ORIGINAL ARTICLE

Bali Journal of Anesthesiology (*BJOA*) 2018, Volume 2, Number 3: 51-55
E-ISSN: 2549-2276

Published by DiscoverSys

PERIOPERATIVE EFFECTS OF CO-ADMINISTRATION OF TCI PROPOFOL COMBINED WITH CLONIDINE AND KETAMINE

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ABSTRACT

Background: Propofol is often used in Total Intravenous Anesthesia (TIVA). Studies found that adding clonidine and ketamine can increase the potential to achieve an adequate level of anesthesia while reducing inflammation and post-operative pain. The goal of this study is to see if the combination of Target Controlled Infusion (TCI) propofol plus clonidine and ketamine is more effective in reducing the IL-6 level, maintaining intraoperative stability, and reducing postoperative pain and morphine consumption.

Methods: Forty patients planned for major oncology surgery were divided into two groups. The treatment group (Group T) received pre-medication with clonidine, induction with TCI propofol, and intraoperative ketamine. The control group (Group C) received normal saline solution.

Results: The difference of IL-6 level increase between the two groups was not statistically significant (13.6 vs. 16.6 pg/mL, $p>0.05$). Mean systolic blood pressure (SBP) and mean arterial pressure (MAP) in group T were higher in 5 and 10 minutes after incision, but lower in minutes 30, 60, and 120 ($p<0.05$). Heart rate in group T was higher in minutes 5, 10, 15, 30, 60, and 120. Visual analog scale (VAS) in 4, 8, 12, and 24 hours post-surgery were lower in group T compared to group C. And post-operative morphine consumptions in group T were also lower. (3.6 ± 1.5 vs 9.9 ± 3.3, $p<0.05$).

Conclusion: TIVA using TCI propofol combined with preoperative clonidine and intraoperative ketamine is effective in maintaining hemodynamic stability, reducing post-operative and reducing morphine consumption compared to TCI propofol alone.

Keywords: *total intravenous anesthesia, IL-6, hemodynamic stability, visual analog score, morphine consumption*

Cite This Article: Aryabiantara, I.W., Sinardja, I.K., Sutawan, I.B.K.J., Sinardja, C.D., Parami, P., Ryalino, C., Junaedi, M.D. 2018. PERIOPERATIVE EFFECTS OF CO-ADMINISTRATION OF TCI PROPOFOL COMBINED WITH CLONIDINE AND KETAMINE. *Bali Journal of Anesthesiology* 2(3): 51-55. DOI:10.15562/bjoa.v2i3.69

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BACKGROUND

The response of trauma caused by surgery includes changes in metabolic, endocrine, and immune systems. These changes are caused by afferent neuronal stimulus from the area of surgery, cytokines release from tissue damaged by trauma, and activation of cellular and humoral immune pathways.[1,2]

Both general and regional anesthesia help to suppress the stress response due to surgical trauma. This happens because anesthesia provides sympathetic and afferent nerve fibers block that modulate the pituitary-adrenocortical system.[2,3] Total intravenous anesthesia (TIVA) by giving propofol in combination with opioids, administrated by TCI (target controlled infusion), are currently popular in the practice of anesthesia.

Propofol is the most common drug used for TIVA. Some advantages of propofol are rapid onset and faster recovery time. The use of TIVA with TCI is expected to provide a more constant plasma concentration of the drug. To improve its ability to cause the triad of anesthesia, some studies use TCI propofol in combination with drugs that have the synergistic effect, like clonidine or ketamine.

Clonidine is an alpha-2 agonist often used as a premedication due to its various effects, like sedation, analgesia, sympatholytic, and may reduce the dose of volatile or intravenous anesthetics.[3,4] Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) antagonist that is used as an induction agent intravenously to maintain stable hemodynamics mainly due to the sympathomimetic effect. Administration of NMDA antagonist and opioid produce the synergistic or additive effect of analgesia.

The goal of this study is to see if the combination of TCI propofol plus clonidine and ketamine is more effective in reducing the IL-6 level, maintaining intraoperative stability, and reducing postoperative pain and morphine consumption.

PATIENTS AND METHODS

This is a double-blind, randomized, pre and post-test control group design. Randomization was designed by permuted blocks. Ethical clearance

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was given by the Research Ethics Committee of Udayana University and Sanglah General Hospital. All involved subjects have provided a written consent to be included in this study.

This study involved 40 patients with ASA physical status I and II, aged 16-65 years, who were planned for unilateral mastectomy, with surgery duration of more than two hours. Those with history of cardiac diseases, hemodynamic instability, chronic pain, and mental disturbance were excluded from this study. Subjects were randomly divided into two groups by permuted blocks. Treatment group (Group T) consists of 20 subjects who received intravenous anesthesia with TCI propofol combined with clonidine and ketamine, and control group (Group C) consists of a similar number of subjects who received intravenous anesthesia with TCI propofol with placebo (NaCl 0.9%). This study involves a third party so that the intervention received by the subjects are not known by both researchers and the research subjects.

After gaining blood sample for preoperative IL-6 level, subjects in Group T received premedication with clonidine 1 mcg/kg in NaCl 0.9% for 10 minutes. Subjects were then induced using propofol TCI plasma mode Schneider target of 4 mcg/ml. Before intubation, fentanyl 2 mcg/kg and atracurium 0.5 mg/kg were administrated. During surgery, continuous ketamine 10 mcg/kg/min was given via syringe pump, and propofol TCI concentration is set to maintain bispectral index (BIS) value of 50-60. IL-6 blood test was again conducted 24 hours after the surgery.

Management of postoperative pain using patient-controlled analgesia (PCA) morphine (demand dose of 1 mg, lockout interval at 4 minutes, and the maximum dose for 4 hours is set at 10 mg). The consumption of PCA and pain assessment were measured every 4 hours using VAS (visual analog scale). IL-6 level tests were examined using enzyme-linked immunosorbent assay (ELISA).

As in C group, all treatments were similar to T group, except for the administration of pre-operative clonidine and intra-operative ketamine. No dropouts were found in this study. Statistical analysis was calculated using SPSS 16.0 for Windows.

RESULTS

Subject characteristics are shown in Table 1. There are no differences in the characteristics of age, body mass index (BMI), and physical status ASA in both groups. The mean age in group T and C were 46.5 and 46.8 years, respectively. The mean BMI was 22.3 kg/m^2 in group T and 22.5 kg/m^2 in group C.

Increased levels of IL-6 is calculated based on the difference in the levels of IL-6 post and preoperatively. The difference of IL-6 level increase between the two groups was not statistically significant.

Systolic blood pressure (SBP), mean arterial pressure (MAP), and heart rate (HR) in both groups were measured at 5 minutes after incision, and then recorded again at minutes 15, 30, 60, and 120. Data is displayed in the mean ± standard deviation (SD) at each measurement time in Table 3, Table 4, and Table 5.

Table 1 Characteristics of study subjects by treatment group

Characteristics	Treatment Group		p-value
	Group T (n = 20)	Group C (n = 20)	
Age (years)	46.5 ± 9.0	46.8 ± 10.7	0.937
BMI (kg/m^2)	22.3 ± 1.9	22.5 ± 2.2	0.726
ASA*			
I	10 (50%)	9 (45%)	0.100
II	10 (50%)	11 (55%)	

*ASA = American Society of Anesthesiology physical status

Table 2 Comparison of IL-6 by treatment group (pg/mL)

Characteristic	Treatment Group		p-value
	Group T (n = 20)	Group C (n = 20)	
Preoperative IL-6	18.0 (2.0-99.8)	23,1 (11.3-64.3)	0.387[a]
Postoperative IL-6	36.6 (10.4-119.4)	38.6 (12.7-193.6)	0.310[a]
Increase of IL-6	13.6 (0.2-57.0)	16.6 (0.3-173.9)	0.588[a]

Data shown in mean ± SD or median (minimum-maximum), [a]Mann-Whitney U test

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Table 3 Comparison of SBP at each measurement time by treatment group

Characteristic	Groups		Mean Difference	CI95	p-value of
	Group T (n = 20)	Group C (n = 20)			
5 minutes	117.7 ± 13.6	116.9 ± 19.1	0.7	11.4 - 9.8	<0.001[a]
15 minutes	118.7 ± 13.6	115.7 ± 17.9	3	13.2 - 7.2	<0.001[a]
30 minutes	115.7 ± 15.6	125.5 ± 18 , 3	9.8	1.1 - 20.7	<0.001[a]
60 minutes	117.0 ± 12.9	125.3 ± 13.3	8.3	0.13 - 16.7	<0.001[a]
120 minutes	117.3 ± 13.5	118.8 ± 13.8	1.5	7.3 - 10.2	<0.001[a]

CI 95% = 95% confidence interval, [a]unpaired t test

Table 4 Comparison of MAP at each measurement time by treatment group

Characteristic	Groups		Mean Difference	CI95	p-value
	Group T (n = 20)	Group C (n = 20)			
5 minutes	84.6 ± 9.3	87.9 ± 10.7	3.3	3.1 to 9.7	<0.001[a]
15 minutes	to 87.6 ± 13.5	to 87.8 ± 13.3	0.1	8.5 to 8.6	<0.001[a]
30 minutes	to 86.5 ± 11.3	95.3 ± 15 , 2	8.8	0.2 to 17 , 3	<0.001[a]
60 minutes	87.7 ± 9.9	93.5 ±to 10.2	5.8	0.6 to 12.2	<0.001[a]
120 minutes	to 86.9 ± 10.0	89.4± 10.7	2.5	4.1 to 9.1	<0.001[a]

CI95% = 95% confidence interval, [a]unpaired t test

Table 5 Comparison of HR at each measurement time by treatment group

Characteristic	Groups		Mean Difference	CI95	p-value
	Group T (n = 20)	Group C (n = 20)			
5 minutes	74.5 ± 11.4	72.0 ± 12.3	2.4	10.0 to 5.1	<0.001[a]
15 minutes	75.9 ± 9.5	72.3 12.6	3.5	10.7 to 3.6	<0.001[a]
30 minutes	75.4 ± 8.9	72, 3 ± 10.6	3.1	9 3 to 3.1	<0.001[a]
60 minutes	73.5 ± 9.6	72.8 ± 9.6	0.6	6.8 to 5.5	<0.001[a]
120 minutes	72.0 ± 11.5	70.4 ± 8.6	1.6	8.1 to 4.9	<0.001[a]

CI 95% = 95% confidence interval, [a]unpaired t test

Table 6 Comparison of VAS (in cm) at each measurement time by treatment group

Hours after surgery	Treatment Group		Mean Difference	95% CI	p-value
	Group T (n = 20)	Group C (n = 20)			
4 hours	2.5 ± 0.9	4.5 ± 1.0	1.9	1.3 to 2.6	<0.001[a]
8 hours	2.3 ± 0.9	3.9 ± 0.7	1.6	1.1 to 2.2	<0.001[a]
12 hours	1.6 ± 0.6	3.2 ± 0.9	1.5	1.0 to 2, 0	<0.001[a]
24 hours	1.3 ± 0.4	1.9 ± 0.6	0.6	0.3 to 1.0	<0.001[a]

CI95 = 95% confidence interval, [a]unpaired t test

Postoperative pain was measured using VAS on the 4th, 8th, 12th, and 24th hours postoperative. Data related to VAS in our study is displayed in mean±SD as seen in Table 6. Total consumption of morphine in both treatment groups was calculated based on the total consumption of morphine recorded by PCA. Data is presented in the form of mean±SD in Table 7.

Table 7 Comparison of total morphine consumption by treatment group

Characteristic	Groups		p-value
	Group T (n = 20)	Group C (n = 20)	
Total consumption of morphine (mg)	3.6 ± 1.5	9.9 ± 3.3	<0.001[b]

[b]Mann-Whitney U test

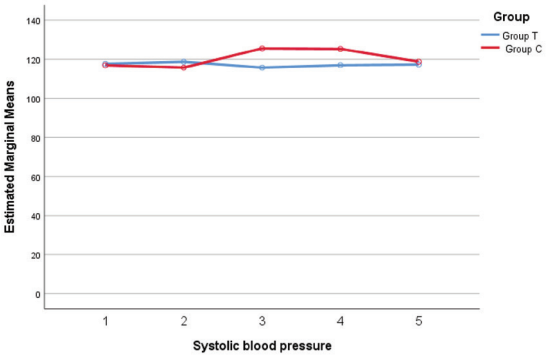

Figure 1 Comparison of mean SBP at each measurement time by treatment group

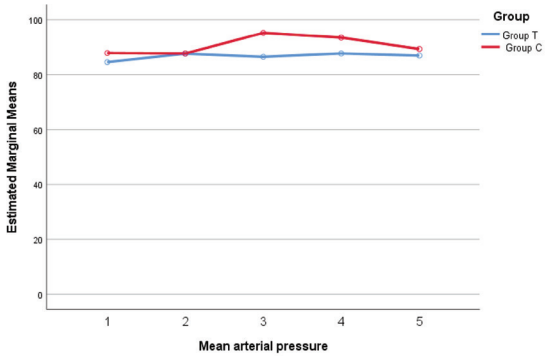

Figure 2 Comparison of the mean MAP at each measurement time by treatment group

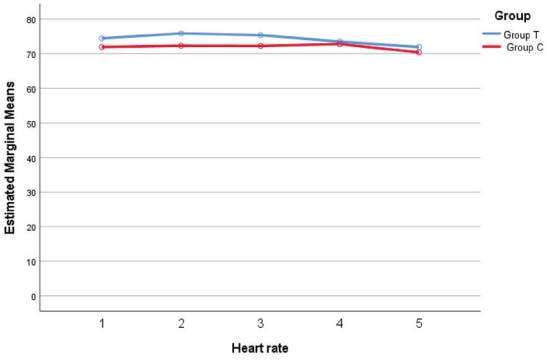

Figure 3 Comparison of mean heart rate at each measurement time by treatment group

DISCUSSION

Effects of anesthesia on cytokines will vary depending on the drug used and patient's response. Anesthesia with propofol may inhibit and reduce the effects of pro-inflammatory cytokines IL-6 compared to volatile inhalational agents. Ketamine is said to increase the production of IL-6.

Clonidine is a selective partial alpha-2 agonist previously used as antihypertensive drugs to lower the sympathetic response of the central nervous system (CNS). Other known effects of clonidine include sedation, analgesia, antianxiety, reducing the anesthetic dose, and providing perioperative hemodynamic stability. While ketamine has sympathomimetic effects like increased blood pressure, heart rate, cardiac contractility, cardiac output and systemic vascular resistance. Clonidine and ketamine have inversely proportional different effects. By combining both drugs, we can expect effects of sedation, analgesia, and hemodynamic stability.

In this study, levels of IL-6 did not differ significantly (p >0.05) between the two groups. Propofol has been found to inhibit IL-6 production.[5] While clonidine reduces central nervous system sympathetic activity, which in turn reduce the neuroendocrine stress response that arises through activation of the autonomic nervous system. In general, the effects of ketamine itself is different with propofol and clonidine which is a sympathomimetic and the effect can increase the production of IL-6.[6]

We also compared changes in SBP, MAP, and HR at each set time of measurement. One effect of clonidine is hemodynamic stability and can be achieved in this study. By lowering the intraoperative sympathetic response, clonidine can retain SBP, MAP, and HR without too many changes.

Clonidine at supra-spinal level affects the nucleus in the brainstem, activating the alpha-2 postsynaptic adrenoreceptor and activating noradrenergic imidazole bond in the lateral reticular nucleus resulting in a reduction in sympathetic tone. In the peripheral level, it affects the presynaptic alpha-2 adrenoreceptor reducing the release of norepinephrine in the sympathetic nerve terminals, causing dilation of blood vessels and reduces the chronotropic effect on the heart. These supra-spinal and peripheral effects are contrary to the effects of peripheral vasoconstriction due to direct stimulation of the receptor alpha-2 and alpha-1 of clonidine.[6,7]

Ketamine is an intravenous anesthetic drug that can increase blood pressure, heart rate, cardiac contractility, cardiac output and systemic vascular

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resistance. It is an indirect effect due to increased central sympathetic tone and increased central catecholamine from the adrenal medulla.

The increase in SBP in adults who received the clinical dose of ketamine ranging from 20-40 mmHg, with a slight increase in diastolic blood pressure. Systemic blood pressure usually rises progressively during the first 3-5 minutes after intravenous injection of ketamine, then declined over the next 10-90 minutes.[8]

The combined effect of clonidine and ketamine are expected to results in the balance of effects that decrease sympathetic of clonidine and ketamine that stimulates the sympathetic response.

All subjects received post-operative analgesia using PCA morphine with PCA dose of 1 mg, lock-out intervals of 6 minutes, and the maximum dose of 10 mg/4 hours. VAS scores were statistically different at each measurement time ($p < 0.05$).

Clonidine as an alpha-2 agonist has an analgesic effect. Clonidine regulates peripheral anti-nociceptive, supra-spinal, and especially spinal cord mechanisms that include alpha-2 receptor activation from descending postsynaptic noradrenergic, cholinergic neurons and the release of nitric oxide pathways.[9]

Intravenous clonidine can penetrate the brain's nerve cell so that it can provide analgesia with local neuroaxial and supra-spinal. Analgesia at Peripheral level occurs by way of debilitating pain nerve stimulation of A delta and C fibers and blocks conduction through increased potassium conductance.[9] If administered intravenously, slow elimination will occur within 2 to 24 hours. VAS scores were lower in the combination propofol TCI could occur due to the effects of clonidine.

Ketamine is a non-competitive NMDA receptor antagonist with a strong analgesic effect. For sedation and analgesia, ketamine administered at a sub-anesthetic dose of 0.2 to 0.75 mg/kg intravenous continuous infusion of 5-20 mcg/kg/min, intramuscular 2-4 mg/kg. Analgesia by ketamine achieved in plasma concentrations of 100-150 pg/ml.[7] This dose is sufficient to achieve plasma concentrations of 100-150 ng/ml. Ketamine dose of 50 µg/kg did not provide sufficient analgesia, but enough to make the drowsiness. These plasma concentrations can be achieved by continuous infusion at a dose of 3-4 µg/ kg/min after the initial bolus and 14 µg/kg/min without an initial dose.[10]

The combination of clonidine and ketamine has a synergistic effect in postoperative analgesia so VAS score in the group T receiving both drugs was lower. Morphine consumption is calculated by looking at the total consumption of morphine recorded in the PCA machine. The mean consumption of morphine per 24-hour on group T is 3.6±1.5 mg, which is lower compared with the placebo group (9.9 ± 3.3 mg) and statistically significant ($p < 0.05$). These results are consistent with postoperative VAS score between the two groups.

CONCLUSION

TIVA using TCI propofol combined with preoperative clonidine and intraoperative ketamine is effective in maintaining hemodynamic stability, reducing post-operative, and reducing morphine consumption compared to TCI propofol alone. However, this study did not prove that it can also suppress pro-inflammatory cytokines IL-6 level.

ACKNOWLEDGEMENT

Nothing to declare.

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