

The Effect of Dexamethasone on the Dynamics of Inflammation, Cortisol and analgesia in Lower Limb Surgery

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Abstract

Background: Dexamethasone is currently used as a part of multimodal analgesia on postoperative pain management. Dexamethasone considered providing effective analgesia as a steroid anti-inflammatory. This study aimed to examine the effects of preoperative single dose of intravenous dexamethasone to the inflammation, cortisol response and analgesia in lower limb surgery.

Methods: This is a clinical experimental study conducted in randomized double-blind trial performed at Wahidin Sudirohusodo Hospital, Makassar Indonesia. Thirty patients with lower limb surgery under spinal anesthesia meet the inclusion criteria were randomly divided into 2 groups: (1) group received 8 mg dexamethasone intravenous preoperatively and perioperative analgesia with paracetamol and PCA morphine (dexamethasone group) and (2) group received perioperative analgesia paracetamol and PCA morphine (control group). Blood samples were taken at the time before anesthesia, immediately post-surgery, 4 and 24 hours after surgery to measure plasma levels of CRP and Cortisol with the ELISA test. We recorded the intensity of rest pain and morphine requirement in 4 and 24 hours after surgery.

Results: Both of groups found increase in CRP plasma levels at the 24 hours after surgery ($p < 0.05$). Cortisol in the dexamethasone group decreased significantly at the 24 hours after surgery while in the control group did not change ($p < 0.05$). Rest pain intensity and morphine requirement in the dexamethasone group was lower in the 24 hours after surgery than the control group ($p < 0.05$). No differences changes in blood pressure, heart rate, respiration and the side effects between the two groups.

Conclusion: The addition of single dose dexamethasone preoperatively on the combination of paracetamol and morphine did not abolish inflammation process but decrease cortisol response after surgery with sufficient analgesia and minimal side effect.

Keywords: Dexamethasone; Inflammation; Cortisol; Perioperative analgesia

Introduction

Surgery will lead to biphasic pain consequences; the pain caused by tissue damage itself is also pain arising as a result of the inflammatory response due to tissue trauma. An acute inflammatory and tissue injury was a stimulus that acts on the hypothalamus and the target organs of secretion that will cause changes in the neuroendocrine response. The amendment called the *stress response* to injury characterized by increased secretion of catabolic hormones (cortisol, glucagon, growth hormone, and catecholamine's) and inhibition of anabolic mediators, especially insulin and testosterone. Surgery is a strong activator of ACTH and cortisol secretion, and increase both can occur in the early minutes of the surgery [1,2].

Postoperative pain management is aimed at the state of pain free and stress free by reducing postoperative pain intensity and followed by the balance of the inflammatory response. Multimodal Analgesia which uses drugs and analgesia technique that works on the peripheral and central sensitization is the main concept in the treatment of post-surgical pain today. According to the American Society of Anesthesiologists, multimodal analgesia should be used whenever possible based on the intensity of pain that may arise as a result of surgery [3].

Opioids are the most effective drug and have long been used in the treatment of postoperative pain. Commonly the used of opioids are morphine which is a natural opioids and fentanyl as a synthetic opioid [4,5]. The use of postoperative opioids formerly associated with the occurrence of side effects such as pruritus, nausea, vomiting and even respiratory depression. Side effects was found decrease 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 and Non-Steroid Anti-Inflammatory (NSAIDs).

The combination of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and opioids is now widely used to treat postoperative pain, especially in surgery with moderate to severe postoperative pain intensity [6]. In the presence of inflammation in a surgery it is considered to need drugs with anti-inflammatory effect to prevent systemic effects of the release of pro-inflammatory mediators such as NSAIDs which have been known to the effectiveness to postoperative pain. However, the negative effect on the coagulation system, gastrointestinal and renal complications that can provide more profound on the use of NSAIDs. In addition, administration of NSAIDs in postoperative patients will suppress the local and systemic immune response that can lead to postoperative complications such as disruption of wound healing period and the possibility of infection and has also been reported to affect the use of NSAIDs in the occurrence of excessive scar injury [7-9]. Some researchers and clinicians suggest the limiting on the use of external anti-inflammatory such as NSAIDs in the surgery with

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minimal skin incision and muscle retraction [10]. Some of the above raises the question about the side effects and complications that can occur due to the use of anti-inflammatory NSAID in perioperative period.

Dexamethasone are often used in postoperative analgesia besides NSAIDs and also been put as part of the concept of multimodal postoperative analgesia. The efficacy of glucocorticoids such as 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 (PACU) and time to requires first analgesia the first and did not increase the incidence of infection and impaired wound healing, but not many report described how the inflammatory response occurs after administration of this powerful anti-inflammatory in the perioperative period especially in intermediate dose analgesia [11].

As we know, no studies that describe the dynamics of inflammation, neurohumoral response and postoperative analgesia occurred after administration of the combination of paracetamol and opioids with or without the addition of steroid anti-inflammatory drugs such as dexamethasone. 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 inflammation by measure C - reactive protein, hormonal response of cortisol and pain in the perioperative period.

Material and Methods

This is a clinical experimental study conducted in randomized double-blind trial held at Wahidin Sudirohusodo Hospital starting on December 2013 after ethical research approved by the Biomedical Research Ethics Committee of Wahidin Sudirohusodo 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 at the Surgical Unit Wahidin Sudirohusodo Hospital who met the inclusion criteria and agreed to participate in this study.

Inclusion criteria include ASA PS 1-2, 20-50 years old, Body Mass Index 18.5 to 25 kg / m², 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, cardiovascular and metabolic disease, hepatic cirrhosis and renal failure, leucocytosis or leukopenia, have a fever (temperature above 37.8 ° C), the use of NSAIDs or corticosteroids (use last less than 2 days before surgery), do not understanding how to use the PCA machine. Drop-out criteria include complications during anesthesia and surgery, duration of surgery more than 180 minutes, conversion technique of spinal anesthesia technique to another and reoperation within 24 hours after surgery.

Patients who met the study criteria undergo elective surgery and has been agreed by inform consent get premedication overnight with alprazolam tablets given 5 mg overnight. Blood samples for examination of the levels of cortisol and CRP pre-treatment was 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 (Th) 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 minutes before the end

of surgery and dexamethasone 8 mg (2 ml) and the control group was given paracetamol 1 g drips in 15 minutes before the end of surgery and 0.9% NaCl (2 cc) intravenously. Postoperative analgesia with opioids morphine PCA starts with loading dose 2 mg (bolus dose 1 ml of 1 mg / ml, lockout interval of 8 minutes, and no background infusion) in both groups. Blood samples for examination of the levels of cortisol and CRP were taken at the time of the operation is complete, the 4 hour and 24 after surgery in both groups. Blood serum samples as specimen preparation collected in BD SST (Serum Separator Tubes) and let at room temperature for 2 hours or overnight at 4 Celsius degree then centrifuged for 15 minutes at 1,000 x g. Serum specimens were stored at -80 Celsius degree for a period of not more than 12 months in the Central Laboratories Installation Wahidin Sudirohusodo Hospital Makassar. Conducted recording of opioid requirements, assessment of pain intensity with Numerical Rating Scale (NRS) at 4 and 24 hours post-surgery on both groups. Subject complaints of pain in both groups with NRS value of more than 4 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 hours after surgery. After the sample has been completed then conducted measurement serum levels of CRP with Human HS ELISA KIT (BIOVENDOR) and cortisol with cortisol immunoassay kit (R & D Systems, USA) in Laboratory Research Unit of the Faculty of Medicine - Hasanuddin University Hospital.

Statistical analysis using SPSS 16 software with the following test methods: homogeneity between the two groups was compared (age, body mass index, surgical duration, estimated of bleeding was tested with independent t-test; gender and physical status were tested by chi-square). Dynamics of serum levels of cortisol and CRP from time to time in each group were tested with the Wilcoxon test. Rest pain intensity in both groups was tested with the Mann-Whitney U test. Comparison of opioid requirement, hemodynamic and respiratory changes in both groups was tested by independent t-test. Side effects that occurred were tested by Chi-Square test.

Result

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 two groups, the treatment group and the control group. Two groups research were based on the characteristics of age, body mass index, duration of surgery, the amount of bleeding and ASA Physical State showed the homogeneity of the two groups to be compared as shown in Table 1.

Changes in the plasma levels of C-reactive protein (CRP) during observation compare with preoperative value are shown in Table 2 with levels of CRP increased significantly at 24 hours postoperatively in both groups.

Dynamics of changes in cortisol levels in the treatment group showed an increase in cortisol upon completion of surgery and then decreased at 4 hours post-surgery, but not significant. Significant decline in cortisol levels occurred 24 hours after surgery. In the control group increased levels of cortisol found at immediately postoperative then decreased at 4 and 24 hours post-surgery, but these do not show a significant difference as shown in Table 3.

The intensity of the pain in rest in the two groups did not differ significantly except at observation 24 hours rest pain intensity were found to be lower in the treatment group as shown in Table 4.

Variables	Dexa Group (n=15)		Control Group(n=15)		
	Mean	SD	Mean	SD	P value
Age (yrs)	31.47	11.38	33.40	14.76	0.691
Body Mass Index (BMI)	21.57	2.96	22.58	2.71	0.337
Duration of surgery (min)	96.00	40.45	109.00	47.25	0.425
Estimated bleeding (ml) ^a	143.33	88.37	88.37	139.60	0.304
Gender (Male/Female) ^a	9/6	-	12/3	-	0.427
ASA Physical State (1/2) ^a	10/5	-	7/8	-	0.462

Data in mean and standard deviation with probability tested with *independent t-test*. ^aStatistic test with Chi square test. P value <0.05 were significant.

Table 1: Patient characteristics, duration of surgery and estimated bleeding.

Time measurement	Dexamethasone Group (n=15)				Control Group (n=15)			
	Min	Max	Median	P value	Min	Max	Median	P value
Preoperative	0.26	23.06	2.09	-	0.37	16.74	3.95	-
Immediately postoperative	0.20	17.98	2.28	0.925	0.23	17.51	4.39	0.775
4 hrs postoperative	0.24	23.56	3.67	0.650	0.39	61.00	1.48	1.000
24 hrs postoperative	0.25	43.54	14.91	0.015*	0.54	59.12	14.66	0.003*

Data in minimum, maximum and median (pg/ml). probability tested with Wilcoxon test. *P value <0.05 were significant compare with basal preoperative value

Table 2: Changes in the plasma concentration of C-Reactive Protein during observation compare with preoperative value.

Time measurement	Dexamethasone Group (n=15)				Control Group (n=15)			
	Min	Max	Median	P value	Min	Max	Median	P value
Preoperative	4.52	594.57	66.80	-	11.54	183.63	62.50	-
Immediately postoperative	9.99	230.64	73.52	0.910	10.47	269.87	73.52	0.281
4 hrs postoperative	7.65	220.63	35.03	0.691	2.63	255.47	71.52	0.955
24 hrs postoperative	4.73	129.30	22.06	0.020*	3.68	317.88	56.91	0.427

Data in minimum, maximum and and median (ng/mL)with probability tested with Wilcoxon test. * P value <0.05 were significant compare with basal preoperative value

Table 3: Changes in the plasma concentration of cortisol during observation compare with preoperative value.

Time observation	Dex Group (n=15)			Control Group (n=15)			P value
	Min	Max	Median	Min	Max	Median	
Preoperative	0	2	0	0	3	0	0.486
Immediately postoperative	0	2	0	0	2	0	0.609
4h postoperative	0	4	0	0	3	1	0.291
24h postoperative	0	1	0	0	2	0	0.032*

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

Table 4: Changes in rest pain intensity.

Time observation	Dexamethasone Group (n=15)		Control Group (n=15)		P value
	Mean	SD	Mean	SD	
4 hrs postoperative	3.73	1.42	4.30	1.42	0.379
24 hrs postoperative	1.07	1.53	3.20	2.21	0.005*
Total consumption	4.80	2.37	7.40	3.29	0.019*

Data in mean (mg) and standar deviation; probability (p value) test with *independent t-test*. *P value <0.05 were significant compare with other group.

Table 5: Morphine consumptions during observation.

Opioid morphine requirement until the 4 hours postoperative in both groups did not differ significantly, The treatment group requiring opioid morphine lower at 24 hours post-surgical than the control group as shown in Table 5.

Changes in systolic blood pressure value (SBP) in both groups at all-time observation showed no significant changes between the two groups. Most subjects experienced changes in systolic blood pressure within normal limits. Changes in diastolic blood pressure value (DBP) in both groups at all-time observation showed no significant changes between the two groups. Most subjects experienced changes in diastolic

blood pressure within normal limits. Changes in heart rate (HR) value in both groups at all-time observation showed no significant changes between the two groups. No difference in the change in the breathing frequency between study groups at all-time observation.

In the treatment group found that subjects experienced nausea, dizziness and vomiting each of the events, while the control group was found three subjects who experienced nausea. The incidence of adverse events between the two groups during the observation period was not significantly different.

Discussion

CRP is one of the acute phase protein levels will raise in the blood when there is inflammation. Sensitivity CRP more than 90% as an indicator of inflammation indicate that the inflammatory process in the subject of this research is undergoing surgery [12,13]. At 4 hours post-surgery have not found a significant increase in serum levels of CRP in this study due to the secretion of CRP increased within 6 hours of the acute inflammatory stimulus and an increase of at least 2-fold at 8 hours after surgery and will continue to increase to peak after 48 hours [14]. Levels of C-reactive protein increased significantly at 24 hours postoperatively in both groups in accordance with previous studies that showed a significant increase at 24 hours in surgery hysterectomy and increased CRP levels in the first 24 hours patients who underwent thoracotomy with analgesia surgery NSAIDs flurbiprofen [15,16].

Once a tissue injury, stimuli neurogenic acts on the hypothalamus and secretion of the target organs or provoke changes in the neuroendocrine response. The amendment called the stress response to injury characterized by increased secretion of catabolic hormones (cortisol, glucagon, GH, catecholamines) and inhibition of anabolic mediators, especially insulin and testosterone. The secretion of cortisol from the adrenal cortex increased rapidly after surgery as a result of stimulation of ACTH (adrenocorticotrophic hormone) and depending on the severity of the trauma pembedahan and inflammation and may be influenced by drugs analgesia and anesthesia [17,18].

Serum levels of cortisol in both study groups showed a tendency to an increase in the immediate postoperative and then decreased until 24 hours after surgery. However, the treatment group found decreased from time to time observation, especially on the 24 hour postoperative basal cortisol values before surgery. Cortisol values after surgery may increase 4-6 times within 4-6 hours after surgery but in subject with dexamethasone found decreased levels of serum cortisol [18].

Dexamethasone is a synthetic glucocorticoid hormone that can prevent and suppress pro-inflammatory mediators when administered in pharmacological doses that would reduce the neuroendocrine response that leads to a decrease in the secretion of cortisol by the adrenal cells. Dexamethasone inhibits the accumulation of macrophages and neutrophils at sites of inflammation and lead to inhibition of the production of inflammatory mediators, especially prostaglandin [17,19]. Glucocorticoids dose preoperative Metilprednisolone will reduce pain, hyperthermia, IL-6 and PGE response led to an emphasis on inflammatory and will reduce the activation of the HPA axis response [20].

Research Mahdi et al, 2002 shows by using Diclofenac show no significant differences in serum cortisol levels within 24 hours after surgery, which means that the effect of a decrease in cortisol levels in the administration of dexamethasone is not only associated with anti-inflammatory effects by inhibiting the formation of prostaglandins such as the possession of NSAIDs but there are other mechanisms affecting decreased cortisol levels, such as a direct effect of dexamethasone on the formation of the pro-inflammatory cytokines, especially IL-6 [21,22].

Decrease cortisol concentrations in the provision due to the presence of dexamethasone as a glucocorticoid in circulation which can lead to negative feedback on the HPA axis, although the mechanism of negative feedback is usually ineffective occurred on postoperative conditions due to the magnitude of immune stimuli that can trigger the release of cortisol [18]. Decreased serum cortisol levels showed reduced stress response due to surgery and some studies suggest that the reduction in the stress response will improve the prognosis of

postoperative including reduced nociception such as inhibition of activity of the enzyme cyclooxygenase [22-24].

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 rest NRS at the all-time of observation. The difference in pain intensity value of the two groups only in the intensity of pain at rest at 24 hours postoperative were lower in the group receiving dexamethasone but pain intensity in both groups were still classified as mild pain intensity. No difference in the pain intensity both groups due in accordance with the principles of Patient Controlled Analgesia 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 was mild pain intensity in postoperative patients.

A difference that may occur is 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 hours 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 hours post-surgery-although not statistically significant and a reduction about 35% of the total opioid requirements in 24 hours 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 sparing* about 10% of the morphine dose equivalent (MDE) at 2 hours post-surgery, and 13% on the needs of morphine in 24 hours after surgery [11].

Doses above 0.1 mg / kg 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 non-opioid analgesic that has opioid- sparing effect with good evidence-based [24-26]. In gynecological surgery reported the use of preoperative doses above 0.1 mg/kg dexamethasone resulted in decreased opioid requirements and improved recovery [27].

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 [28-30]. Those changes will reduce the formation of impulses in the transduction process that will be delivered to the dorsal horn in 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 HPA axis and suppress hypothalamic and pituitary hormone production as corticotrophin and finally cortisol released by adrenal [19,31,32].

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 [28,32].

No significance hemodynamic and respiratory changes in all time observation in both groups were found which showed that pain and neuroendocrine responses did not cause cardiovascular and respiratory complications. It is seen from the value of the pain intensity in both groups were not much different and most are mild pain intensity.

Activation of the sympathetic nervous system by the hypothalamus will result in an increase of catecholamines by the adrenal medulla and Norepinephrine on presynaptic nerve endings which some will go into circulation. Increased sympathetic activity is causing cardiovascular effects that can include hypertension and tachycardia; and may also have an effect on visceral organs and the gastrointestinal [17]. This does not happen in both groups showing that not too dominant sympathetic activity occurs on the subject of this study.

Activation of the sympathetic autonomic system by nociceptive stimuli determined by the balance of inflammation that causes the transmission of nociception through spin reticular tract to the central nervous system that will activate the central noradrenergic mechanisms in Locus Coeruleus (LC) [28]. In addition, the activity of LC is also influenced by the presence of Corticotrophin Releasing Hormone [33]. The central adrenergic activity will stimulate the sympathetic response adrenal release of catecholamine's (Epinephrine and Norepinephrine) into circulation which will work in the target organ as an increase heart rate, breathing and other organs [28]. Effects on target organs such as the heart and breathing is not found in this study in the group receiving both anti-inflammatory and that only get paracetamol and morphine which may indicate a lack of nociceptive transmission and adrenergic response on the subject of this study. A meta-analysis reported a protective effect of low-dose corticosteroids as effective as higher doses in cardiac surgery to reduce the risk of cardiac and respiratory complications [34].

Patient controlled analgesia allows the patient to maintain analgesia in mild intensity that they can tolerate will cause pain intensity did not differ between the two groups and enables to prevent changes in the respiratory and cardiovascular systems. Significant hemodynamic and respiratory responses such as hypertension, tachycardia and increase respiration rate will usually occur in the moderate to severe pain intensity.

Although the side effects that occurred between the two study groups was not statistically significant, but in the control group was found 3 incidences of nausea from 15 samples (20%) while in the group with dexamethasone only found one occurrence (6.63%). This is related to the effect of dexamethasone which reduces the incidence of postoperative nausea and vomiting (PONV) and has been widely used in clinical use [35,36]. Many of the mechanisms associated with the anti PONV effects of dexamethasone as reducing the activity of 5-HT (hydroxyl-tryptophan) by reducing precursor tryptophan which acts on vomiting center stimulation in the nervous system; reduced serotonin products in the intestinal tract. What's interesting is the anti-emetic activity of dexamethasone are the presence of antagonism prostaglandins effect and the ability to stimulate the release of endorphine, an endogenous analgesia [35,37].

In conclusion, the addition of single dose dexamethasone 8 mg preoperatively to the combination of paracetamol and morphine did not abolish inflammation process but decrease cortisol response after surgery at the 24 hour after surgery. The addition of dexamethasone provides sufficient analgesia which reduces opioid requirements and did not affect the cardiorespiratory system with minimal side effects.

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