Effects of Propofol and Midazolam Infusions on Serum Lipid and Glucose Levels in Hyperlipidemic Patients Undergoing Coronary Artery Bypass Surgery

Koroner Arter Baypas Ameliyatı Geçiren Hiperlipidemili Hastalarda Propofol ve Midazolam İnfüzyonlarının Serum Lipidleri ve Glukoz Düzeyleri Üzerine Etkileri

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Geliş Tarihi/*Received:* 13.01.2014
Kabul Tarihi/*Accepted:* 13.03.2014

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doi: 10.5336/medsci.2014-38844

ABSTRACT Objective: Propofol has been accused for increasing plasma lipid levels during continuous infusion due to its lipid content. We aimed to show the effect and the risk of propofol infusion on plasma lipid and glucose levels in patients with hyperlipidemia undergoing coronary artery bypass graft surgery (CABG), and to compare them with a midazolam used control group. **Material and Methods:** In this randomized controlled study, 15 patients in the propofol group had anesthesia induction with intravenous propofol 1%, 2 mg/kg, fentanyl 10-15 mcg/kg, pancuronium 0.1 mg/kg, and the anesthesia was maintained with 1% 2-5 mg/kg/h propofol infusion, fentanyl 5-10 mcg/kg/hr, and an hourly pancuronium dose of 0.03 mg/kg The anesthetia management of 15 patients in midazolam group included induction with midazolam 0.1 mg/kg, fentanyl 10-15 mcg/kg, pancuronium 0.1 mg/kg, and infusion of midazolam 0.05-0.07 mg/kg/hr, fentanyl 5-10 mcg/kg/hr, and an hourly pancuronium dose of 0.03 mg/kg Plasma lipid [total cholesterol (CHL), triglyceride (TRG), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL)] and glucose concentrations were measured in both groups perioperatively, at seven different time points until 72 hours after the operation. **Results:** The decreases of TRG and HDL levels were statistically significant in the midazolam group. There were no significant differences for the decreases in CHL, LDL and VLDL levels between the groups. In both groups, plasma glucose levels increased significantly, independent from the propofol and midazolam infusions. **Conclusion:** We observed that propofol and midazolam anesthesia used in patients with hyperlipidemia undergoing to CABG did not have any effect on plasma lipid or glucose levels.

Key Words: Propofol; midazolam; hyperlipidemia, familial combined; lipids; glucose

ÖZET Amaç: Lipid içeriğinden dolayı propofol, devamlı infüzyonu süresince plazma lipid düzeylerini arttırmakla suçlanmıştır. Koroner arter baypas greft cerrahisi (KABG) geçirecek hiperlipidemili hastalarda propofol infüzyonun plazma lipid ve glukoz düzeyleri üzerine etkisi ve riskinin, midazolam kontrol grubu ile karşılaştırılarak çalışılması amaçlandı. **Gereç ve Yöntemler:** Bu randomize kontrollü çalışmada, propofol grubunda 15 hastaya anestezi indüksiyonunda: %1 propofol 2 mg/kg intravenöz, fentanil 10-15 mcg/kg, pankuronium 0,1 mg/kg, ve anestezi devamında: %1 propofol 2-5 mg/kg/sa, fentanil 5-10 mcg/kg/sa infüzyonları, ve pankuronium 0,03 mg/kg/sa kullanıldı. Midazolam grubunda 15 hastaya indüksiyonda: Midazolam 0.1 mg/kg, fentanil 10-15 mcg/kg, pankuronium 0,1 mg/kg, ve anestezi devamında: midazolam 0,05-0,07 mg/kg/sa, fentanil 5-10 mcg/kg/sa infüzyonları, pankuronium 0,03 mg/kg/ sa kullanıldı. Plazma lipidleri [total serum kolesterolü (KOL), trigliserid (TRG), yüksek dansiteli lipoprotein (HDL), düşük dansiteli lipoprotein (LDL), çok düşük dansiteli lipoprotein (VLDL)] ve glukoz seviyeleri her iki grupda perioperatif olarak, postoperatif 72. saate kadar 7 dönem halinde izlendi. **Bulgular:** TRG ve HDL düzeylerindeki düşüşler, midazolam grubunda istatistiksel olarak anlamlı bulundu. CHL, LDL, VLDL düzeylerinde görülen düşüşler bakımından gruplararası anlamlı fark bulunmadı. Plazma glukoz düzeylerinde her iki grupta midazolam ve propofol infüzyonlarından bağımsız olarak anlamlı artışlar gözlemlendi. **Sonuç:** KABG ameliyatı olacak hiperlipidemili hastalarda kullanılan propofol veya midazolam anestezisinin, plazma lipidleri ve glukoz değerleri üzerinde etkili olmadığı gözlemlendi.

Anahtar Kelimeler: Propofol; midazolam; hiperlipidemi, ailesel kombine; lipidler; glukoz

Turkiye Klinikleri J Med Sci 2014;34(2):267-72

Propofol infusion during maintenance of cardiac anesthesia has been presented as a safe alternative therapy in patients with good ventricular function due to a short recovery time.[1-4] Since the formulation of propofol is composed of egg-lecithin emulsions containing 0.1 mg/ml soybean oil, continuous infusion is thought to increase serum lipid levels, and particularly triglyceride levels.[2,3,5,6]

In coronary artery bypass graft (CABG) surgery, perioperative myocardial ischemia and myocardial infarction has been associated with higher morbidity and mortality.[7] The rise of free lipid acids in blood has a potential risk to increase the myocardial ischemic damage, and may cause arrythmias.[8,9]

Several studies have investigated the effect of 1% propofol infusion during cardiac surgery on blood lipid and glucose levels in patients with normal lipid levels.[10,11]

In this study, we compared the effects and the risks of propofol and midazolam infusions on serum lipids and glucose levels in patients with hyperlipidemia undergoing elective CABG surgery.

MATERIAL AND METHODS

ETHICS

The Regional Committee for Medical Research Ethics of Siyami Ersek Heart Surgery Hospital reviewed the study, and the Ethics Committee approved the study since human subjects were involved. Ethical and humans rights were complied with. Written permissions were obtained from all patients. Researchers informed all participants that they would hold all information confidential, and their information would only be used for scientific purposes. Patients were assured that their participation was voluntary, and they could withdraw from the study at any time, without incurring any penalty.

DESIGN AND SETTING

This research was designed as a prospective, randomized clinical study, and was carried out in Siyami Ersek Heart Surgery Hospital (400 beds) in İstanbul, Turkey.

SELECTION AND DESCRIPTION OF PARTICIPANTS

Thirty patients undergoing CABG, had an American Society of Anaesthesiologists (ASA) status 3, an ejection fraction (EF) of 40% and higher, between the ages of 41 and 76 years, without any history of diabetes mellitus, alcoholism or liver disease, and had high blood lipid levels (triglyceride > 160 mg/dl and/or total cholesterol > 220 mg/dl) were enrolled in the study.

PROCEDURE

Group P (n=15): The induction of anesthesia was made with propofol (P) (2 mg/kg), fentanyl (10 mcg/kg), and pancuronium (0.1 mg/kg). For the maintenance of anesthesia, P (2 mg/kg/h), fentanyl (10 mcg/kg/h) IV infusion, and pancuronium (0.03 mg/kg/h, IV) were administered.

Group M (n =15): Induction of anesthesia was made with midazolam (M) (0.1 mg/kg), fentanyl (10 mcg/kg), and pancuronium (0.1 mg/kg). For the maintenance of anesthesia, M (0.05 mg/kg/h), fentanyl (10 mcg/kg/h) IV infusion, and pancuronium (0.03 mg/kg/h) IV were used. All patients were given 10 mg diazepam peroral, the night before the operation. Approximately 30-45 minutes prior to surgery, all patients were pre-medicated with M (0.05 mg/kg) and atropine (05 mg) via intramuscular (IM) administration.

Upon entering the operating room, patients were monitored with chest lead V5 and D2 standard lead (Lohmeier M2 11). A digital pulse oximeter probe (Nellcor N-180) was used to monitor arterial oxygen saturation (SpO2). Venous and radial artery catheterizations were performed using 16 gauge (G) and 20 G cannula, respectively. Internal jugular vein was cannulated to provide central vascular access.

After sufficient anesthesia depth and muscle relaxation had been achieved, patients were intubated with an endotracheal tube which was connected to the volume respirator.

Following completion of the surgical intervention, anesthetic drugs were discontinued, and the patient was transferred into the postoperative intensive care unit (PICU), still intubated. Electro-

cardiography electrodes were placed and connected to the monitor for the follow-up of D2-V5 leads (Lohmeier M211). A digital pulse oximeter probe was placed to monitor SpO2. Systemic arterial and central venous pressures were followed up through hemodynamic monitoring. Patients were connected to the mechanical ventilator (SERVO-600) in the synchronized intermittent mandatory ventilation (SIMV) mode, and values were gradually lowered. Patients were then extubated. Patients did not receive M or P during the postoperative period.

Cardiopulmonary bypass (CPB) was used in all patients. Cold blood cardioplegia was delivered. The patients were cooled to 32˚C (hypothermic CPB). Systemic heparinization was introduced at the dose range of 300-400 IU to keep the activated clotting time (ACT) at the range of 400-500 seconds.

DATA COLLECTION

Relavant preoperative information of the patient was gathered by researcher nurse. In addition, chemistry profiles for preanaesthesia care according to the American Society of Perianaesthesia Nurses (ASPAN) standards of nursing practice were obtained.[12,13]

In each group, arterial blood samples were obtained to measure the concentrations of serum lipids [triglyceride (TRG), total cholesterol (CHL), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL)] (mg/dl) and plasma glucose (GLU) (mg/dl). Blood samples were drawn by the researcher nurse under the supervision of primary investigator at the time settings of T1 (before induction of anesthesia), T2 (before CPB), T3 (at the end of CPB), T4 (2 hours after CPB), T5 (4 hours after operation), T6 (24 hours after operation), T7 (72 hours after operation).

STATISTICAL ANALYSIS

Descriptive statistics (mean, standard deviation) were used to summarize the data. Two-way ANOVA for repeated measures was used to examine differences between the two groups. Mauchly's test of sphericity was significant for all parameters, and therefore multivariate tests were used with consideration of Wilks' lambda. Paired t-tests were used for parameters when there was a significant interaction between trial group and time. The Bonferroni corrected paired t-test was used to examine paired comparisons within groups. Bonferroni corrected t-test was used to examine differences between the groups. In multivariate comparisons between groups, the baseline (PI-control value) were taken into account for the baseline biological values. Independent samples t test was used for patient characteristics, and Chi square Fisher's Exact test was used for the gender parameter. Statistical significance was set at two tailed $p< 0.05$.

RESULTS

We did not find any statistically significant difference for age, weight, height, body mass index (BMI), aortic cross clamp (ACC) and CPB time between two groups ($p>0.05$) (Table 1). We did not obsorve any myocardial ischemic attack in any of the groups.

When TRG levels were compared in both groups, it was seen that TRG levels decreased starting from T1 to T2-T7 ($p<0.05$). The decreases at T2, T3 and T6 in Group M were statistically significantly different when compared to Group P ($p<0.05$) (Table 2) (Figure 1).

There was no significant difference between the groups for total CHL levels. Within the group, the level at T1 showed a significant decrease when

TABLE 1: Patient characteristics.

	Group P (n=15)	Group M (n=15)	Two tailed significance
Male/Female	12/3	10/5	0.681¶
	Group P (mean±SD)	**Group M (mean±SD)**	
Age (year)	58.46±10.72	54.20±9.45	0.258§
Height (cm)	169.93±7.73	155.73±38.76	0.175§
Weight (kg)	80.66±15.13	87.93±32.25	0.435§
BMI (kg/m^2)	28.06±5.68	31.31±13.08	0.384§
Duration of surgery (min)	246.00±42.72	260.00±24.49	0.284§
Duration of ACC (min)	73.73±24.01	84.40±37.30	0.359§
Duration of CPB (min)	99.33±27.83	105.40±22.85	0.239§

¶: Fisher's Exact test; §:Independent samples t-test.

P: Propofol; M: Midazolam; BMI: Body mass index; CPB: Cardiopulmonary bypass; ACC: Aortic cross clamp.

TABLE 2: Triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, very low density lipoprotein, and plasma glucose levels at measured time points in both groups.

	Group	T1	T2	T3	T4	T5	T6	T7
TRG	P	215.06±3.60	211.40±68.71*	144.86±75.03*#	145.80±45.72	150.33±47.84	144.86±46.59*#	161.73±31.08
	M	237.66±47.46	185.80±68.5*#	95.93±28.86*#	113.67±51.33	128.87±54.98	116.26±42.99*#	136.73±40.94
CHOL	P	236.86±30.12	186.20±39.70*	135.20±27.30*	119.33±19.31	117.93±27.50	112.60±20.99*	142.93±25.45
	M	236.26±42.56	178.93±32.77*	143.20±35.87*	134.20±29.21	123.60±34.39	116.66±26.04*	130.47±25.23
HDL	P	33.46±5.48	39.13±11.00*#	24.66±10.52*	27.27±11.18	28.13±10.01	24.73±6.35*	25.27±5.04
	M	32.40±9.06	27.80±7.27*	23.46±9.02*	23.33±6.70	22.67±8.18	24.33±5.24*	24.80±6.00
LDL	P	149.00±34.16	102.33±38.35*	83.33±27.06*	64.07±23.25	63.13±27.13	59.93±19.26*	77.27±26.10
	M	150.06±41.26	121.40±33.09*	100.66±29.25*	88.13±24.74	76.53±30.57	69.73±22.97*	79.20±20.67
VLDL	P	48.13±17.57	44.46±13.33*	27.33±14.42*	28.93±8.91	28.47±7.43	18.06±10.60*	34.80±11.10
	M	47.06±9.41	37.00±13.64*	19.06±5.45*	22.80±10.14	25.87±10.80	23.20±8.67*	27.27±7.80
GLUC	P	123.80±18.18	140.86±20.51*	180.20±43.81*	183.93±39.19	175.20±26.01	165.26±25.87*	130.33±24.51
	M	113.00±22.76	127.53±36.63	163.80±31.20*	159.53±29.09	158.07±23.03	136.40±23.53*	122.60±28.06

T1: Before induction of anesthesia; T2: Before cardiopulmonary bypass; T3: At the end of cardiopulmonary bypass; T4: Two hours after cardiopulmonary bypass; T5: Four hours after operation; T6: 24 hours after operation; T7: Seventy-two hours after operation.
According to T1 (level 1): *p<0.05 (in the same group), # p<0.05 (between the groups).
TRG: Triglyceride; CHOL: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; GLUC: Plasma glucose; P: Proposal; M: Midazolam.

compared to T2, T3 and T6 values (p<0.05) (Table 2).

When HDL levels were compared between two groups, the level at T2 was statistically significantly higher in group P. Group P showed a significant increase at T2, and the decreases at T3 and T6. The decreases of the levels at T2, T3 and T6 were statistically significant in group M (p<0.05) (Table 2) (Figure 2).

The comparison of LDL values in both groups did not yield statistically significant differences. Within the group, each group showed a decrease in the values at T2-T7 when compared to T1 level (p<0.05) (Table 2).

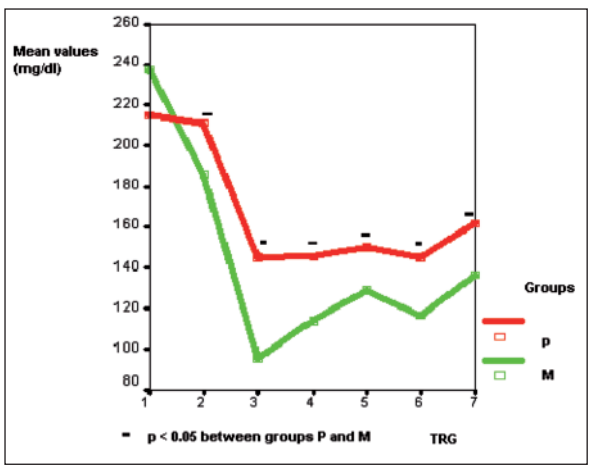

FIGURE 1: Mean plasma triglyceride levels (mg/dl) at different time points prior to and following CABG in two groups.
T1:Before induction of anesthesia; T2: Before cardiopulmonary bypass; T3: At the end of cardiopulmonary bypass; T4: Two hours after cardiopulmonary bypass; T5: Four hours after operation; T6: 24 hours after operation; T7: Seventy-two hours after operation; P: Propofol; M: Midazolam; TRG: Triglyceride.
(See color figure at http://www.turkiyeklinikleri.com/journal/tip-bilimleri-dergisi/1300-0292/)

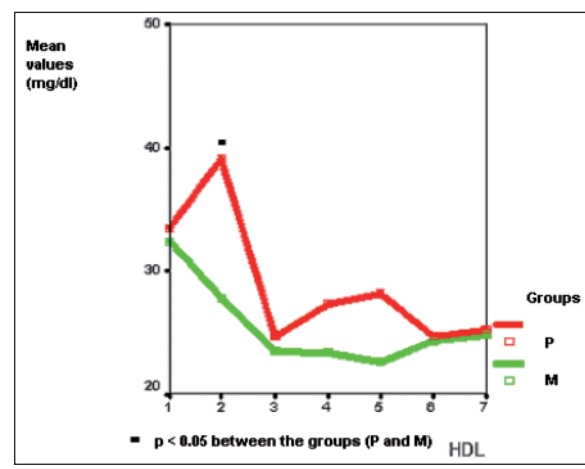

FIGURE 2: Mean plasma high density lipoprotein levels (mg/dl) at different time points prior to and following CABG in two groups.
T1: Before induction of anesthesia; T2: Before cardiopulmonary bypass; T3: At the end of cardiopulmonary bypass; T4: Two hours after cardiopulmonary bypass; T5: Four hours after operation; T6: 24 hours after operation; T7: Seventy-two hours after operation; P: Propofol; M: Midazolam; HDL: High density lipoprotein.
(See color figure at http://www.turkiyeklinikleri.com/journal/tip-bilimleri-dergisi/1300-0292/)

The comparison of VLDL values between the groups did not yield statistically significant differences. Both groups showed significantly decreases at T2, T3 and T6 when compared to T1 level ($p<0.05$) (Table 2).

GLU values were similar when two groups were compared. The GLU levels at T2, T3, T6 were significantly higher than the level at T1 in Group P. On the other hand, GLU levels at T3 and T6 were significantly higher than the level at T1 in Group M ($p<0.05$) (Table 2).

DISCUSSION

There are several reports in literature about the life-threatening complications of propofol infusion.[14,15] When propofol is used for prolonged sedation, arrhythmia and serum TRG levels must be further monitored.

In CABG, perioperative myocardial ischemia or infarction is associated with increased morbidity and mortality. The ischemic changes in the early postoperative period may result in undesirable consequences and adverse events after surgery.[7] Several studies reported contribution of high free fatty acid levels to an increased ischemic myocardial damage, and possibility of increased risk of arrhythmogenicity in this setting.[8,9]

Reports suggest that propofol formulation, comprised of egg-yolk lecithin containing 1% soybean oil, elevates serum lipids, and particularly TRG.[12,16] In other studies, no significant increases have been observed.[10,17,18]

The goal of our study was to determine the risk of elevation in plasma lipid levels in patients with hyperlipidemia undergoing CABG. Our findings demonstrated that use of propofol for induction of anesthesia and its infusion did not contribute to a statistically significant change in plasma lipid levels when compared to the control (M) group in patients with hypertrygliceridemia and hypercholesterolemia. Although plasma TRG levels decreased in both groups, the reduction was less significant in the group P when compared to the group M, and this was attributed to the TRG content of the drug.[11] Öztekin et al.[11] found statistically significant decreases in TRG and VLDL levels on postoperative4th hour in the ones who were administered 1% propofol when compared to the preoperative period. The authors pointed out that this result might be associated with the possibility of higher TRG and VLDL fractions of 1% formulation.[11]

The comparison of plasma HDL values showed a significant rise in Group P at T2, after anesthesia induction, when compared to the Group M which showed low HDL levels throughout all time periods. The reason of this rise in hyperlipidemic patients was thought as the high level of HDL in propofol. Gottardis et al. showed a rise in HDL plasma levels in ICU patients.[19] The cause of this rise was not clearly explained, but it was thought to be related with propofol use, and it was supposed as a beneficial side effect.[19]

Inoue et al. showed that plasma TRG levels were maintained in Group P whereas it decreased compared to the baseline level in Group M, in normolipidemic patients.[17] Although infusion and CPB-related hemodilution may cause an increase in the levels of chylomicrons, the maintenance of plasma TRG and VLDL levels was attributed to the addition of TRG to propofol. This artificial TGRs were converted to chylomicrons and VLDL (lipoprotein rich in triglycerides) with apolipoproteins. Maintenance of TRG and VLDL levels, despite liquid administration and hemodilution, was associated with TRG co-administered with propofol.[17] In the present study, however, we never determined any increase in VLDL levels at any measurement point.

The analysis of the plasma levels of CHL, LDL and VLDL showed that there were significant decreases when compared to preoperative levels in both groups, and the difference was not statistically significant when two groups were compared. This decrease in plasma levels was attributed to the infusions and the dilution effect of CPB.[18-20]

Low CHL content of propofol may be related to this finding as its effect continues throughout propofol infusion.[16] The noncardiac surgical studies support these data, since the decrease in plasma

CHL level continues even in the absence of the dilutional effect of CPB.[18-20]

The results of our study showed that plasma GLU concentration in both groups increased significantly during surgery, and continued 72 hours postoperatively when compared to the baseline preoperative level. There is no difference between two groups for plasma GLU levels. These results are in agreement with the literature. Hyperglycemia was thought to result from hypothermia, stress of major surgical intervention, the rise in catecholamines, heparin, hypoinsulinemia and insulin resistance.[21-30] This study can not provide enough data to differentiate these factors from each other. The infusions of propofol or midazolam do not have significant effects on plasma GLU concentration.

CONCLUSION

We showed in our study that propofol %1 in an infusion dose of 2 mg/kg/h in patients with hyperlipidemia undergoing to surgery did not affect the serum lipid and glucose levels. In addition, use of propofol was regarded as safe for induction and maintenance of anesthesia, as an alternative to midazolam. Randomized studies with the a larger patient cohort would provide more valuable data.

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