ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Effectiveness of Intravenous Subanesthetic Dose of Ketamine on the Subarachnoid Block to Attenuate Inflammation Response in Transurethral Resection of the Prostate Surgeries

Tjokorda Gde Agung Senapathi*, Made Wiryana, I Gusti Agung Gede Utara Hartawan, Christopher Ryalino, Adinda Putra Pradhana, Prajnaariayi Prawira Kurnia

Department of Anesthesiology and Intensive Care Faculty of Medicine, Udayana University.

***Corresponding Author: Tjokorda Gde Agung Senapathi**

Abstract

Background: Perioperative anesthesia and surgery can induce a stress response in the body. Regional anesthesia with local anesthetic drugs in the transurethral Resection of the Prostate (TUR-P), has been proven to minimize inflammation. Patients and Methods: Forty-eight patients of ASA I-II, scheduled for TUR-P with spinal subarachnoid anesthesia were randomly divided into two groups, group A with ketamine and group B without ketamine. The blood level of interleukin (IL)-10, IL-8, C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and IL-10/IL-8 ratio were measured in both groups at 1 hour before operation, also at 1 and 24 hours after operation. Results: Blood level of IL-10 ($p<0.001$) and IL-10/IL-8 Ratio ($p<0.05$) were significantly different with higher values on group A. Other parameters were not found to be different. Conclusion: Subanesthetic dose of ketamine on spinal subarachnoid anesthesia technique done for TUR-P operation was found able to control inflammation and prevent the deterioration of immune system perioperatively.

Keywords: *IL-10, IL-8, CRP, NLR, Benign prostatic hyperplasia.*

Introduction

Surgery and anesthesia can induce a stress response in the human body [1]. Surgery stress response will induce inflammation reaction, starting from tissue damage caused by surgery incisions. Anesthesia, especially general anesthesia, may worsen stress response [1, 2] Overwhelmed inflammation will suppress the immunology function, which can alter the patient's condition after surgery and cause many postoperative complications. Deterioration of immune system can happen via disturbance inside the immune system itself or via immune suppression from overactivity of hypothalamus-pituitary-adrenal (HPA) axis and sympathetic nervous system [2].Inflammation response has a dual function, as a protector from infectious agents or tumor cells, and to rebuilt body tissue after traumatic injury or surgical injury [3]. Disturbance of the inflammation process will make the body more prone to infection, induce growth and metastatic process of tumor cell, and alter postoperative healing process that can lead to infection, sepsis, multiple organ dysfunction, and even death [4].Inflammation is conducted via the release of cytokines from immune cells [2]. These cytokines can act as a pro-inflammatory or anti-inflammatory mediator. Cytokines are heterogenous protein which is produced from the body, like lymphokine, monokine, interleukin (IL), and interferon (IFN). Cytokine works at the surface receptor of the cell, to regulate cell's growth, evolution, and regeneration [2].Cytokine is the bridge between immune dan inflammation systems [2]. Pro-inflammatory cytokines are IL-1α, IL-1ß, IL-6, IL-8, and tumor necrosis Factor-α (TNF-α). Anti-inflammatory cytokines are IL-2, IL-4, IL-10, and IFN-γ. The balance between them is a vital factor in the acute phase of immune-inflammation reaction following surgical and anesthesia stress response [2, 5].

Anesthesiologist's role is to minimize the inflammation process during the perioperative period to maintain the function of the immune system [5, 6].Patients will easily be exposed to any stress like hemodynamic disturbance, massive bleeding, blood transfusion, hyperglycemia, hypoglycemia, hypothermia, and pain. The contradiction part is that anesthesia agents can also cause the suppression of immune system directly by causing disturbance in the function of immune cells or indirectly by up-regulation of the inflammatory reaction [5].Regional anesthesia has been proven to be able to suppress the inflammation process perioperatively [9].Local anesthetic agents like lidocaine and bupivacaine, given with regional anesthesia technique, have other effects than blocking the sodium channel. The dose of local anesthetic agents to achieve this anti-inflammation function is smaller than the analgesic dose [9].Inflammation response, which is caused by inflammation cells like polymorphonuclear (PMN) cells, can be controlled by local anesthetic agents.

These side effects, including thrombosis and endothelial blood vessel wall breakdown, caused by overactivity of PMN cells can be prevented [10].Ketamine, an anesthesia agent that functions as an antagonist of the N-methyl-D-aspartate (NMDA) receptor, has been frequently used synergically with opiate agents in post operation pain management [11].The dose of the opiate agents during this perioperative period will be reduced [11].Ketamine also works to reduce the inflammation process, by blocking the production of inflammatory cells and proinflammatory cytokines, and by up-regulating the metabolism of pro-inflammatory mediator [11].In vivo, subanesthetic dose of ketamine results in significant reduction of proinflammatory cytokines production like TNF-α, IL-8, and IL-6 [12, 14].

Subanesthetic dose of ketamine (0,125-0,75 mg/kg body weight) can reduce inflammation postoperatively [13].Benign Prostatic Hyperplasia is a condition of the proliferation of the prostate cells that is induced by chronic inflammation [15].This process started at the age of 40 years old. Inflammatory mediators like neutrophils, endothelial, and histamine are accumulated inside the prostate gland. This phenomenon will enhance the growth and mitotic process of the prostate cells. The cause of this event is the release of proinflammatory cytokines, especially IL-8, IL-6, and TNF-α [15].The postoperative inflammation process in patients undergoing Transurethral Resection of the Prostate (TUR-P) operation is very high [15].This is happened because of cell injury caused by surgical incisions that are involved the use of electric current and heat force from the cauter tools, traction of the urine catheter, and postoperative pain. Postoperative pain can reach up to scale of 7 to 8 of the Visual Analog Scale (VAS), if not properly managed [15].Regional anesthesia and ketamine have an important role in suppression of the inflammation process postoperatively, so complications, like re-bleeding of the surgical wounds or spasm of the urethra canal, can be avoided [15, 16]. The aims of this research are to get the information about the effectiveness of intravenous subanesthetic dose of ketamine on subarachnoid spinal anesthesia technique to control inflammation response in TUR-P. TUR-P was chosen because of its minimally invasive nature and its short duration.

Patients and Method

This is a true experimental clinical trial with parallel double-blind randomization. The study was carried out at Sanglah General Hospital, Bali, Indonesia. Inclusion criteria include male patients aged 40-79 years old with ASA I-II physical status who underwent TUR-P with subarachnoid block. Patients were divided into two groups with double-blind randomization technique, group A who received ketamine 0, 15 mg/kg body weight, and group B who received placebo. Blood samples collected at 1 hour preoperative, 1 hour and 24 hours postoperative. Blood pressure and heart rate monitored and recorded every 5 minutes, starting from 5 minutes before spinal subarachnoid anesthesia until patients in the recovery room (RR).

Patients were given combination of fentanyl 0, 15 mcg/kg body weight/hour with ketamine 0,015 mg/kg body weight/hour continuously with a syringe pump and intravenous paracetamol 15 mg/kg body weight every 8 hours as postoperative analgesia. Patients admitted to the High Intensive Care Unit if the condition was stable in the RR, Bromage scores 1 or 0 at both lower extremities, and no sign of rebleeding. Inflammation mediators and hemodynamic parameters

were compared between the two groups. Data were analyzed with the Shapiro-Wilk test at α=0, 05. Independent t-test was used to compare the alteration of IL-10, IL-8, CRP, NLR, IL-10/IL-8 ratio, and hemodynamic parameters. All of the analyzing processes were carried out with SPSS 24.0.

Results

Group A and B both contained 24 patients. The youngest patient was 45 years old and the oldest was 79 years old. The characteristics of each group were presented in Table 1.

Table 1.1: Subject characteristic according to group treatment

Variable	Group		p
	A (Ketamine) (n=24)	B (Control) (n=24)	
Age(years), mean±SD	62.0±8.4	59.2±10.8	0.329
BMI (kg/m²), mean±SD	23.5±2.5	23.9±2.8	0.633
ASA physical status, n(%)			
1	7 (29.2)	6 (25.0)	0.745
2	17 (70.8)	18 (75.0)	
BPH grade, n(%)			
2	10 (41.7)	9 (37.5)	0.768
3	14 (58.3)	15 (62.5)	
Operation duration, mean±SD	58.3±10.5	55.8±6.2	0.321

A descriptive analysis of the characteristics spreading between two groups showed that distribution of both groups was the same with similar mean score. Statistic analysis also found that differentiation between the two groups was not significant (p >0.05).

Table 2: Comparison between preoperation and postoperation inflammatory mediator according to group treatment

Time	IL-10 (pg/mL)		P	IL-8 (pg/mL)		P	CRP (mg/L)		P	NLR		P	Ratio IL-10/IL-8		P
	A	B		A	B		A	B		A	B		A	B	
1H PreOp ± SD	13,1 ± 2,8	13,4 ± 2,8	0,722	36,2 ± 4,5	35,2 ± 3,2	0,371	2,7 ± 1,4	2,6 ± 1,2	0,949	2,9 ± 0,9	2,8 ± 0,9	0,807	0,36 ± 0,07	0,38 ± 0,08	0,390
1H PostOp ± SD	50,9 ± 4,5	46,2 ± 3,0	<0,001	48,0 ± 5,6	47,7 ± 5,1	0,853	5,5 ± 1,9	5,8 ± 2,1	0,604	5,3 ± 1,3	4,9 ± 1,5	0,351	1,07 ± 0,16	0,98 ± 0,10	0,014
24H PostOp ± SD	47,8 ± 4,3	43,3 ± 3,6	<0,001	43,9 ± 4,8	42,9 ± 4,3	0,438	3,5 ± 1,3	4,1 ± 1,8	0,222	4,1 ± 1,1	4,3 ± 1,4	0,589	1,10 ± 0,13	1,02 ± 0,11	0,027

A: group with ketamine subanesthetic
B: group without ketamine subanesthetic
H: hour

Analysis of both IL-10 and ratio of IL-10/IL-8 between the two groups showed significant difference statistically at 1 hour and 24 hours postoperative, where group A showed higher level of IL-10 (p<0,001) and ratio of IL-10/IL-8 (p <0.05). Both groups showed elevation of IL-10 level 1 hour postoperative and lowering of IL-10 level 24 hours postoperative but not up to the basal level. Other comparisons of inflammation mediators including IL-8, CRP, and NLR between the two groups did not show significant difference statistically at any time of measurement (p>0.05). Both groups showed elevation of IL-8, CRP, and NLR level 1 hour postoperative and lowering of IL-8, CRP, and NLR level 24 hour postoperative but not up to the basal level

Discussion

Interleukin-8 is a chemokine mainly produced by the macrophage cell. It was found in 1987. This cytokine has important role in the proinflammation process. IL-8 is the main mediator in chronic process of prostate cell inflammation, as seen in Benign Prostate Hyperplasia (BPH). IL-8 triggers growth and enlargement of prostate cell via accumulation of neutrophil cells [5, 6]. IL-10, known as human cytokine synthesis inhibitory factor (HCSIF), is an anti-inflammatory cytokine [5]. This cytokine was first founded in 1991. IL-10 also used in cancer therapy because of their activity on the metastatic process of cancer cells [5].C-Reactive Protein (CRP), an acute-phase protein, which is synthesized by the liver, holds an important role in inflammation cascade [6, 7].The production of CRP is initially begun by the release of IL-6 by the macrophage cells. Its physiologic function is to activate the complement system by binding with the lysophosphatidylcholine molecule at the surface of the dying or dead cells and a few species of bacteria. Activated complement system will elevate the phagocytic activity of macrophage cells in order to get rid of the dead cells and bacteria from the host body [6, 7].

Neutrophil-to-Lymphocyte Ratio (NLR) has been proven to be able to predict the prognosis of cardiovascular disease, infection, inflammation process, pain, and a few types of cancer (esophageal cancer, pancreas cancer) [8].This ratio is calculated by dividing the number of neutrophil cells with the number of lymphocyte cells from peripheral blood samples. A high score of NLR is usually correlated with worsen prognosis of cardiovascular, cancer, and infectious diseases [8].This study found statistically significant increase in IL-10 levels at 1 hour and 24 hours postoperative, where the ketamine group was higher than the placebo. Ketamine significantly reduces the production of proinflammatory cytokines without reducing the production of anti-inflammatory cytokines [17].

Ketamine suppresses macrophage cell's activities in producing IL-1, IL-6, IL-8, and TNF-α at situations where there are endotoxins or lipopolysaccharide membranes from bacteria [17]. Ketamine also induces apoptosis from proinflammatory cells. The effect of ketamine will not occur if there is no inflammatory stimulus so that ketamine is best given before the induction of anesthesia or before inflammatory stimulus from surgery incisions [17]. Ketamine will reduce the perioperative opiate's dose. This is beneficial because opiate can suppress the production of anti-inflammatory cytokines and increases the production of proinflammatory cytokines, which will trigger chronic pain mechanisms via central sensitization.

Ketamine inhibits glutamate receptors in the central nervous system and prevents chronic pain because glutamate is an excitatory neurotransmitter for pain impulses in the anterior dorsal horn of the spinal cord [13].This was similar to the results of studies by Amin OA and Salah HE in 2011, which found an increase in postoperative IL-10 levels [18]. This was also consistent with the theory put forward by Wiryana *et al*. in 2017 [13].The change in IL-10 levels automatically affected the value of the IL-10/IL-8 ratio at 1 hour and 24 hours postoperative. Ketamine group also found had a higher ratio than the placebo group. Higher anti-inflammatory cytokine to pro-inflammation ratio is expected to help patients to avoid excessive inflammatory reactions and postoperative complications [13]. Levels of proinflammatory parameters such as IL-8, CRP, and NLR did not show significant differences between the two groups. This showed that a subanesthetic dose of ketamine does not stimulate or elicit excessive perioperative systemic inflammatory responses, which can cause an increase in proinflammatory cytokines [19]. Ketamine inhibits the transcription of Activator Protein-1 and NF-κB from liver cells so that the production of proinflammatory mediators decrease. Ketamine also triggers apoptosis process of acute proinflammatory cytokine cells such as IL-6, IL-8, and TNF-α through intrinsic and extrinsic apoptotic pathways [19].Ketamine stimulates the formation of the protease caspase-8 and caspase-9 enzymes so that the process of apoptosis will start by breaking down of cell DNA chains [19].

Apoptosis from IL-6, IL-8, and TNF-α will decrease acute phase protein production, including CRP by the liver [19].Ketamine is also known to reduce inflammatory process by inhibiting COX-2 enzyme produced by the liver. This COX-2 enzyme plays a role in the inflammatory process through the prostaglandin cascade [19]. Prostaglandin plays a significant role in the process of delivering pain and vasodilation of blood vessels by affecting endothelial cells [19].Research by Zura, *et al*. and Luggya, *et al*. also found similar results [16].Hemodynamic parameters, which did not experience significant changes in this study, also showed that a subanesthetic dose of ketamine did not cause hemodynamic disturbance through activation of the sympathetic autonomic nervous system.

Activation of the sympathetic autonomic nervous system must be avoided because it can produce catabolic hormones such as the cortisol hormone, adrenocorticotropic hormone, which further can stimulate macrophage cells to produce more pro-inflammatory cytokines [20].Research by Ozkan *et al* [21].Found that hemodynamic stability was maintained by administering ketamine 1 mg/kg in patients undergoing TUR-P surgery with subarachnoid spinal anesthesia and 15 mg bupivacaine regimen. The study also raised data on side effects arising from administration of ketamine such as hallucinations, nystagmus, headaches, and nausea-vomiting. In this study there were no side effects of ketamine in all subjects who got it.

Conclusion

Intravenous subanesthetic dose of ketamine 0.15 mg/kg before subarachnoid spinal anesthesia in patients undergoing TUR-P surgery results in an increase in IL-10, an anti-inflammatory cytokines, and IL-10 / IL-8 ratio that is higher than placebo at 1 hour and 24 hours postoperatively.

The subanesthetic dose of ketamine did not show any difference in pro-inflammatory mediators values, which were IL-8, CRP, NLR, and hemodynamic profiles that were statistically significant than placebo.

Acknowledgment

The authors report no conflict of interest.

References

1. Iwasaki M, Edmondson M, Sakamoto A, et al (2015) Anesthesia, Surgical Stress, and Long-Term Outcome. Acta Anaesthesiologica Taiwanica, 53: 99-104.
2. Homburger JA, Meiler SE (2006) Anesthesia, Drugs, Immunity, and Long term Outcome. Current Opinion Anesthesiology, 19: 423-428.
3. Cruz FF, Rocco PRM, Pelosi P (2017) Anti-inflammatory Properties of Anesthetic Agents. Journal of Critical Care, 21: 67. doi: 10.1186/s13054-017-1645-x
4. Elenkov IJ, Chrousos GP (2002) Stress Hormones, Pro-inflammtory and Anti-inflammatory Cytokines, and Autoimmunity. Annual New York Academic Science, 966: 290-303. doi: 10.1111/j.1749-6632.2002.tb04229.x
5. Dinarello CA (1997) Pro-inflammatory and Anti-inflammatory Cytokines as Mediators in the Pathogenesis of Septic Shock. Chest, 112: 3215-3275.
6. Gandaglia G, Briganti A, Gontero P, et al (2013) The Role of Chronic Prostatic Inflammation in the Pathogenesis and Progression of Benign Prostatic Hyperplasia (BPH). BJU International, 112: 432-441. doi : 10.1111/cju.12118
7. Cole DS, Watts A, Scott-Coombes D, et al (2008) Clinical Utility of Perioperative C-Reactive Protein Testing in General Surgery. Annual College Surgery, 90(4):317-321.
8. Forget P, Khalifa C, et al (2017) What is the Normal Value of the Neutrophil-to-Lymphocyte Ratio? BioMed Central Research Notes; 10: 12. doi: 10.1186/s13104-016-2335-5
9. Kerbel I, Weiss M (2001) Anaesthetics and Immune Function. Current Opinion at Anesthesiology, 14: 685-691.
10. Procopio MA (2001) The In Vivo Effects of General and Epidural Anesthesia on Human Immune Function. Anesthesia Analgesic, 90: 460-465.
11. Cherry DA, Plummer JL, Gourlay GK, et al (1995) Ketamine as an Adjunct to Morphine in Treatment of Pain. Pain, 62: 119-121.
12. Welters ID, Hafer G, Menzebach A, et al (2010) Ketamine Inhibits Transcription Factors Activator Protein-1 and Nuclear Factor-Kappa B, Interleukin-8 Production, as well as CD11b and CD16 Expression: Studies in Human Leukocytes and Leukocytic Cell Lines. Anesthesia Analgesic, 110: 934-941. doi: 10.1213/ANE.0b013e3181c95cfa
13. Wiryana M, Sinardja IK, Budiarta IG, et al (2017) Low Dose Ketamine. Bali Journal of Anesthesiology, 1(1): 13-19
14. Roytblat L, Talmor D, Rachinsky M, et al (1998) Ketamine Attenuates TheInterleukin-6 Response After Cardiopulmary Bypass. Anesthesia Analgesic; 87: 266-271
15. Kramer G, Mitteregger D, Marberger M (2007) Is Benign Prostatic Hyperplasia (BPH) an Immune Inflammatory Disease? European Urology Journal, 51: 1202-1216.
16. Zura M, Kozmar A, Sakic K, et al (2012) Effect of Spinal and General Anesthesia on Serum Concentration of Pro-inflammatory and Anti-inflammatory Cytokines. Zagreb. Immunobiology, 217: 622-627.
17. Lisowska B, Szymanska M, Nowacka E, et al (2013) Anesthesiology and the Cytokine Network. Postepy High Medicine, 67: 761-769.
18. Amin OA, Salah HE (2011) The Effect of General or Spinal Anaesthesia on Pro and Anti-inflammatory Intracellular Cytokines in Patients Undergoing Appendicectomy Using Flowcytometric Method. Egyptian Journal of Anaesthesia, 27: 121-125.

19. Braun S, Gaza N, Werdehausen R, et al (2010) Ketamine Induces Apoptosis via the Mitochondrial Pathway in Human Lymphocytes and Neuronal Cells. British Journal of Anaesthesia, 105 (3): 347-354.

20. Beilin B, Rusabrov Y, Shapira Y, et al (2007) Low Dose Ketamine Affects Immune Responses in Human During The Early Postoperative Period. British Journal of Anesthesia, 4: 522-527. DOI: 10.1093/bja/aem218

21. Ozkan F, Kaya Z, Suren M (2011) The Effect of Intravenous Ketamine on Prevention of Hypotension during Spinal Anesthesia in Patients with Benign Prostatic Hyperplasia. Turkey. Nobel Medicus, 7(3): 82-88.

