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Research Article

Tourniquet-induced cardiovascular responses in anterior cruciate ligament reconstruction surgery under general anesthesia: Effect of preoperative oral amantadine

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KEYWORDS

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Abstract *Objective:* The aim was to test the effect of amantadine, an NMDA antagonist, on tourniquet induced cardiovascular responses under general anesthesia.
Method: In a randomized, double blind, placebo-controlled study; thirty adult male patients with ASA physical status I or II, aged 18–50 years underwent anterior cruciate ligament reconstruction with a tourniquet under general anesthesia, were divided to receive either oral amantadine 200 mg capsule in the evening before surgery and 200 mg capsule 60 min before surgery (group A) or placebo capsules (group P). Heart rate, systolic and diastolic blood pressures were recorded (before induction of anesthesia, every 15 min after tourniquet inflation, before tourniquet deflation, and 10 min after tourniquet deflation). Incidence of tourniquet-induced hypertension, and postoperative tramadol consumption were also recorded.
Results: Systolic and diastolic pressures significantly increased in both groups compared to baseline values ($P < 0.05$) at 15, 30, 45, 60, 75 min after tourniquet inflation, and before tourniquet deflation with significantly lesser increase with amantadine compared to placebo at 45, 60, and 75 min after tourniquet inflation ($P < 0.05$). Heart rate significantly increased at 45, 60, and 75 min after tourniquet inflation in both groups compared to baseline values ($P < 0.05$) with significantly lesser increase with amantadine compared to placebo ($P < 0.05$). Development of tourniquet induced hypertension was less with amantadine (5 out of 15) than with placebo (8 out of 15).The total tramadol consumed during the first 24 h postoperative was significantly less with amantadine compared to placebo ($P < 0.05$).

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Conclusion: Preoperative oral amantadine reduced tourniquet induced hypertension and postoperative analgesic requirements in anterior cruciate ligament reconstruction surgery under general anesthesia.

1. Introduction

Pneumatic tourniquets are widely used during the upper or lower limbs orthopedic surgery to provide bloodless surgical field. However, the associated pain and increase in the arterial blood pressure are frequently observed 30–60 min after tourniquet inflation in spite of adequate level of anesthesia and they are often resistant to profound depth of anesthesia and analgesic drugs [1]. Tourniquet induced hypertension occurs more frequent under general anesthesia than spinal anesthesia and more with lower limb tourniquet than with upper limb tourniquet and can be serious in patients with cardiovascular diseases, neurological diseases, or glaucoma. The exact mechanism of its development is still unclear [2].

Several methods were used to attenuate tourniquet pain and hypertension intra-operatively such as the use of regional anesthesia, intravenous (IV) opioids (remifentanil) [3], α_2 agonists (clonidine and dexmedetomidine) [4,5].

There are several attempts to use *N*-methyl-D-aspartate (NMDA) receptor antagonists (Ketamine, magnesium, and dextromethorphan) to attenuate tourniquet-induced pain and hypertension and have reported to be effective [1,2,4,6,7].

Amantadine (1-aminoadamantane), a non-competitive NMDA antagonist, was used for long period as an antiviral against influenza and for the treatment of Parkinsonism. It has been used in some studies to reduce postoperative analgesic requirements [8,9] but to our knowledge there were no studies used this drug to reduce tourniquet induced hypertension. Therefore, the purpose of this study was to test the effect of preoperative oral amantadine, as an NMDA antagonist, on tourniquet-induced hypertension under general anesthesia as a primary outcome and postoperative analgesic requirements and side effects as a secondary outcome.

2. Method

After approval of the local ethical committee, informed written consents were obtained from 30 adult male patients, American Society of Anesthesiologists (ASA) physical status I or II, age ranging between 18 to 50 years old, scheduled for elective anterior cruciate ligament reconstruction with a tourniquet under general anesthesia.

This randomized, double blind, placebo controlled study was carried out in Dar Alshifa hospital (State of Kuwait) during the period from April 2013 to September 2013.

Patients were excluded from the study if they had sickle cell disease, peripheral vascular disease, history of DVT, poorly controlled hypertension, history of allergy to the studied drug or recent ingestion of cough suppressant (dextromethorphan), morbid obesity (BMI > 35).

Patients were randomly assigned into two equally divided groups (15 patients each) by using the closed envelop technique. The studied drugs were given by an anesthesia nurse unaware of the study medication as per the sealed envelope instruction (to maintain the blind nature of the study) as follows:

Amantadine group (group A): the patients received oral amantadine 200 mg capsule in the evening before surgery and 200 mg capsule 60 min before surgery (Symmetrel®, Novartis pharma AG., Basel, Switzerland) using the dose used in the study of Snijdelaar et al. [8]

Placebo group (group P) (control group): the patients received placebo capsules.

During the preoperative anesthesia visit, the patients were informed about the study and how to use the patient controlled analgesia (PCA) machine postoperatively. The patients were premedicated with i.v. metoclopramide 10 mg and oral midazolam 5 mg 60 min before surgery.

When the patients reached the operation room, the monitors were attached including ECG, pulse oximetry, non-invasive arterial blood pressure cuff, skin temperature probe and bispectral index (BIS) (the BIS electrodes were placed on the forehead and were connected to the BIS monitoring system) (Aspect Medical Systems, Leiden, The Netherlands) with infusion of Ringer's lactate solution according to fasting volumes, and maintenance volumes.

General anesthesia was induced with fentanyl 2 μg/kg, propofol 2 mg/kg, lidocaine 1 mg/kg and cisatracurium 0.15 mg/kg intravenously. The patients were intubated with oral cuffed tube lubricated with lidocaine gel 2% 2 min after cisatracurium administration and mechanically ventilated to maintain end tidal CO_2 between 35 to 40 mmHg.

Anesthesia was maintained with sevoflurane 1.5% in 50% air/O_2 mixture with adjustment of the sevoflurane concentration to maintain BIS value between 40 to 60. Analgesia was maintained by additional dose of fentanyl 50–100 μg if there were signs of inadequate analgesia (>20% increase in the heart rate and mean arterial blood pressure from the baseline). Esmolol 25 mg increments were given when systolic blood pressure (SBP), diastolic blood pressure (DBP) or heart rate (HR) increased >30% from the baseline reading. Muscle relaxation was maintained with cisatracurium boluses 0.03 mg/kg guided by peripheral nerve stimulator.

The pneumatic tourniquet (PTS ii portable tourniquet system, Delfi Medical Innovations Inc, Vancouver, Canada) 20 cm width was applied over cotton layer on the thigh of the operated limb which was elevated at 45° for 5 min with exsanguination using crepe bandage and inflation of the tourniquet pressure at 300 mmHg.

At the end of the surgery, the tourniquet was deflated with discontinuation of all anesthetics and the patients were extubated after reversal of neuromuscular blockade with intravenous 0.05 mg/kg neostigmine and 0.02 mg/kg atropine, and the patients were shifted to postanesthesia care unit (PACU) for monitoring and observation. The postoperative pain was treated according to our hospital protocol with tramadol 25 mg intravenous followed by intravenous PCA tramadol