The preoperative single dose dexamethasone effect to pro-and anti-inflammatory cytokine during orthopedic surgery

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ABSTRACT

Background: The efficacy of glucocorticoids like dexamethasone in reducing postoperative pain has been investigated and showed that a single dose of dexamethasone significantly analgesia has advantages in terms of reduction in pain intensity, opioid requirements, rescue analgesia, and did not increase the incidence of infection and impaired wound healing. The aim of this study was to evaluate the effects of preoperative single dose of intravenous dexamethasone to the dynamics of pro- and anti-inflammatory cytokine in orthopedic surgery perioperative period.

Materials and Methods: Thirty patients were studied and randomly into two groups: 15 patients received 8 mg dexamethasone intravenous preoperatively and perioperative analgesia with paracetamol and patient-controlled analgesia (PCA) morphine (dexamethasone group) and 15 patients received perioperative analgesia paracetamol and PCA morphine only (control group). Blood samples were taken at the time before anesthesia, immediately postsurgery, 4 h and 24 h after surgery to measure plasma levels of interleukin 6 (IL-6) and IL-10. We recorded the pain intensity and morphine requirement in 4 h and 24 h after surgery.

Results: IL-6 levels in the dexamethasone group did not increased from immediately after surgery to 24 h after surgery but increased in the control group ($P < 0.05$). There is no difference of IL-10 levels in both groups at all measurement time. Rest and moving pain intensity from time to time in the two groups did not differ except the rest pain at 24 h postoperative ($P < 0.05$). Morphine requirement in the dexamethasone group was lower in the 24 h after surgery than the control group.

Conclusion: The addition of dexamethasone preoperatively on the combination of paracetamol and morphine did not change plasma levels of IL-6 and IL-10 cytokines Dexamethasone provides sufficient analgesia and decrease postoperative opioid requirement.

Key words: Analgesia, dexamethasone, inflammation, perioperative

Introduction

Cytokines are mediators which required to regulate the inflammatory response in the event of damage and support the appropriate wound healing, but excess production of pro-inflammatory cytokines will lead to systemic manifestations such as hemodynamic instability and metabolic changes. When the pro-inflammatory cytokine response long lasting and in large amounts will cause organ damage, but the anti-inflammatory cytokines will be produced anyway to minimize the negative effects of excessive pro-inflammatory cytokines. Interleukin 6 (IL-6) is a pro-inflammatory cytokine and IL-10 is classified as cytokine anti-inflammatory.[1]

Maintaining the balance between the two kinds of cytokines is very important to immune homeostasis after surgery. Excessive release of pro-inflammatory cytokines can cause damage to the host tissue and systemic inflammatory conditions, but instead suppression of local immune response and inflammation can lead to other complications such as disruption of the wound healing process and the possibility of infection.[2,3] Cytokine
balance between pro- and anti-inflammatory associated with decreased survival.\textsuperscript{[4]} In the treatment of postsurgical pain, opioids are the most effective drug and have long been used in the treatment of postoperative pain. Commonly, the use of opioids are morphine which is a natural opioids and fentanyl as a synthetic opioid. The use of postoperative opioids formerly associated with the occurrence of side effects such as pruritus, nausea, vomiting, and even respiratory depression. Side effects have now rarely found with the use of a combination of opioid analgesic with drugs which have an opioid-sparing effect in the concept of multimodal analgesia such as paracetamol, non-steroid anti-inflammatory drugs (NSAIDs) and steroid anti-inflammatory.\textsuperscript{[5,6]}

The efficacy of glucocorticoids like dexamethasone in reducing postoperative pain has been investigated in recent years by a systematic review and meta-analysis showed that a single dose of dexamethasone as analgesia significantly has advantages in terms of reduction in pain intensity, opioid requirements, rescue analgesia, length of postoperative anesthesia care unit and time to requires first analgesia the first and did not increase the incidence of infection and impaired wound healing, but not many reports described how the inflammatory response occurs after administration of this anti-inflammatory agent in the perioperative period especially in intermediate dose analgesia.\textsuperscript{[7]}

We interested in examining the effects of the addition of dexamethasone in combination of paracetamol and opioids morphine in the treatment of postoperative pain associated with the dynamics of pro-and anti-inflammatory in the perioperative period.

**Materials and Methods**

This clinical experimental study conducted in randomized double-blind trial held at Wahidin Sudirohoso Hospital Makassar Indonesia started on December 2013 after ethical research approval by the Research Ethics Committee of Wahidin Sudirohoso Hospital and Faculty of Medicine Hasanuddin University until the number of samples are met. Consecutive samples were selected randomly from the entire population of the lower extremity orthopedic elective surgery performed on the installation of central surgery at Wahidin Sudirohoso Hospital, who met the inclusion criteria and agreed to participate in this study.

Inclusion criteria include American Society of Anesthesiologists physical status (ASA PS) 1-2, 20-50 years old, body mass index (BMI) 18.5-25 kg/m\textsuperscript{2}, agree to performed spinal anesthesia techniques and approval of orthopedic physicians. Exclusion criteria included history of allergy to the drug use in the study, history of stomach ulcers and bleeding, suffering from cardiovascular and metabolic disease, hepatic cirrhosis and renal failure, leukocytosis or leukopenia, have a fever (temperature above 37.8°C), the use of NSAIDs or corticosteroids (use last <2 days before surgery), do not understand how to use the patient-controlled analgesia (PCA) machine. Drop-out criteria include complications during anesthesia and surgery, duration of surgery more than 180 min, conversion technique of spinal anesthesia technique to another and reoperation within 24 h after surgery.

Patients who met the study criteria undergo elective surgery and has been agreed by informed consent get premedication overnight with alprazolam tablets given 5 mg overnight. Blood samples for examination of the levels of IL-6 and IL-10 pretreatment were taken before anesthesia. Anesthesia begins with spinal anesthesia using 15 mg of 0.5% bupivacaine with 25 G quincke spinal needle at the L3-L4 segment. Height of the block checked with cold test up to a height of thoracic 10 for the purposes of lower extremity surgery, and the patient was given 2 mg midazolam for sedation. The treatment group was given paracetamol 1 g drips in 15 min before the end of surgery and dexamethasone 8 mg (2 ml) and the control group was given paracetamol 1 g drips in 15 min before the end of surgery and 0.9% NaCl (2 cc) intravenously. Postoperative analgesia with opioids morphine PCA starts with the loading dose 2 mg (bolus dose 1 ml of 1 mg/ml, lockout interval of 8 min, no background infusion) in both groups. Blood samples for examination of the levels of IL-6 and IL-10 were taken at the time of the operation is complete, the 4 h and 24 h after surgery in both groups. Blood serum samples as specimen preparation collected in Becton-Dickinson serum separator tubes and let at room temperature for 2 h or overnight at 4°C then centrifuged for 15 min at 1000 \times g. Serum specimens were stored at −80°C for a period of not more than 12 months in the Central Laboratorium Installation Wahidin Sudirahosodo Hospital Makassar. Conducted recording of opioid requirements, assessment of pain intensity, and pressure pain threshold measurement value at 4 h and 24 h postsurgery on both groups. Subject complaints of pain in both groups with numeric rating scale (NRS) value of more than four will give an additional analgesic (rescue) 1 mcg fentanyl/kg intravenously. Observation and recording of additional analgesic requirement, side effects and vital signs in both
groups during 24 h after surgery. After the sample has been completed then conducted measurement serum levels of IL-6 using the reagent Human HS IL-6 ELISA kit (R and D Systems, USA) and IL-10 with Human HS IL-10 ELISA kit (R and D Systems, USA) in Laboratory Research Unit of the Faculty of Medicine-Hasanuddin University Hospital.

Statistical analysis using Statistical Package for Social Science, SPSS 16 Inc. software with the following test methods: Homogeneity between the two groups were compared (age, BMI, surgical duration, estimated of bleeding was tested with independent t-test; gender and PS were tested by Chi-square). Dynamics of serum levels of cytokines IL-6 and IL-10 from time to time in each group were tested with the Wilcoxon test. Pain intensity in both groups was tested with the Mann–Whitney U-test. Comparison of opioid requirement in both groups was tested by independent t-test.

Results

This study was conducted from December 2013 to July 2014 at Wahidin Sudirohusodo Hospital in Makassar on 30 patients as the research samples, divided into 15 people each group randomly, so that individual variation is divided evenly in both groups, the treatment group and the control group. Two groups research were based on the characteristics of age, BMI, duration of surgery, the amount of bleeding and ASA PS showed the homogeneity of the two groups to be compared as shown in [Table 1].

Table 1: Patient characteristic, duration of surgery and estimated bleeding

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dex group (n = 15)</th>
<th>Control group (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Mean 31.47 SD 11.38</td>
<td>Mean 33.40 SD 14.76</td>
<td>0.691</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>21.57 2.96</td>
<td>22.58 2.71</td>
<td>0.337</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>96.00 40.45</td>
<td>109.00 47.25</td>
<td>0.425</td>
</tr>
<tr>
<td>Estimated bleeding*</td>
<td>143.33 88.37</td>
<td>88.37 139.60</td>
<td>0.304</td>
</tr>
<tr>
<td>Gender (Male/Female)*</td>
<td>9/6</td>
<td>12/3</td>
<td>0.427</td>
</tr>
<tr>
<td>ASA Physical State (1/2)*</td>
<td>10/5</td>
<td>7/8</td>
<td>0.462</td>
</tr>
</tbody>
</table>

Table 2: Changes in the plasma concentration of IL-6 during observation compare with preoperative value

<table>
<thead>
<tr>
<th>Time measurement</th>
<th>Min 0.35</th>
<th>Max 26.56</th>
<th>Median 2.46</th>
<th>P value</th>
<th>Min 0.17</th>
<th>Max 6.22</th>
<th>Median 1.30</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h postoperative</td>
<td>0.35</td>
<td>26.56</td>
<td>2.46</td>
<td>0.691</td>
<td>0.17</td>
<td>6.22</td>
<td>1.30</td>
<td>0.017</td>
</tr>
<tr>
<td>24 h postoperative</td>
<td>0.35</td>
<td>26.56</td>
<td>2.46</td>
<td>0.156</td>
<td>0.17</td>
<td>6.22</td>
<td>1.30</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The increases did not occur in the group receiving a single dose of dexamethasone 8 mg as an anti-inflammatory in this study which found no significant differences occurred between the serum levels of IL-6 at each time of observation compared to basal levels before surgery, showed a decline in plasma levels of IL-6 upon completion of surgery and then increased in at 4th and 24th postsurgery.
Table 3: Changes in the plasma concentration of IL-10 during observation compare with preoperative value

<table>
<thead>
<tr>
<th>Time measurement</th>
<th>Dex group (n = 15)</th>
<th>Control group (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
<td>Median</td>
</tr>
<tr>
<td>Immediately postoperative</td>
<td>0.21</td>
<td>33.32</td>
<td>1.68</td>
</tr>
<tr>
<td>4 h postoperative</td>
<td>0.19</td>
<td>9.08</td>
<td>2.19</td>
</tr>
<tr>
<td>24 h postoperative</td>
<td>0.21</td>
<td>33.32</td>
<td>1.68</td>
</tr>
</tbody>
</table>

Value in maximum, minimum and median with probability tested with Wilcoxon test, P value < 0.05 were significant compare with basal preoperative value.

Table 4: Changes in pain intensity

<table>
<thead>
<tr>
<th>Time observation</th>
<th>Dex group (n = 15)</th>
<th>Control group (n = 15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Max</td>
<td>Median</td>
</tr>
<tr>
<td>Preoperative</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Immediately postoperative</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4 h postoperative</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>24 h postoperative</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Value in maximum, minimum and median with probability tested with Mann Whitney-U test, P value < 0.05 were significant compare with other group.

Table 5: Morphine consumptions during observation

<table>
<thead>
<tr>
<th>Time observation</th>
<th>Dex group (n = 15)</th>
<th>Control group (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>4 h postoperative</td>
<td>3.73</td>
<td>1.42</td>
<td>4.30</td>
</tr>
<tr>
<td>24 h postoperative</td>
<td>1.07</td>
<td>1.53</td>
<td>3.20</td>
</tr>
<tr>
<td>Total consumption</td>
<td>4.80</td>
<td>2.37</td>
<td>7.40</td>
</tr>
</tbody>
</table>

Value in mean and standard deviation; probability (p value) test with independent t-test, P value < 0.05 were significant compare with other group.

but not statistically significant. The use of intermediate dose of 8 mg in these studies gives different results in several studies using high doses of steroids that cause decreased levels of IL-6 in the high-dose administration of 100 mg dexamethasone in cardiac surgery and a slight decrease in response to IL-6 with combination of epidural analgesia and high-dose prednisolone in patients with colon resection surgery.\cite{13-16}

Corticosteroids inhibit the accumulation of macrophages and neutrophils in the inflammatory so it acts as an anti-inflammatory in addition to the inhibition of prostaglandin E2 (PGE2) formation by corticosteroids can reduce the formation of IL-6 as PGE2 can stimulate the synthesis of IL-6 through cAMP activation and nuclear factor (NF)-κβ.\cite{14,15} Mechanism above clearly demonstrate the role of glucocorticoids in suppressing the inflammatory process by inhibiting the formation of cytokines such as IL-6 pro-inflamasi so that the group who receive the dexamethasone has no significant differences in serum concentrations of IL-6 at each time of observation while the group that did not get dexamethasone increased significant at each time of observation. Several studies using NSAIDs to look at the role of pro-inflammatory cytokines showed a decline in pro-inflammatory cytokine response postoperative characterized by decreased levels of the cytokine IL-6 by giving Diclofenac, Keterolac, and Fluriprofen\cite{15,16} probably reflects the effect of PG inhibition by NSAIDs greater than dexamethasone dose given in this study.

Dexamethasone as a glucocorticoid have the ability to suppress the production of IL-6 via the mechanism such as penetrate the cell membrane and binds to specific cytoplasmic receptors which will trigger response transcription factor NF-modification κβ, NF-AT and activator protein-1 as well as through the process of mRNA degradation of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, and IL-8.\cite{16,17}

In both groups, the study found no significant changes in cytokine levels of IL-10 from time to time of observation ranging from changes after the surgery is completed until the end of the observation at 24 h post surgery. Different results are found in the research of Kim et al., 2001, the use of ketorolac shows increased IL-10 at the 4 h postoperative correlated with increased levels of IL-6;\cite{18} Mahdy et al., 2002, also reports an increase in IL-10 on the 6 and 12 h postsurgery in the subject who get Diclofenac but not significant increase in the 24 h after surgery.\cite{19} This show that dexamethasone with a moderate dose that we used did not cause excessive inflammation suppression like the other result using NSAIDs. Pro-inflammatory and anti-inflammatory cytokines produced to regulate the immune process, and the balance both cytokine determine the level of the inflammatory response.

Analgesia produced on the subject in both group assessed from the intensity of pain and morphine PCA opioid requirements. Most of the subjects in both groups experienced a decline in the value of NRS rest at all time of observation. The difference in pain intensity value of the two groups only in the intensity of pain at 24 h postoperative were lower in the group receiving dexamethasone but pain intensity in both groups were still classified as mild pain.\cite{15,16}
intensity. No difference in the pain intensity both groups due in accordance with the principles of use PCA opioids in all subjects in which patients will be pressing button for analgesia when it began to feel the pain, so the results of the good PCA programmed were mild pain intensity in postoperative patients.

Differences that may occur are the amount of opioid analgesia is needed to achieve the same analgesia. In this study, it was found that the group receiving dexamethasone requires lower morphine on the 24 h postoperative than the control group who only get paracetamol and morphine. There was a decrease opioid requirements morphine is about 13% (average of opioid requirement of 3.7 mg treatment group compared to the control group 4.3 mg) at 4 h postsurgery although not statistically significant and a reduction about 35% of the total opioid requirements in 24 h after surgery (average of opioid needs 4.8 mg treatment group compared to the control group 7.4 mg). This is according to a meta-analysis that demonstrates the ability dexamethasone in reducing postoperative opioid requirements are referred to as opioid effects sparring about 10% of the morphine dose equivalent at 2 h postsurgery, and 13% on the needs of morphine in 24 h after surgery.[9]

Doses above 0.1 mg/kg BW as part of a multimodal analgesia on perioperative pain can effectively reduce postoperative pain and decrease postoperative opioid requirement and dexamethasone is considered as a nonopioid analgesic that has opioid-sparing effect with good evidence-based.[8] In gynecological surgery reported, the use of preoperative doses above 0.1 mg/kg dexamethasone resulted in decreased opioid requirements and improved recovery.[9]

Dexamethasone effect in reducing the formation of inflammatory mediators will greatly affect the reduction in peripheral sensitization in peripheral nerve endings injury then reduction sensitizing of high threshold nociceptors and can reduce the rise of silent nociceptors.[20] All that thing will reduce the formation of impulses in the transduction process that will be delivered to the dorsal horn in the spinal cord, which will reduce opioid requirements needed in the modulation process.

Opioids also stated to have suppressive effect on the immune system after surgery which at therapeutic doses is able to suppress the hypothalamic-pituitary-adrenal axis and suppress hypothalamic and pituitary hormone production as corticotropin and finally cortisol released by adrenal.[21-23] Effective use of opioids is very clearly seen in patients with most postsurgical pain, but not quite effectively suppress the stress response in the upper abdominal surgery.[21,24]

In inflammatory conditions has been reported release of endogenous opioid peptides from cells-immune cells that are in the inflammation area. This endogenous opioid will suppress sensitization of C-fibers nerve ending and suppress the release of inflammatory mediators that play a role in the nociceptive process.[20,25] This opioid effects on peripheral is trying to be developed at this time to provide a peripheral opioid analgesia without significant systemic effects.[22]

**Conclusion**

The addition of dexamethasone to the combination of paracetamol and morphine did not find significant changes in the levels of pro-inflammatory cytokines IL-6 and anti-inflammatory cytokine IL-10 within 24 h after surgery. The addition of dexamethasone provides adequate analgesia and reduces opioid requirements.

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