Long term effect of general and regional anesthesia on bone turnover markers and fracture healing in adult patients

Erişkin hastalarda genel ve reyonel anestezinin kemik belirteçleri ve kırık iyileşmesi üzerine uzun dönem etkileri

Ebru Biricik, Feride Karacaer, Ersel Güleç, Selçuk Matyar, Murat Ilgınel, Ömer Sunkar Biçer, Dilek Ozcengiz

Abstract

Purpose: Bone metabolism can be monitored quantitatively by measuring bone turnover markers in serum and/or urine. We aimed to investigate long-term effect of the type of the anesthesia on bone turnover markers and fracture healing.

Materials and Methods: Thirty patients with American Society of Anesthesiologist physical status I-II whom were aged 40-70 years, scheduled for hip fracture were recruited. Patients were divided into the two groups as general anesthesia and regional anesthesia. Only morphine and tramadol were used for postoperative analgesia till the 12th week. Serum bone-specific alkaline phosphatase, osteocalcin, β-C terminal telopeptide and urine β-C terminal telopeptide levels were measured at preoperative, 4th week and 12th week of fracture.

Results: A total of 25 patients were eligible for the study. There were no statistically significant between groups for values of bone turnover markers at the time point of preoperative, 4th and 12th week. With using linear regression analysis, serum β-CTX levels at 12th week can be predict by 4th weeks β-CTX levels (R2: 0.944) and urine β-CTX levels at 12th week can be predict by first week level.

Conclusions: This pilot study showed that both general and regional anesthesia has similar effect on bone turnover markers and fracture healing.

Keywords: Bone turnover markers, fracture healing, general anesthesia, regional anesthesia
INTRODUCTION

Bone metabolism can be followed by serum and urine turnover markers. Formation and resorption are balanced during normal homeostasis of bone. At the stage of bone formation process, formation markers such as bone-specific alkaline phosphatase (BAP), osteocalcin (OC) and N-terminal propeptide of type I collagen released from osteoblasts and broken matrix components. Bone resorption markers such as crosslinked C-(CTX) and N-(NTX) telopeptides of type I collagen indicate bone catabolic process. Both formation and resorption rates rise up at the repair process of bone fractures. Increasing in bone metabolism can be detected as elevation on bone turnover markers (BTM). Higher levels of BTM are associated with bone loss and elevated risk of future fracture.

But some studies showed that increasing BTMs are not independently associated with the risk of hip or nonspine fracture. A large meta-analysis showed that the GR (gradient of risk) for hip fracture is similar both sexes and bone mineral density (BMD) is a risk factor for fracture. Also fracture risk with BMD is age dependent.

So many factors such as age, gender, fracture type and size, osteoporosis, different methods of surgical stabilization, BMD and drug therapies may affect fracture healing.

Regional techniques for orthopedic surgery have many advantages both patients and surgeons. Particularly, regional anesthesia can provide good pain control and better recovery process. However, long term effect of type of anesthesia on BTM and fracture healing unknown.

In this pilot study, we aimed to investigate effect of type of anesthesia on BTM and fracture healing. Primary objective of this pilot study is evaluation to effect of regional and general anesthesia on BTM in patients who underwent orthopedic surgery with hip fracture during fracture healing process. Secondary objective is effect of the type of anesthesia on fracture healing.

MATERIALS AND METHODS

Our study protocol was registered at clinicaltrials.gov (principal investigator’s name: EB, and identifier: NCT02621255) on November, 2015 and approved by ethics committee (decision number: 41/10 and Date: June 18, 2015). After obtaining written informed consent, 30 patients with ASA I to II between to ages of 40-70 years, scheduled for hip fracture were recruited. Exclusion criteria were the presence of malignancy, inflammatory disease, polytrauma, kidney failure, drug usage which can affect bone metabolism [estrogen, nonsteroidal anti-inflammatory drugs (NSAID), calcium, anticonvulsants and vitamin D] and fracture history in the past and ASA III-IV patients.

Figure-1: Consort flow diagram

First blood samples were taken in a fasting state after 24 h of injury preoperatively. All patients were randomly allocated in to the two groups as group general anesthesia (Group G) and group regional anesthesia (Group R) with computer-generated randomization list.

After admitted to the operation room, all patients were monitored by non-invasive arterial blood pressure, electrocardiogram, and peripheral oxygen saturation (SpO2) (Draeger-Primus Anesthesia Device Monitor, Draeger Medical Systems, Inc., Denver MA). An intravenous (IV) cannula (18 G) was inserted.

General anesthesia was performed for first group of patients (Group G). Propofol 2 mg/kg and rocuronium 0.6 mg/kg intravenously (IV) were applied for anesthesia induction. Anesthesia...
Fasting blood and first urine samples were obtained from patients and collected in 5 mL vacuum collection tubes with no anticoagulant (Becton Dickinson Vacutainer® ref. 369032). The tubes with no anticoagulant were allowed to clot at room temperature for 15-20 min and separated by centrifugation at 3000 r.p.m for 20 min. and the sample was frozen (−20°C) and analyzed within six month.

When specimens were available, they were thawed, mixed, again centrifuged (at 3000 r.p.m for 20 min) and analyzed at room temperature. The urine and serum samples were thawed once.

Biochemical marker measurements
The collected serum and urine samples were studied using a Human C- telopeptide of type I collagen (CTX- I) ELISA kit (Catalogue No.: 201-12-1350) and serum samples were studied using a Human bone alkaline phosphatase (BALP) ELISA kit (Catalogue No.: 201-12-1494) according to the manufacturer’s instructions (Sunred Biological Technology Co., Ltd. Shanghai PR China). For the samples terminating with the enzyme substrate reaction, the samples were spectrophotometrically measured at a wavelength of 450 nm with Triturus Instruments (Barcelona, Spain). Detection ranges of this kit were 6ng/ml - 1500ng/ml for CTX- I and 3U/L - 900U/L for BALP.

Serum osteocalcin levels were analyzed with electrochemiluminescence immunooassay (ECLIA) using a standard assay kit for in vitro diagnostics (kit catalogue number: 12149133122). Reactions and quantification were performed by using a fully-automatized Cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Reference values were 0-1000 ng ml⁻¹ for males and females.

Serum creatinine was analyzed with Beckman Coulter kits (CA), which were manufactured to use on Beckman UniCel DXC 800 Synchro (Beckman Coulter Inc., CA, USA) auto-analyzer. Creatinine: Jaffe method (rate-blanked kinetic alkaline picrate) measured at 520 nm, at 37°C (ref: 472525). Reference values were 0.3-1 mg/dl for 0 to 19 age’s males, 0.7-1.2 mg/dl for 20 to 120 age’s males and 0.4-1 mg/dl for 20 to 120 age’s females.

Radiological assessment
Radiological assessment of fracture union was carried out by same orthopedic surgeon and radiologist who interest in musculoskeletal imagining. Direct radiography was taken immediately after the fracture and at 4th and 12th weeks.

At the point of 12th weeks bone mineral density (BMD) was detected with bone densitometry. T-score < −2.5 was accepted as osteoporosis according to the World Health Organization criteria for diagnosis.

Statistical analysis
All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package.
RESULTS

Thirty patients were recruited to this pilot study but 25 patients could complete to the study, and data from 25 patients were used in the statistical analysis. (Figure 1) Demographic data was similar between two groups. (Table 1)

Table 1. Demographic Data of the Groups and Type and Duration of Surgery

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=18)</th>
<th>Group II (n=17)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (39)</td>
<td>9 (53)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (61)</td>
<td>8 (47)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totally hip replacement</td>
<td>12 (67)</td>
<td>11 (65)</td>
<td></td>
</tr>
<tr>
<td>Partially hip replacement</td>
<td>6 (33)</td>
<td>6 (35)</td>
<td></td>
</tr>
<tr>
<td>Postoperative discharge time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd day</td>
<td>1 (5)</td>
<td>2 (12)</td>
<td></td>
</tr>
<tr>
<td>3rd day</td>
<td>8 (44)</td>
<td>7 (41)</td>
<td></td>
</tr>
<tr>
<td>4th day</td>
<td>4 (22)</td>
<td>4 (23)</td>
<td></td>
</tr>
<tr>
<td>5th day</td>
<td>4 (22)</td>
<td>3 (17)</td>
<td></td>
</tr>
<tr>
<td>6th day</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td></td>
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</tbody>
</table>

Percentages are presented as % within group; a Independent sample T test; b Chi-Square test.

Table 2. Bone Turnover Markers and BMD-T score levels

<table>
<thead>
<tr>
<th></th>
<th>Group G (N=15)</th>
<th>Group R(N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>4th week</td>
</tr>
<tr>
<td>Formation Markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-Bone ALP(U/L)</td>
<td>28.8±15.07</td>
<td>28.8±12.27</td>
</tr>
<tr>
<td>(P value)</td>
<td>0.605</td>
<td>0.461</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>24.3±11.79</td>
<td>25±7.9</td>
</tr>
<tr>
<td>(P value)</td>
<td>0.428</td>
<td>0.849</td>
</tr>
<tr>
<td>Resorption Markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-CTX(ng/L)</td>
<td>332.26±190.4</td>
<td>362.26±179.49</td>
</tr>
<tr>
<td>(P value)</td>
<td>0.285</td>
<td>0.160</td>
</tr>
<tr>
<td>U-CTX(ng/L)</td>
<td>436.4±179.9</td>
<td>477.4±73.7</td>
</tr>
<tr>
<td>(P value)</td>
<td>0.567</td>
<td>0.765</td>
</tr>
<tr>
<td>Mean T score</td>
<td>-0.65±0.73</td>
<td>-0.74±1.78</td>
</tr>
<tr>
<td>BMD</td>
<td>0.85±0.01</td>
<td>0.83±0.09</td>
</tr>
<tr>
<td>(p value)</td>
<td>0.935</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as Mean±SD; Mann Whitney U test was used; S-Bone ALP; serum bone alkaline phosphatase, S-CTX; serum C-telopeptide, U-CTX; urine C-telopeptide, BMD; bone mineral density.

Study patients were 10 males (40%) and 15 female (60%). There was no statistically significance between groups for the levels of serum BAP, serum OC, serum β-CTX and urine β-CTX at the time of 24th h,
osteoblast proliferation at the subsequent sequence of necrotic tissues. Formation markers increase with fracture, due to the osteoclastic removal of the necrotic tissues. Formation markers increase with osteoblast proliferation at the subsequent sequence.

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Biocic et al investigated prognostic potential of biochemical BTMs in delayed-union formation and resorption markers. They also observed that both bone formation and resorption markers peaked at the eighth week following the fracture. All turnover markers elevates at fracture healing process. During the fracture healing process, resorption markers increase at earlier stage of the fracture, due to the osteoclastic removal of the necrotic tissues. Formation markers increase with osteoblast proliferation at the subsequent sequence.

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In this study, the authors prohibit to the drugs which can affect to bone metabolism such as NSAID. Because, some animal models showed that NSAID's can impair fracture healing in rats. However, the effect of NSAID's and cyclooxygenase-2 inhibitors on fracture healing in human is controversy. Therefore, we preferred to use tramadol for postoperative analgesia.

This pilot study showed that long term effect of general and regional anesthesia on BTM and fracture healing were investigated. All patients were followed up for 12 weeks and found that the levels of serum BAP, serum OC, serum β-CTX and urine β-CTX were similar between groups of general and regional anesthesia. All values of the BTM increased over the time and this acceleration was similar previous studies. The elevation was most pronounced after hip fracture. Bone turnover markers can be predicted by first week level.

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studies need to clarify effect of anesthesia on BTM and fracture healing.

REFERENCES


