatory response in these patients, and also the induction of oxidative stress defence gene expression as part of the preconditioning mechanism.

METHODS:

Ethical approval for this study was granted by the ethics committee of the Mater Misericordiae University Hospital, Dublin, Ireland. Informed consent was obtained from each patient before enrolment in the study. Patients undergoing unilateral primary knee arthroplasty (n = 20) were randomised to control (n=10) and IPC (n=10) groups. Patients who had an ankle/brachial index of less than 1 were excluded as were diabetic patients.

The IPC protocol consisted of three five-minute periods of tourniquet insufflation on the upper thigh of operative limb, interrupted by five minute periods of reperfusion. Following this, the tourniquet was again insufflated and the operation started. The control group simply had tourniquet insufflation as normal prior to the start of surgery.

Peripheral blood was collected from patients pre-operatively and at 15 min, 4, 24 and 48 h post-operatively. Samples were analyzed for cytokine expression (TNF-α, IL-6, IL-10, IL-8) using a commercially available ELISA kit (Meso Scale Discovery, USA).

A muscle biopsy was taken from the quadriceps muscle of the operative leg at the immediate onset of surgery, and again, at one hour into the surgery. Total RNA was extracted from these muscle biopsies, and the gene expression patterns of several oxidative stress defence genes were determined by real time PCR.

Clinical evaluation was performed using WOMAC, SF36 and knee society scoring systems. Time to discharge and any adverse events were also recorded.

Statistical analyses were performed with MiniTab15 using the one-way analysis of variance (ANOVA) and the paired t-test.

RESULTS:

Following reperfusion, serum TNF-α, IL-6 and IL-10 concentrations increased significantly compared with baseline levels in both control and preconditioned patients (*p<0.05). However, twenty four hours after surgery the levels of each of these cytokines were found to be reduced in preconditioned patients, as compared to control patients.

In addition, gene expression analysis revealed an up-regulation in the expression of a number of important oxidative stress defence genes in muscle biopsies taken from the operative knee of preconditioned patients following one hour of ischaemia including catalase, glutathione-S-transferase and sequestosome 1 (p < 0.05).

There was no significant difference between the two groups in terms of functional knee score, time to discharge or adverse events.

DISCUSSION:

The release of pro-inflammatory mediators such as cytokines and reactive oxygen species is a key element of the post-operative inflammatory response. The modulation of these systemic effects has the potential to limit reperfusion injury, which may in turn, lead to improvements in patient outcome following surgery.

As part of this study, we investigated the effect of IPC on the systemic inflammatory response to ischaemia-reperfusion in total knee arthroplasty patients. It was found that patients who received preconditioning prior to surgery had reduced serum levels of a number of key inflammatory markers (TNF-α, IL-6) 24 hours after surgery. Levels of the anti-inflammatory cytokine, IL-10, were also reduced. These findings indicate that IPC can indeed suppress the post-operative inflammatory response in these patients and that the requirement for an anti-inflammatory stimulus (IL-10) is lessened in these patients.

Muscle biopsies taken from preconditioned patients also showed increased expression of several important anti-oxidant genes following one hour of ischaemia, including catalase and glutathione S-transferase theta 1. These findings indicate that the induction of an oxidative stress response may be an important factor in the protection provided by ischaemic preconditioning.

SIGNIFICANCE:

The application of this simple, non-invasive intervention prior to surgery may lead to clinically relevant outcomes. A reduction in the release of pro-inflammatory mediators such as cytokines and reactive oxygen species may limit reperfusion injury, which in turn, has the potential to limit post-operative swelling, wound problems, venous thrombosis and pain.