Original Article

Effects of acetylcysteine and ischaemic preconditioning on muscular function and postoperative pain after orthopaedic surgery using a pneumatic tourniquet

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Summary

Background and objective: The use of a pneumatic tourniquet can induce muscular and neurological complications in the operated limb. The genesis of these injuries could involve an ischaemia/reperfusion phenomenon and a compression under the cuff. We evaluated effects of an antioxidant, acetylcysteine and ischaemic preconditioning on the rhabdomyolysis and postoperative pain following a knee ligamentoplasty using a pneumatic tourniquet. Methods: We included 31 patients scheduled for a knee ligamentoplasty randomly assigned in three groups (control, acetylcysteine 1200 mg the day before and 600 mg at the operative day, ischaemic preconditioning). Results: There was a moderate rise in myoglobin and creatinine phosphokinase with no significant difference between the three groups. The muscular functional parameters were similar in all the groups. However, the morphine consumption within the first 48 h was smaller in the treatment groups (0.22 ± 0.31 mg kg⁻¹ and 0.22 ± 0.23 mg kg⁻¹ in the preconditioning and antioxidant groups, respectively) than in the control group (0.47 ± 0.33 mg kg⁻¹, \( P < 0.05 \)). Conclusions: Acetylcysteine and ischaemic preconditioning do not decrease the extent of rhabdomyolysis related to the use of a pneumatic tourniquet and do not improve the postoperative muscle recovery. On the other hand, they allow a significant reduction in the postoperative morphine consumption.

Keywords: TOURNIQUET; ACETYLCYSTEINE; REPERFUSION INJURY; ORTHOPAEDICS; PAIN, postoperative.

Introduction

The pneumatic tourniquet is frequently used to get a bloodless field during limb surgery. Its use has however been associated with some complications such as muscular weakness, rhabdomyolysis, paraesthesia or paralysis [1,2]. Two hypotheses could explain the injuries related to pneumatic tourniquet. The mechanical hypothesis assumes that the tissue insult is due to direct compression of the muscles and nerves located just beneath the cuff [3]. In this case, tissue damage comes from ischaemia and mechanical deformation. Therefore, it is possible to reduce these injuries by decreasing the inflation pressure of the tourniquet. The second hypothesis implies an ischaemia/reperfusion phenomenon that is involved in many other types of surgery such as abdominal aneurism resection, reimplantation of extremities or transplantation [4–6]. Many experimental studies demonstrated that cell death after ischaemia/reperfusion occurs by different ways [7–10]: sodium overloading, activation of membrane phospholipases, opening of the mitochondrial permeability transition pore and generation of reactive oxygen species (ROS). Several means have been proposed to reduce the ischaemia/reperfusion injury: antioxidants, inhibitors of the Na/H exchanger, ciclosporin or ischaemic preconditioning [11,12]. However only a few clinical studies, involving mainly antioxidants and ischaemic preconditioning, showed some beneficial effects of drugs or methods...
against ischaemia/reperfusion injury. In addition, ischaemia/reperfusion induces an inflammation that could be involved in the postoperative pain [13]. To date, no clinical study was interested in reducing the clinical ischaemia/reperfusion injury related to the use of a pneumatic tourniquet. We decided to evaluate the effects of the antioxidant acetylcysteine and of ischaemic preconditioning on the muscular function and postoperative pain after orthopaedic surgery using a pneumatic tourniquet.

Methods

This was a controlled, randomized, single-blind study approved by our local Ethics Committee. Informed consent was obtained from each patient participating in the study. We included 31 ASA physical status I patients scheduled for an elective knee ligamentoplasty with use of a pneumatic tourniquet. No patients were receiving vitamin supplement or antioxidant medication.

Anaesthesia

All the patients were premedicated with 5 mg of midazolam (Hypnovel®, Roche, Neuilly-sur-Seine, France) 60 min prior to entering the operating room. A peripheral venous access was inserted in a forearm vein with a 18-G cannula. Then, an infusion of 500 mL of hydroxyethyl starch (Voluven®, Fresenius Kabi France, Sèvres, France) was begun followed by an infusion of Ringer–Lactate solution (Braun Medical, Boulogne, France) during the surgery. Throughout the anaesthesia, 5-lead continuous electrocardiogram, non-invasive blood pressure and pulse oximetry were monitored. The anaesthesia protocol was a spinal injection of 15 mg of hyperbaric bupivacaine (Aguettant, Lyon, France) and 50 µg of fentanyl (Renaudin, Itxassou, France) in the L4–L5 interspace. When anaesthesia of the legs was obtained, a pneumatic tourniquet (ATS™ 500, Aspen Medical, Boulogne, France) was placed on the thigh of the operated limb. Then the leg was lifted 5 min and deflated 10 min before inflation of the tourniquet. No patients were receiving vitamin supplement or antioxidant medication.

Protocol

The patients were divided randomly in three groups: control, acetylcysteine and ischaemic preconditioning. The patients were blinded to the allocated treatment according to this procedure: all the patients were given fruit flavoured water the day before and 1 h before the surgery which served as a placebo in the control and preconditioning groups. In the acetylcysteine group, the patients were given orally 1200 mg of acetylcysteine (Upsa, Paris, France) the day before and 600 mg 1 h before the surgery both diluted in the flavoured water. In the ischaemic preconditioning group, the pneumatic tourniquet was inflated 5 min and deflated 10 min before inflation for the surgery. The patients were also blinded to this treatment because of the surgical drapes.

Measurements

Blood samples were obtained from venous function of the arm before tourniquet inflating (T0) and at 1 (T1) and 6 (T6) h after tourniquet deflating. We measured myoglobin (Access®2, Beckman Coulter, Fullerton, CA), creatinine phosphokinase (CPK), potassium, phosphorus and lactate (Modular®, Roche Diagnostics, Meylan, France).

We evaluated the muscular strength of the quadriceps muscle of the operated limb with the American Spine Injury Association (ASIA) motor score on the second postoperative day [14]. The ASIA motor score is a six points scale ranging from 0 (total paralysis) to 5 (normal, active movement with full range of movement against full resistance).

The overall morphine consumption was counted up after 48 h use of the PCA. The VAS was measured every 4 h in the surgical ward. The side-effects related to acetylcysteine such as nausea and vomiting were collected on day 2 after the surgery.

Statistical analysis

We calculated that the sample size necessary to observe a difference in CPK change of 50% with an alpha risk of 5% and a power of 80% was 10 for each group. The statistical analysis was carried out with the data-processing software Statview 5.0 (SAS Institute Inc, Cary, NC). The results are presented as mean ± SD. The comparison of several means was
carried out using an analysis of variance (ANOVA) test for repeated measurements or factorial analysis as appropriate. *Post hoc* analyses were performed with Scheffé tests. The proportions were compared by a χ²-test. *P* value <0.05 was considered as statistically significant.

**Results**

We included 31 patients randomly assigned to three groups (control 11 patients, acetylcysteine 10 patients and ischaemic preconditioning 10 patients). The patient characteristics data of the population are described in Table 1. There was no significant difference between the three groups regarding age, weight, height and duration of tourniquet application. There were no differences between the three groups for occurrence of nausea and vomiting.

**Effects of acetylcysteine and ischaemic preconditioning on biological muscular injury**

There was a significant increase in myoglobin (*P* < 0.0001) and CPK (*P* < 0.0001) at all the times after tourniquet deflation in the three groups (Fig. 1). Potassium (*P* < 0.005), phosphorus (*P* < 0.005) and lactate (*P* < 0.01) also changed significantly (Figs 2 and 3). Potassium increased at T1 and returned to baseline values at T6. Plasma phosphate increased significantly only at T6. Lactate levels were not different from baseline at T1 but showed a significant decrease at T6. These variations were not statistically different between the three groups. Thus acetylcysteine and ischaemic preconditioning did not exert any protective effect against the tourniquet-induced rhabdomyolysis.

**Effects of acetylcysteine and ischaemic preconditioning on muscular rehabilitation**

The ASIA motor scores of quadriceps muscle at day 2 were similar in the control, acetylcysteine and ischaemic preconditioning groups (4.1 ± 0.6, 4.3 ± 0.9 and 4.2 ± 0.8 respectively, *P* = 0.80).

**Effects of acetylcysteine and ischaemic preconditioning on morphine consumption**

All the patients completed the analgesia protocol during the first 48 h. The VAS scores were always less than 30 and were not different between the control, acetylcysteine and ischaemic preconditioning groups.

![Figure 1](https://example.com/figure1.png)

Myoglobin (a) and CPK (b) blood levels in the different groups measured at baseline, 1 and 6 h after tourniquet deflation. Measurements are presented as mean ± SD. For myoglobin (a): *P* < 0.0001 compared to baseline values; §*P* < 0.0001 compared to baseline values. For CPK (b): *P* < 0.01 compared to baseline values; §*P* < 0.0001 compared to baseline values; #*P* < 0.0001 compared to T1 values.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Acetylcysteine</th>
<th>Preconditioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>33.5 ± 12.9</td>
<td>24.5 ± 7.5</td>
<td>31.7 ± 13.3</td>
</tr>
<tr>
<td>Ratio (male/female)</td>
<td>9/2</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 ± 6</td>
<td>170 ± 13</td>
<td>174 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.2 ± 7.9</td>
<td>66.4 ± 16.8</td>
<td>68.9 ± 16.5</td>
</tr>
<tr>
<td>Tourniquet duration (min)</td>
<td>81.6 ± 24.9</td>
<td>88.0 ± 12.9</td>
<td>90.0 ± 8.4</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
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morphine consumption was lower in the acetylcysteine and ischaemic preconditioning groups (0.22 ± 0.31 mg kg⁻¹ and 0.22 ± 0.23 mg kg⁻¹, respectively) than in the control group (0.47 ± 0.33 mg kg⁻¹, P < 0.05). There was no significant difference between the acetylcysteine and ischaemic preconditioning groups (Fig. 4).

Discussion

Rhabdomyolysis

Our study showed that the pneumatic tourniquet induced mild rhabdomyolysis. The majority of the clinical studies being interested in the muscular consequences of the tourniquet found similar results [15,16].

Our work does not show any protective effect of acetylcysteine on muscular injuries induced by the pneumatic tourniquet. Although many clinical studies showed its effectiveness on oxidative stress under different conditions [17–19], only a few works evaluated its effects on a clinical setting of ischaemia/reperfusion. Recently, Saricaoglu and colleagues showed that low-dose acetylcysteine decreased the oxidative stress markers after knee ligamentoplasty with use of a pneumatic tourniquet [20]. Two clinical studies demonstrated that propofol, that is a powerful antioxidant, decreased the oxidative stress markers after use of the pneumatic tourniquet [21,22]. However these studies did not concern the effect of propofol on rhabdomyolysis. Thus it is difficult to establish a clear link between oxidative stress and rhabdomyolysis induced by the pneumatic tourniquet. With this intention it would have been interesting to measure the ROS or the oxidative stress markers in order to directly evaluate the antioxidant effects of acetylcysteine. However ROS measurement is a complicated technique that is unfortunately not available in our institution.

Our study could not show any protective effect of ischaemic preconditioning on the rhabdomyolysis induced by the pneumatic tourniquet. Although the beneficial effects of this technique were shown in many experimental models, only a few clinical studies...
proved its effectiveness, primarily on the myocardium [12,23]. In coronary aortic bypass grafting surgery studies, two periods of 2 min of ischaemia followed by 3 min of reperfusion were able to decrease the injuries and the clinical phenomena of myocardial ischaemia/reperfusion [24]. No clinical study has evaluated the effect of ischaemic preconditioning on skeletal muscle although a recent experimental study showed an absence of effect of ischaemic preconditioning on the neuromuscular dysfunction induced by the pneumatic tourniquet [25]. Last, it is possible that the oxidative stress is not responsible for the rhabdomyolysis. In this case, it would be due to the direct compression of the muscles located beneath the tourniquet which are subjected to ischaemia but also to mechanical deformation. That would explain why neither acetylcysteine, nor ischaemic preconditioning had effect on the rhabdomyolysis induced by the pneumatic tourniquet.

We observed a slight increase in blood potassium at 1 h and phosphorus at 6 h after the tourniquet release. Similar results have been already reported by others [26,27]. Our study showed a mild decrease in lactate level at the 6th hour after tourniquet release. To our knowledge, this has never been reported after use of a pneumatic tourniquet. It could give evidence to an enhancement of lactate consumption by ischaemic muscles during the recovery phase [28].

Postoperative muscular recovery
The evaluation of the muscular strength did not show any difference between the control, acetylcysteine and ischaemic preconditioning groups. However, the method that we used to assess the muscular strength probably lacked sensitivity to show a small difference.

Postoperative pain
In our study, postoperative pain was evaluated with a VAS. Although this one explores only the intensity of pain, it is the most widely used scale because of its precision, its simplicity and its speed of execution. We did not find any significant difference between the control, acetylcysteine and ischaemic preconditioning groups with average values lower than 30. This implies that the results observed in term of morphine consumption reflect the intensity of the postoperative pain and that they are not distorted by differences in term of analgesia between the groups.

Our work showed a reduction in the morphine consumption during the first 48 postoperative hours in the acetylcysteine group. To date, nearly nothing is known about the implication of the ROS in the pathophysiology of the pain. Only one clinical study has already demonstrated that an antioxidant was able to decrease pain after surgery implying an ischaemia/reperfusion phenomenon [29]. In this one, allopurinol improved recovery of sensation and especially decreased postoperative pain after thumb reimplantation surgery. In addition, experimental work showed that ROS and nociception are linked at the central nervous system level [30]. Finally Molnar and colleagues [31] showed that acetylcysteine is able to decrease the inflammatory response after major abdominal surgery. As the inflammation takes part in the postoperative pain, it is possible that, in our study, the reduction in morphine consumption in the acetylcysteine group was due to an antiinflammatory property of this molecule.

Our study showed that ischaemic preconditioning decreased the morphine requirements after elective knee ligamentoplasty with use of a pneumatic tourniquet. To date no clinical studies evaluated the effects of ischaemic preconditioning on pain, inflammation and ROS generation. But experimental works showed that ischaemic preconditioning decreased the markers of systemic inflammation in a porcine model of hindlimb ischaemia/reperfusion [32]. It is possible that ischaemic preconditioning decreases postoperative pain by a reduction of ROS generation and inflammation. It is very unlikely that our results were influenced by the infusion of ketoprofen because this drug was given to all the patients.

Study limitations
We did not measure ROS generation directly in the blood for several reasons. First, after use of a pneumatic tourniquet, the change in ROS concentration is probably mild and it is therefore likely to be detected only on the operated limb. This means that such a measurement would require the insertion of a femoral venous catheter downstream to the operated limb for blood sampling, but this procedure was too invasive for this minor surgery.

In conclusion, this work has shown that acetylcysteine and ischaemic preconditioning do not decrease the pneumatic tourniquet-induced biological and functional muscular injury. On the other hand, acetylcysteine and ischaemic preconditioning reduce postoperative morphine consumption significantly. According to these results we hypothesize that ROS are implicated in postoperative pain but further work will be necessary to confirm this.

References


