Original article

Title: Midazolam infusion might preserve glucose and lipid homeostasis during surgery under general anesthesia: Placebo-controlled comparative study.

Running Title: Midazolam infusion preserves glucose homeostasis during general anesthesia.

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Abstract

Background: Anesthesia and surgery each per se is a stressful condition that may affect the postoperative patients' outcomes. Hyperglycemia is the commonest result of surgical stress response and must be adjusted not only in diabetics to improve outcomes.

Objectives: To determine changes in blood glucose (BG) and serum lipids and cortisol levels after intraoperative midazolam infusion for patients undergoing surgery under general anesthesia.

Patients & Methods: 160 ASA I or II non-diabetic patients were randomly divided as Control patients received placebo infusion and Study patients received midazolam infusion (0.35 µg/kg/min). All patients gave blood samples before (S1) and 30-min after the start (S2) and at end of infusion (S3) for estimation of BG and serum lipids and cortisol levels. The study outcome was the change of the levels of estimated parameters in relation to their preoperative levels.

Results: BG levels estimated in S2 and S3 samples were significantly higher than S1 levels of all patients, but were significantly lower in samples of study than control patients. Serum levels of triglycerides and very low-density lipoproteins (VLDL), and cortisol in S3 study samples were significantly lower than in S3 control samples.

Conclusion: Intraoperative midazolam infusion could minimize surgical stress response with a significant decrease in serum cortisol, triglycerides, and VLDL and significantly lower BG concentrations in comparison to placebo infusion.

Keywords: Midazolam, Surgical stress, Blood glucose, Serum cortisol, Serum triglycerides

Introduction

Stress response could be considered as the body adaptation process to the environmental perturbation to provide effective strategies for survival; however, exaggerated stress response results in stress injury [1]. Surgical procedures especially under general anesthesia induce widespread body disturbances mostly through the induction of secretion of chemical mediators involving hormones and multiple cytokines [2].

Activation of the sympathetic nervous system and the rostral ventrolateral medulla during acute stressful conditions was implicated in differential control of sympathetic outputs [3]. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter [4] and many general anesthetics potentiate its receptor type-A (GABA$_A$) [5]. GABA agonists induce their sedative effect through the GABAergic neurons in the rostromedial tegmental nucleus that send inhibitory projections to multiple arousal-promoting nuclei causing the sedation [5].

Moreover, GABA receptors can modulate glucose and lipid homeostasis partly through inhibition of the α2δ1 thrombospondin receptor, which plays an essential role in promoting the activity of steroidogenic factor 1 neurons in the ventromedial hypothalamus [6]. On the other side, the brain contributes to maintaining whole-body metabolism via enhancing the sympathetic nerve tone through GABA suppression [7].

Midazolam is a benzodiazepine receptor agonist that causes sedation through activation of GABA$_A$ receptors [8] that requires predominance of the K^+-Cl^- co-transporter isoform 2 to cause chloride ion influx with subsequent neuronal hyperpolarization [9]. The sedative, anxiolytic, and anticonvulsant properties of midazolam are characterized by being fast in onset with a short duration of action than other benzodiazepines [10]. However, the effects of midazolam on metabolic and endocrinal surgical stress response were poor, so the current placebo-controlled study tried to evaluate these effects.

Hypothesis:

The study proposed that intraoperative (IO) administration of midazolam infusion may control altered blood glucose (BG) secondary to general anesthesia and/or surgery.

Objectives:

This study tried to evaluate the effect of intraoperative (IO) midazolam infusion on surgery-induced alteration of blood glucose (BG) and serum levels of lipids and cortisol during surgery under general anesthesia (GA)

Design

Prospective double-blinded randomized placebo-controlled study

Setting

Anesthesia & ICU department, Faculty of Medicine, Benha University in conjunction with multiple private surgical centers

Ethical considerations

The study was started in Jan 2019 after obtaining the preliminary approval of the study protocol by the Local Ethical Committee and extended till July 2021 and the final approval by number: RC2.9.2021 was obtained at the end of the study. The study protocol was discussed with each patient and those who accepted to participate in the study signed written consent.

Patients & Methods

Adult patients assigned for elective hernia repair were evaluated for eligibility to be included in the study.

Inclusion criteria

Unilateral uncomplicated inguinal hernia in ASA I patients, aged 18-40 years, had body mass index (BMI) of <30 kg/m^2, and free of exclusion criteria are the inclusion criteria

Exclusion criteria

Patients out of age range and BMI of >30 kg/m^2, had a complicated hernia, chest, cardiac, renal, or hepatic diseases, presence of unresolved participating cause for the development of hernia, coagulopathy, endocrinal or metabolic diseases especially diabetes mellitus or presence of hypersensitivity to the study drugs or refused to sign the informed consent were also excluded.

Randomization and grouping

Patients were randomly allocated into two groups using computer software to develop a 1: 1 sequence. Patients were grouped according to the IO infusion using either plain saline (0.9% NaCl) for patients of a control group or midazolam infusion, which is prepared to provide 0.35 µg/kg/min as previously documented [11].

Blood sampling and investigations

Patients were asked to attend the hospital lab the day before surgery fasting for 12 hours and giving a blood sample for estimation of serum lipids and to re-attend on the day of surgery fasting for 6 hours to give another blood sample for estimation of fasting blood glucose and serum cortisol (S1 sample). Other blood samples were obtained 30 minutes after the start of infusion (S2 sample) and at end of infusion (S3 sample) for estimation of the same parameters.

Anesthetic procedure

No preoperative premedicated was provided, anesthesia was induced with propofol 2 mg/kg and fentanyl 1-2 ug/kg. Intravenous (IV) rocuronium was given at a dose of 0.6 mg/kg to facilitate tracheal intubation and re-administered according to the patient's physiological reaction to surgical stimuli. Study infusions were started after intubation until wound closure. Anesthesia was maintained with 50% air in oxygen and 2-3% sevoflurane. Patients were non-invasively continuously monitored for heart rate, blood pressure, pulse oximetry, and end-tidal CO_2 during the operation. At the end of the surgery, muscle relaxation was reversed with neostigmine 0.05 mg/kg plus atropine 0.01 mg/kg and patients were extubated and maintained on a 100% oxygen mask till being fully recovered.

Study outcome

The primary study outcome was the impact of midazolam infusion of the change of BG levels. The secondary outcome is the effect of infusion on serum lipids and cortisol estimated in S3 samples relative to levels estimated in S1 samples.

Statistical analysis

Intra-group comparisons were evaluated using the paired t-test, inter-group variations were analyzed using the One-way ANOVA test and non-parametric results were analyzed using the Chi-square test and Mann-Whitney test. Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

The study included 160 patients after the exclusion of 13 patients; 2 were hypertensive, 3 were diabetic, 5 were obese with BMI>30 kg/m^2 and three had previous attacks of irreducibility (Fig. 1). The demographic, clinical and operative data of patients of both groups showed non-significant differences (Table 1).
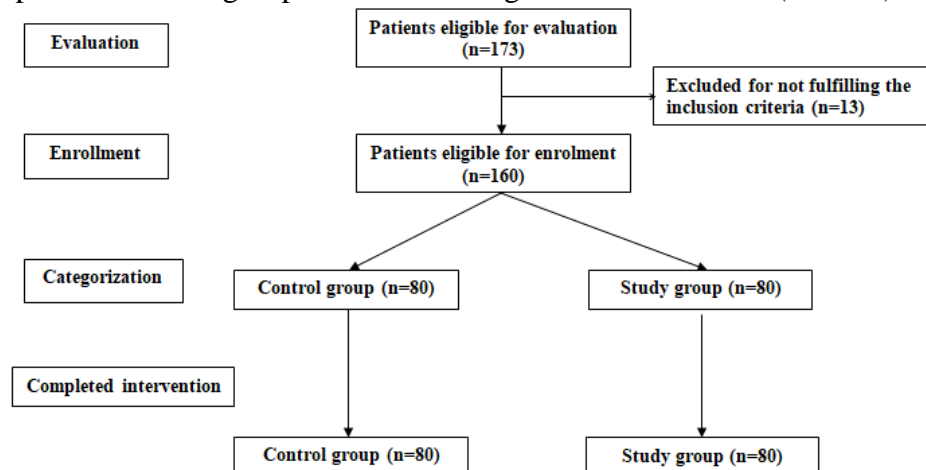

Fig. (1): Study Flow Chart

Table (1): Baseline data of patients of both groups

Group Variables	Control (n=80)	Midazolam (n=80)
Age (years)	28.7 (6.1)	29.7 (5.5)
Sex; Male: Female	58: 22	52: 28
Body weight (Kg)	81.5 (5.15)	79.5 (6.1)
Body height (cm)	169.2 (3.2)	169.3 (3.4)
Body mass index (kg/m^2)	28.5 (1.5)	27.8 (1.9)
Laterality; Right: Left	58: 22	55: 25 (68.75%)

Data are shown as mean, standard deviation, and ratios.

Blood glucose levels were progressively increased during surgery with significant differences between successive estimations but were significantly higher in samples of controls than in study patients. Serum levels of total cholesterol, triglycerides, low-density, and very low-density lipoproteins, and serum cortisol were decreased significantly in S3 samples of study patients compared to the levels estimated in S1 samples, while the differences between levels estimated in S3 and S1 samples of control patients were non-significant. Moreover, the differences between serum levels of triglycerides, VLDL, and cortisol were significantly lower in S3 samples of study patients (Table 2).

Table (2): Laboratory data of patients of both groups

		Control	Midazolam
Blood glucose (mg/dl)	Preoperative	106.4 (8.1)	107.3 (9.1)
	30-min IO	143.5 (11.2) *‡	131.4 (10.5) *
	At the end of the infusion	126.3 (6.4) *†‡	118.8 (8.9) *†
Total cholesterol (mg/ml)	Preoperative	186.8 (33.2)	192.2 (30.2)
	At the end of the infusion	184.5 (33.3)	176.1 (26.9)*
Triglycerides (mg/ml)	Preoperative	145 (45.7)	135.2 (29.6)
	At the end of the infusion	152.8 (47.4)	122.7 (25.4)*‡
Low-density lipoprotein (mg/ml)	Preoperative	92.9 (31.9)	101 (25.1)
	At the end of the infusion	86.7 (31)	88.2 (23.2)*
Very low-density lipoprotein (mg/ml)	Preoperative	22.7 (5)	21 (5.2)
	At the end of the infusion	24.4 (7.2)	18.8 (4.5)*‡
High-density lipoprotein (mg/ml)	Preoperative	42.2 (5.8)	43.2 (3.8)
	At the end of the infusion	42.85 (4.2)	44.6 (4.1)
Serum Cortisol (nmol/L)	Preoperative	394.6 (26.8)	542.7 (60.6)
	At the end of the infusion	382.6 (42.3)	499.7 (68.8)*‡

*: significant difference in comparison to preoperative level; †: significant difference between at the end and 30-min after the start of IO infusion; ‡: significant difference between both groups

Discussion

Midazolam IO infusion significantly controlled the elevations of BG and serum levels of lipid and cortisol in comparison to placebo infusion. This finding indicated the necessity of anesthetic manipulations to control the stress responses to general anesthesia and surgical interventions and go in hand with previous studies that used oxycodone [12], caudal block [13], or epidural analgesia [14] with general anesthesia. Also, a recent study reported significantly higher levels of BG with general than spinal anesthesia [15].

In line with the use of midazolam to lessen the operative stresses, one previous study documented that patients who received midazolam or propofol sedation showed increased IO blood glucose levels compared to their preoperative levels, but at end of surgery patients who received midazolam had significantly lower BG levels than those who received propofol [16]. Another two studies reported significantly lower serum lipid concentration with midazolam than with placebo and propofol [17, 18].

The reported decrease in BG levels and serum concentrations of VLDL and triglycerides indicated a possible inhibitory effect of midazolam on lipolysis and metabolic modulation in the anti-glucogenic direction. Multiple studies attributed these metabolic effects of midazolam to the widespread distribution of GABA receptors in human pancreatic beta and non-beta-cells and suggested that GABA can be involved in the regulation of somatostatin and glucagon secretion, thereby regulating BG homeostasis [19]. Another study found GABA-shunt' metabolite depolarizes β-cells and stimulates insulin secretion [20] with synchronized pulsatile effluxes of GABA from a cytosolic pool with the pulsatile insulin secretion and attributed diabetes pathogenesis to depletion of GABA content in β-cells [21]. Using animal models, it was found that oral administration of GABA-producing *Last. brevis* increased insulin secretion, improved plasma cholesterol clearance and reduced corticosterone production [22], pharmacological modulation of the GABA receptor ameliorated systemic insulin resistance, enhanced insulin-dependent glucose uptake in adipose tissue [23], and manipulations of the central GABAeric receptors were documented to be required to overcome stress-dysfunction [24].

Conclusion

Anesthetic manipulation could be an effective modality to minimize the body's stress response to general anesthesia and surgery. Intraoperative midazolam infusion significantly decreased serum cortisol, triglycerides, and VLDL with concomitant significant control on BG concentrations in response to manipulation in comparison to placebo infusion.

Limitation

The study limitations included the comparison versus placebo infusion and the application during inguinal hernia which induces moderate stress response for the shorter operative time and the minimal manipulations.

Recommendations

Intraoperative midazolam infusion may be advocated to be used as a modulator for endocrine and metabolic surgical stress response. However, wider-scale studies are required to evaluate these outcomes during major surgeries and/or in comparison to other drugs.

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