Journal of Biology and Today's World
ISSN 2322-3308
http://www.journalbio.com

Received: 23 October 2014 • Accepted: 03 December 2014

Research

doi:10.15412/J.JBTW.01040103

Effects of Isoflurane and Propofol on Serum Immunoglobulins in off-pump Coronary Artery Bypass Graft Patients

Mohammad Hasan Abdollahi[1], Azade Boostani[2*], Seyyed Omid Mahdavi[3], Habibollah Hosseini[1], Seyed Hossein Hekmatimoghaddam[4], Ali Akbar Rahimianfar[5]

[1] Department of Anesthesiology, Yazd Cardiovascular Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Anesthesiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of oral and maxillofacial medicine, Faculty of Dentistry, Islamic Azad University, Shiraz, Iran
[4] Department of Laboratory Science, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5] Department of Critical Care Nursing, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

*correspondence should be addressed to Azade Boostani, Department of Anesthesiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; Tell: +989171772134; Fax: +9835335231421; Email: azade.boostani@gmail.com.

ABSTRACT

Both anesthesia and major surgeries may affect the immune system, especially the cell-mediated immune responses, but also the humoral immunity. Our goal was to assess the effect of propofol and isoflurane on the serum concentration of immunoglobulins G, M, A and E in patients undergoing off-pump coronary artery bypass graft (CABG) surgery. This study was a double-blinded randomized clinical trial. Sixty patients were randomly divided into two equal groups receiving either isoflurane or propofol as the inhaled anesthetic agent during operation. Other parts of the medical conditions, anesthesia and surgery were quite similar in two groups. Baseline serum immunoglobulins G, M, A and E in both groups were measured by enzyme immunoassay one day prior to and four days after the surgery. Data were analyzed by the SPSS ver. 15 (SPSS, USA) using t-test, paired t-test and chi-square test. The mean serum IgG (p=0.378), IgM (p=0.593), IgA (p=0.095) and IgE (p=0.404) did not differ significantly between the isoflurane group and propofol group before the surgery. Serum immunoglobulins were significantly decreased after the surgery. However, the means of IgG (p=0.452), IgM (p=0.239), IgA (p=0.153) and IgE (p=0.482) did not show any significant difference between the two groups. In patients who undergo off-pump CABG surgery, both isoflurane and propofol cause decrease in serum IgG, IgM, IgA and IgE; however, there is no significant difference between them regarding the amount of this fall.

Key words: Isoflurane, Propofol, Immunoglobulin, CABG, Anesthesia

1. INTRODUCTION

Anesthesia and major surgeries affect the response and equilibrium of immune system, particularly cell-mediated immunity (1). Impairment of immune processes subsequent to surgical operations may lead to deficiencies in healing, increased disposition to infection, malfunction of organs, increased risk of malignancies, and increase in metastasis. Furthermore, general anesthesia may result in a defect in inflammatory response, which is effective either directly by malfunction of immune system or indirectly through induction of stress responses (2). Some immunologic modifications stemming from the stress of surgery that may appear in body affect even the final result of surgery. On the other hand, the impact of anesthetic agents on immune system response causes cognitive problems of combined effects of surgery and anesthesia on operation final result (3). Catecholamines that are released in response to surgery and anesthesia stimulations, result in increase in Th2 lymphocytes as well as decrease in Th1 lymphocytes, and thus lead to a fall in Th1/Th2 ratio and suppression of immune system as a consequence (4). On the other hand, some studies have reported that anesthesia with isoflurane results in more catecholamine accumulation in serum in comparison with propofol (5, 6). Thus, considering the type of anesthetic agent and anesthesia method is essential in predicting the outcome of surgical operation. Most of the previous studies on these two anesthetic agents had focused on their effect on innate immune cells, cellular immunity or cytokines, but limited research has been carried out on the effect of those agents on the rate of immunoglobulins. The complement system and plasma

immunoglobulins are significant factors in provision and maintenance of body immune status (7). We intended to analyze and evaluate the effects of propofol and isoflurane on immunoglobulins G, M, A, and E (as the markers of humoral immune status) in off-pump coronary artery bypass graft (CABG) surgery patients.

2. MATERIALS AND METHODS

This double-blinded randomized clinical trial was carried out on 60 patients (z_1-α/2=1.96, z_1-β=0.842, δ=3.5, d=1.26,) (equation 1)

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 \times \sigma^2}{d^2} \quad (1)$$

After the patients' consent to the surgery and taking approval by the Ethics Committee of Shahid Sadoughi University of Medical Sciences in Yazd, Iran. Inclusion criteria were the age ≥50 years, and indication for off-pump CABG surgery. Totally 60 patients were enrolled in the study through simple random sampling. Any patient who had allergy to drug, consumed any immune system suppressor drug, showed chronic inflammatory diseases, had any current infection or ejection fraction<30% was excluded. Patients holding the conditions to be included in the study were divided to two groups (n=30) as isoflurane group and propofol group through double-blinded random allocation. They received premedication consisting of morphine 0.1 mg/kg and promethazine 0.5 mg/kg intramuscularly 30 minutes prior to operation. In the operation room, the patients were monitored by electrocardiography, pulse oximetry, capnography and invasive arterial monitoring devices. To evaluate the depth of anesthesia (preserved at the range of 40-50), CSM (Cerebral State Monitor, model CSM- 2 Danmeter A/S Kildemosevej 13-DK 50000 dense C, Denmark) was utilized. Anesthetic induction of all patients was carried out by an identical method. To manitain anesthesia, isoflurane Mac=1-1.2% was used in group isoflurane, while the other group received propofol 100-200 µg/kg. Intubation was done, and ventilation was adjusted to 35-40 mmHg for end tidal CO_2. Heparin 150 IU/kg was adminstered before the first anastomosis for activated clotting time (ACT) to be kept at range of 250-350 s, which reached to 150-170 s after anastomosis with prothamine. The surgical technique was identical for all patients, and all anastomoses were implemented by intracoronary shunt. For each patient a demographic inquiry was filled out. Moreover, the baseline concentration of serum immunoglobulins G, M, A and E of both groups was recorded one day before operation and also on the fourth day after operation. Serum IgE level was determined by enzyme-linked immunosorbent assay (ELISA) method, while other immunoglobulines were measured by immunoturbidimetric assay using autoanalyzer (model BT 3000). Data were analyzed by the software SPSS ver.15 using t-test, paired t-test, and chi-square test.

3. RESULTS AND DISCUSSION

The mean±SD age of patients in the isoflurane group was 55±4.06 years and in the propofol group it was 55.27±4.25 years. In each group, 16 men and 14 women were existed (p=0.805). There was no significant difference between the mean serum concentrations of IgG (p=0.378), IgM (p=0.593), IgA (p=0.095) and IgE (p=0.404) before the operation between isoflurane group and propofol group.

When comparing mean serum IgG before and after the operation in propofol group (p=0.001) and isoflurane group (p=0.001) it showed a significant difference in both, which reflects the effect of isoflurane and propofol on IgG reduction; however, there was no significant difference between the two groups for IgG after the operation (p=0.578) (Table 1).

Table 1. Mean serum IgG (mg/dL) before and after CABG between groups

Drug	Time						P value*
	Before surgery		After surgery		Difference		
	mean	SD	mean	SD	mean	SD	
Isoflurane	1462.47	621.86	1013.23	460.72	449.23	352.27	0.001
Propofol	1345.5	364.69	939.87	263.22	405.63	240.25	0.001
P value**	0.378		0.452		0.578		

*: Paired t-test; **: t-test

Comparison of mean serum IgM in isoflurane group before (91.10±28.02 mg/dL) and after (69.73±22.45 mg/dL) surgery showed a significant decrease due to the procedure (p=0.001); also, in propofol group before (97.40±57.69 mg/dL) and after (80.80±45.67 mg/dL) the operation there was a significant fall (p=0.001). However, the mean serum IgM after the operation did not show any significant difference comparing the two groups (p=0.239), which indicates that anesthetic agent type has no role in the above-mentioned change (Table 2).

Table 2. Mean serum IgM (mg/dL) before and after CABG between groups

Drug	Time						P value*
	Before surgery		After surgery		Difference		
	Mean	SD	Mean	SD	Mean	SD	
Isoflurane	90.1	28.02	69.73	22.45	21.36	11.03	0.001
Propofol	97.4	57.69	80.8	45.67	16.6	22.49	0.001
P value**	0.592		0.239		0.302		

*: Paired t-test; **: t-test

Mean concentration of IgA before and after the surgery showed that they decreased in two groups and there is a significant difference in both groups (p=0.001), although the mean serum IgA between the two groups did not show any significant difference after the surgery (p=0.153) (Table 3).

Table 3. Mean serum IgA (mg/dL) before and after CABG between groups

Drug	Time						P value*
	Before surgery		After surgery		Difference		
	mean	SD	mean	SD	mean	SD	
Isoflurane	311.27	158.93	246.7	144.5	64.56	38.82	0.001
Propofol	264.63	106.84	201.6	90.93	63.03	53.73	0.001
P value**	0.095		0.153		0.9		

*: Paired t-test; **: t-test

Mean concentration of IgE before and after the operation in isoflurane group showed a significant difference (p=0.001) quite similar to that of the propofol group (p=0.001) which represents the effect of isoflurane and propofol on IgE decrease. Again, mean IgE had no significant difference before and after the operation (p=0.482) (Table 4).

Table 4. Mean serum IgE (micg/L) before and after CABG between groups

Drug	Time						P value*
	Before surgery		After surgery		Difference		
	mean	SD	mean	SD	mean	SD	

Isoflurane	260.83	193.87	245.07	178.18	15.77	30.57	0.001
Propofol	220.73	175.09	212.73	175.33	8	40.59	0.001
P value**	0.404		0.482		0.407		

*: Paired t-test; **: t-test

All of above show the effect of anesthetic agents on reduction of serum immunoglobulins but the type of drug has no effect on the change in serum concentration of immunoglobulins. The present study was carried out on 60 off-pump CABG surgery candidate patients to identify variations in serum immunoglobulins after anesthesia with isoflurane and propofol. It was found that in each group, mean rate of immunoglobulins G, M, A and E has significantly decreased four days after the operation, which implies the probable effect of anesthetic agents on reduction of those immunoglobulins. In comparison of the two groups, although the immunoglobulins variation rate in the isoflurane group was greater than the propofol group, but it was not statistically significant. According to the reference interval of serum immunoglobulins which are IgG=700-2100, IgM=50-370, IgA=85-490, and IgE<200 mg/dL (based on the commercial ELISA kits), it should be mentioned that in our study, despite decreased in circulating immunoglobulins in the fourth day after operation, it is still within normal range; i.e., it does not mean a reduction in humoral immune system, and can not be referred to as hypogammaglobulinemia. A study by Pirsttikangas on the effect of anesthesia by propofol and isoflurane on immune response of hysterectomy patients showed that anesthesia with isoflurane leads to more increase in catecholamines in serum (6) and stimulation of sympathetic system can result in degradation of immune system activity (4). These results are in line with the results of our study on immunoglobulines reduction subsequent to anesthesia with isoflurane and propofol. Kjell showed in a research that there is a relationship between surgical operations and variations in secretion of some cytokines (8). Also, Inada et al performed a study on the effect of propofol and isoflurane on immune response in surgeries, and showed that surgery causes partial immune system suppression (9). It suggests that serum immunoglobulin reduction subsequent to coronary artery surgery may be due to the stress emerged from surgery itself rather than the above-mentioned anesthetic agents. Lahteenmaki et al. showed in a research that non-immunologic oral mucosal defence becomes modified after major surgeries but immunoglobulin response remains. Both anesthetic methods led to decrease in salivary flow (10). The reduction in serum IgG in that study is consistent with our study, but IgM and IgA rates were decreased in our study which was not seen intheir research. Suzanne et al. compared the effects of isoflurane and propofol in CABG surgeries. Their aim was evaluation of TLR-4 monocytes expression as well as cytokine release in both patients' groups. They showed that the number of leukcyets and TLR-4 monocytes as well as cytokines IL-10, IL-8, IL-6, and TNF-α release had no significant difference between both groups ($p>0.05$) (11). Also, in that research, the impact of both anesthetic agents on cellular immune modifications was identical, which is in line with our study results. Inada et al. studied the effect of propofol and isoflurane on immune response in craniotomy surgery. Their study showed that the ratio of Th1/Th2 lymphocytes was significantly decreased subsequent to applying anesthetic agent isoflurane, while steadiness in that ratio was seen following anesthesia with propofol (9). In our study the modifications were greater during applyication of isoflurane for anesthesia, but there was no significant difference between isoflurane and propofol statistically.

Yu et al. evaluated the effect of propofol and isoflurane on cytokine response during tongue cancer surgery. Their study results showed that IL-6 and IL-10 (as markers of cellular immunity function) were significantlly increased in both groups immediately after operation and also at 1 and 2 days after operation compared to pre-operative time, but this increase was greater in the propofol group vs. the isoflurane group . Their results reflect the status of cellular immunity but we studied the humoral immunity (12). Mahmoud et al studied the immunomodulatory effects of isoflurane and propofol in thoracic surgery, and concluded that isoflurane reduces the inflammatory response relevant to one-way ventilation during thoracic operations using propofol, which is not in agreement with our study (13). To summarize, the findings of study imply that although the decremental effect of isoflurane on serum immunogobulines was greater than propofol one, but the difference was not statistically significant.

4. CONCLUSION

The study found that in patients who underwent off-pump CABG surgery and Isoflurane and propofol were used for maintenance of anesthesia, The immunoglobulins M, G, E, A was reduced in the postoperative in two groups. Although the change in the isoflurane group more than the propofol group, but this difference was not statistically significant.

ACKNOWLEDGMENT

No mentioned any acknowledgment by authors.

AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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