International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

The Differences in Level of Interleukin 6 in Lower Limb Orthopedic Surgery with General Anesthesia Technique Compared with Regional Anesthesia Combined Spinal Epidural Block Technique

M. Wiryana[1], K. Sinardja[2], G.Budiarta[3], Tjokorda G.A. Senapathi[4], I.M.G.Widnyana[5], Dennis Prakas[6]

[1]Professor, Department of Anesthesiology and Intensive Care, Udayana University, Sanglah General Hospital, Denpasar, Bali Indonesia

[2]Senior Lecturer, Department of Anesthesiology and Intensive Care, Udayana University, Sanglah General Hospital, Denpasar, Bali Indonesia

[3-5] Lecturer, Department of Anesthesiology and Intensive Care, Udayana University, Sanglah General Hospital, Denpasar, Bali Indonesia

[6]Resident, Department of Anesthesiology and Intensive Care, Udayana University, Sanglah General Hospital, Denpasar, Bali Indonesia

Abstract: ***Background: Trauma and surgery caused tissues damage and these will trigger local and systemic inflammation as a defense mechanism and adaptation to injury. Assessment the level of interleukin 6(IL-6) as an acute phase cytokine is expected to be used as a marker of inflammation caused by the surgery.Anesthesia technique also attenuatesthe inflammatory response. Objective: to find a best anesthesia technique to minimize the inflammatory response in patient with lower limb bone's fracture undergoing orthopedic surgery in Operating Theater of Sanglah General Hospital, Denpasar, Bali.Methods:This is anobservational study, the observation conducted from August to October 2016 in Operating Theatre of Sanglah Hospital. The study involved 28 patients who eligible with a total population sampling technique. Divided into 2 groups; 14 patients received general anesthesia (GA) and 14 patients received regional anesthesia combined spinal epidural block(RA) for the surgery. IL-6 is obtained from peripheral blood before anesthesia conducted and 24 hours after the surgery. Results:Patients received RA had a lower level of IL-6 compared to patients received GA 24 hours after surgery. Conclusion:Regional anesthesia combined spinal epidural block has a better effect of reducing inflammatory response caused by surgery compared to general anesthesia.***

Keywords: Cytokine, IL-6, Inflammatory Response, General Anesthesia, Regional Anesthesia.

1. Introduction

Surgery caused tissues damage in varying degrees. This led to the local and systemic inflammatory response as the body's defense mechanism and adaptation. Systemic inflammatory respose occurs when tissue damage cannot be solved by local response.

Systemic inflammatory response caused by surgery, commonly known as the stress response. In this condition, a series of changes in humoral responses, immune, haematological and autonomic (sympathetic nervous system stimulation) in an effort to minimize damage body tissue.

Anesthesia technique also affects the inflammatory response. Some studies suggest that anesthesia can depress the inflammatory response function in varying degrees. General anesthesia cause malfunctioning of lymphocyte cells, suppression of natural killer cells (NK cells) and increasing concentrations of pro-inflammatory cytokines. It is able to worsen the inflammatory process in major surgery.

Several studies suggest there is a correlation between the pro-inflammatory cytokine responses with postoperative complications. The release of cytokines trigger an inflammatory response that causes a variety of complications such as postoperative ileus, ischemia-reperfusion syndrome, hypercoagulable syndrome (deep venous thrombosis) and postoperative pain.

The aim of this study isdetermine the inhibitory effects of general anesthesia technique(GA) compared to regional anesthesia (RA) on interkeukin 6(IL-6) level in patients undergoing lower limb orthopedic surgery. Assessment of cardiac output with.

2. Methods

This study is an observational analitic study usingpre- and post test. Various data used in this study was gathered from patients who will undergone lower limb orthopedic surgery.The study took place in the Operating Theatreand Clinical Pathology laboratorium of SanglahGeneral Hospital from August to October 2016, with the inclusion criteria: (1) Patients who are planned to undergone lower limb orthopedic surgery (2) Patients with ASA classification class I and II, (3) aged 18-65 years. Exclusion criteria included: (1) The patient's family that refused to participate in the study, (2) Patients who have problems or diseases of the liver, (3) Patients who had an antiinflamatory drug before surgery.Drop out criteria included: (1) Duration of surgery more than 4 hours (2) Class 3 bleeding with

Sampling was done by using a total population sample. The peripheral blood sample of eligiblepatients would be taken before anesthesia and surgery commenced, and 24 hours after the surgery. All the blood sample would be centrifuged, and the plasma divided into 2 eppendorf tube, freezed until the number of the samples are sufficient. After the samples are sufficient, the IL-6 level are measured by Enzyme-linked immunosorbent assay(ELISA) technique. Normality data test was the Shapiro-Wilk,Homogenity of the data was Lavene's test. Furthermore, the IL-6 level was analyzed by Mann-Whitney test. Analysis of data using Strata program SS 12.1.

3. Results

There were32 egible patients, 17 under GA group and 15 under RA; 2 samples from GA and 1 sample from RA group were excluded during the surgery because of class 3 bleeding and unstable hemodynamic. Sampling was done after obtaining informed consent from the patient and patient's family.Descriptive statistical analysis conducted on the characteristics of the study subjects, including age, gender, BMI, and ASA class. The characteristic feature of the study subjects are shown in Table 1.

Table 1: The Sample Characteristic

Variable	*Description*	*Group*		*P Value*
		RA(n=14)	GA(n=14)	
Age	Mean (SD)	41,1 (15,6)	34,4 (14,3)	0,243
Gender	Male, n(%)	7 (50%)	9 (64,3)	0,445
	Female, n(%)	7 (50%)	5 (35,7)	
BMI	Mean (SD)	24,3 (2,9)	23 (3,7)	0,309
ASA class	ASA I, n(%)	8 (57,1%)	6 (42,9)	0,445
	ASA II, n(%)	6 (42,9%)	8 (57,1)	

Variable of age and BMI were done by t-test; Gender and ASA class by chi square

From t-testThe mean age of RA group 41,1 years (SD± 15,6 years), GA group 34,4 (SD ±14,3 years); p value 0,243;The mean of BMI was 24,3 kg/m^2 (SD ± 2,9 kg/m^2), p value 0,309. From chi square test for male gender in RA group 7(50%), female 7(50%); male in GA group 9(64,3%); female 5(35,7%) with p value 0,445. ASA class I in RA group is 8(57,1%) ASA class II 6(42,9%). IN GA group; ASA class I is 6(42,9%), ASA class II is 8(57,1%). P value is 0,445. With Mann-Whitney test shows a normal distribution of the samples.

Table 2: The difference level of IL-6 between 2 groups

Variable	*Description*	*Group*		*P Value*
		RA n=14	GA n=14	
Increased level of IL-6, 24 hours after surgery	Median (IQR) 44,3	5,2	19,2	0,069

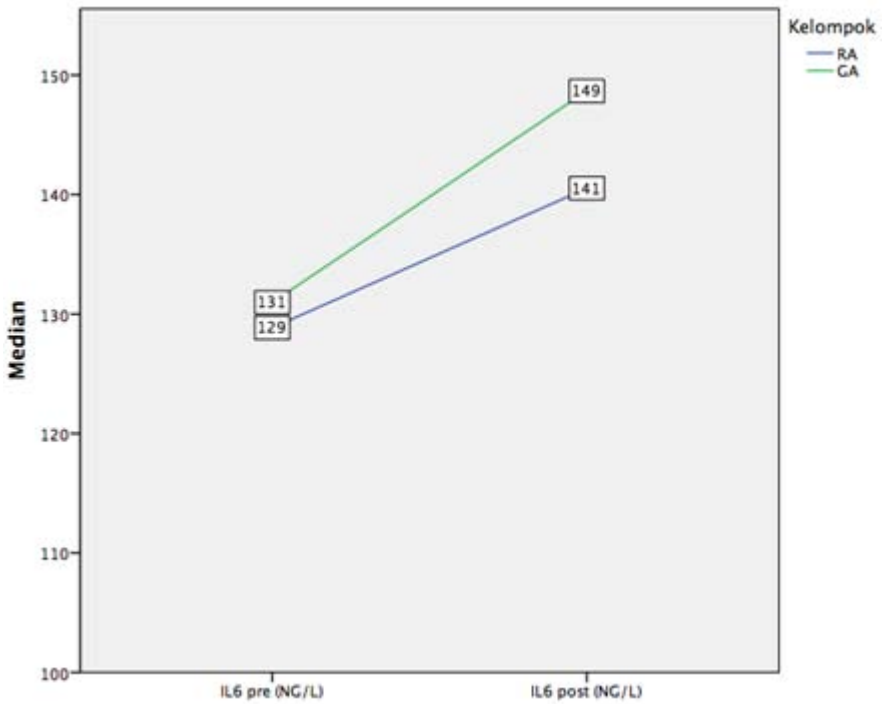

Figure 1: Increased level of IL-6 before and 24 hours after surgery between 2 groups

From the Mann-Whitney test of level IL-6 with p value less than 0.069 (moderate evidence)

4. Discussion

Surgical trauma produces alterations in the hemodynamic, metabolic, and immune responses of patients in the postoperative period. Like most physiological responses, the injury response is a dynamic process that follows a specific pattern that has been defined based on clinical and scientific observations.

General anesthesia has an impact on the stress response to surgery. Regional anesthesia show a better suppression of the stress response compared to general anesthesia. Neurohumoral pathway inhibition by administering a local anesthetic provide better benefits in reducing perioperative

inflammatory response, as part of the suppression of the stress response to surgery.

Bone fracture is an injury that will cause inflammatory response. The body's response to fracture of the bone is divided into three phase.

1st phase is inflammatory phase, will be a peak in 24 hours after injury. In this phase, the complex cascade of proinflammatory signaling and growth factor will be released into circulation including IL-1,IL-6,IL-11,IL-18, TNF- are significantly elevated within the first few days.These signals recruit inflammatory cells and promote angiogenesis. Platelets are activated by injury to blood vessels at the fracture site, and release transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor. Osteoprogenitor cells at the fracture site express bone morphogenetic proteins. These factors, along with inflammatory mediators, recruit mesenchymal stem cells and then guide their differentiation and proliferation.

2nd phase is the renewal phase. At the periphery of the fracture site, stem cells differentiate into osteoblasts. As a result, bone forms via intramembranous ossification 7–10 days after injury. Chondrogenesis occurs in the bulk of the injured tissue, which is mechanically less stable. Inflammatory mediators are absent during this phase. TGF-β2 and -β3, bone morphogenetic proteins, and other molecular signals induce endochondral bone formation in the cartilaginous callus.The cartilage calcifies, and then is replaced with woven bone.

The last phase is remodelling. Osteoprogenitor cells differentiate into osteoblasts, which express IL-1, IL-6, and IL-11, and other factors that promote osteoclast formation. The renewing and resorptive actions of these two cell types replace the initial woven bone with lamellar bone. This remodeling phase is regulated by several proinflammatory signals. In addition to IL-1, IL-6, and IL-11, elevated levels of TNF-α, IL-12, and interferon-γ (IFN-γ) are also detectable at the fracture site. Rodent and porcine models indicate that growth hormone and parathyroid hormone also play key roles in this phase, speeding healing and strengthening the fracture callus. Although the original structure and mechanical properties of the skeleton are restored within several weeks of fracture, molecular and cellular signaling can take up to several years to return to its normal state. In human patients, hormones regulating bone metabolism remain at elevated levels for up to 1 year after hip fracture. Bone turnover is significantly accelerated in humans for at least 6 months following bone fracture, and does not return to baseline for several years. For bone remodelling to be sucessful, an adequate blood supply and a gradual increase in mechanical stability is crucial.

IL-6 is a multifunctional lymphokine, expressed by various cells after many stimuli and underlies complex regulatory control. It has a role to regulate immune response, acute phase reaction and hematopoiesis. This substance stimulate liver to produce acute phare phase protein and increasing neutrofil production, IL-6 also help B cell proliferation and maturation to produce immunoglobulin.

IL-6 level also can be used to predict severity of injury,and a marker to predict post operative sepsis after major surgery.

5. Conclusion

This study shows that regional anesthesia combined spinal epidural technique has a superior effect of reducing inflammatory response compared to general anesthesia by supressing level of IL-6, median (IQR) 44,3 in RA increased 5,2 compared to RA increased 19,2 with p value 0,069. There is an advantage of performing regional anesthesia by suppresing level of IL-6, will also reduce postoperative pain and fever.

References

[1] James E. Heavner., Local anesthetics. Current Opinion in Anaesthesiology,2007; 20:336-342
[2] Watkins LR, Maier SF, Goehler LE. Immune activation:the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995;63:289-302
[3] Choileain N, Redmond HP., Cell response to surgery. Arch Surg,2006;141:1132-40
[4] Desborough J.P., The stress response to trauma and surgery. Br J Anaesth,2000;85:109-17
[5] Prentice W.E., Principles of athletic training: a competency-based approach.5e.New York: McGraw-Hill.2014.266 p.
[6] Paschalla M,Antonios G. Modulation of the inflammatory response for enhanced bone tissue regeneration. Tissue Eng Part B Rev. 2008;14(2): 179-186
[7] Carano RA, Filvaroff EH. Angiogenesis and bone repair. Drug Discovery Today. 2003;8(21):980–9.
[8] Gebhard F., Pfetsch H, Steinbach G., Strecker W., Kinzi L., Bruckner UB., Is interleukin 6 an early marker of injury severity following major trauma in humans?. Arch Surg. 2000;135(3):291-5
[9] Mokard D, Merlin M, Sannini A, Brun JP, Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth, 2005 Jun; 94(6): 767-73
[10] Olfat A.I Amin, Hosam E.,The effect of general or spinal anaesthesia on pro-and anti-inflammatory intracellular cytokines in patients undergoing appendicectomy using flowmetric method. Egyptian journal of Anesthesia. April 2011, vol 27(2): 121-125
[11] Chachkhiani I, Gurlich R, Maruna P, Frasko R, Lindner J., The postoperative stress response and its reflection in cytokine network and leptin plasma levels. Physiol. Res. 2005;54:279-285
[12] Feldmann, jeremy S,. Proinflammatory cytokines in cytokine and cellular immunology division, london, doi:10.1006/rwrc.2000.02004
[13] Hollmann MW, Strumper D, Durieux ME. The poor man's epidural: systemic local anesthetics for improving postoperative outcomes. Med Hypothesis. 2004;63(3):386-9
[14] Jawa RS, Anillo S, Huntoon K, Baumann H.,Interleukin 6 in surgery, trauma and critical care part II:clinical

implication. J Intensive care med. 2011 Mar-Apr;26(2):73-87
[15] Kehlet H, Holte K., Effect of postoperative analgesia on surgical outcome. Br J Anaesth 2001;87:62-72
[16] Kress M., Nociceptor sensitization by proinflammatory cytokines and chemokines. The open pain journal,2010;3:97-107
[17] Lisowska B, Maldyk P, Konty E, Michalak C, Postoperative evaluation of plasma interleukin-6 concentration in patients after total hip artroplasty. Ortop Traumatol Rehabil. 2006 Oct 31;8(5):547-54
[18] Sfeir C. Ho L. Doll B.A. Azari K. Hollinger J.O. Fracture repair. In: Lieberman J.R., editor; Friedlaender G.E., editor. Bone Regeneration and Repair. Totowa, NJ: Humana Press; 2005. pp. 21–44.