A randomized clinical trial for the effects of halothane and isoflurane anesthesia on blood glucose levels in the diabetic patients.

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ABSTRACT

*Background***:** Halothane and isoflurane inhibit glucose-induced insulin secretion in animal and in vitro experiments.A randomized trial was designed to determine their in vivo effects in diabetic patients.

Methods: Sixty diabetic patients with various malignancies were randomized to receive anesthesia with either halothane or isoflurane. Blood glucose level (BGL) was measured before induction and every 30 minutes during surgery and then after operation in the recovery room.

Results: Patients in both arms matched with gender, age, operation time, and initial BGL. In both arms an increase in blood glucose level could be detected 30 minutes after induction of anesthesia, but higher in the halothane arm. This difference was maintained for the next 30 minutes as well as the rest of duration of the anesthesia. Both arms had higher blood glucose levels after operation compared to initial, pre-anesthesia state, and this increase was more conspicuous in the halothane arm. No Halothane toxicity was detected during hospitalization.

Conclusion: Although the effects of stress hormones was not evaluated, halothane anesthesia caused a greater degree of hyperglycemia compared to isoflurane anesthesia. This might be secondary to halothane's greater inhibitory effect.

Keywords: Halothane, isoflurane, anesthesia, diabetes**.**

INTRODUCTION

The prevalence of diabetes mellitus in both adults and children has been steadily rising throughout the world for the past 20 to 30 years (1-3).

Recent changes in diagnostic criteria, if widely adopted, will probably also lead to more patients being classified as having diabetes (4).

Anesthetic techniques and the choice of agents are of great importance while anesthetizing the diabetic patients.

While an animal study shows halothane and isoflurane induce similar degree of hyperglycemia (5), our unpublished observations in diabetic patients were in contrast to this reports. Therefore a prospective, randomized trial was designed to evaluate the effect of anesthesia with halothane and isoflurane on blood glucose level (BGL) in these patients.

METHODS AND MATERIALS

Between May 2006 and February 2007, 60 patients with ASA class (American society of Anesthesiologists) less than IV who were operated in the Cancer Institute, Tehran university of Medical Sciences for colorectal cancers were studied. The eligibility criteria were documented history of diabetes mellitus which were managed with oral hypoglycemic and recent HbA_{1c} between 7 to 9 mg/dl, an operation requiring general anesthesia with endotracheal intubation, abdominal or thoracic operation, and an operation time of at least 60 minutes. There was no restriction concerning the pre-operative stage at diagnosis or the type of operation. Informed consent was obtained from each patient prior to enrollment. This consent mainly concerned multiple blood sampling, since administration of halothane and isoflurane is a routine practice in our operating rooms. Patients were randomly allocated to either halothane or isoflurane arms. Randomization was based on 60 numbered opaque envelopes containing small pieces of paper on which either halothane or isoflurane was printed (30 of each). The small papers were shuffled several times and then placed in the envelopes. Before induction of anesthesia, the anesthesiologist allocated each patient to pick up the remaining envelope of the least number. Then anesthesia was induced according to the patient arms. In Halothane arm, anesthesia was induced using sufentanyl 15 μg at the beginning and then 7.5 μg every 30 mins, thiopental 5 mg /kg, and

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cis-atracurium 1 mg/ kg at the beginning and then 1 mg every 30 mins. The anesthesia was maintained using 1.5% halothane then was reduced to 1.25%. Reversal was performed using prostigmine 1.25 mg and atropin 0.75 mg. For the patients in isoflurane arm, anesthesia was induced using 15 μg sufentanyl at the beginning and then 7.5 μg every 30 mins, thiopental 5 mg/ kg, and cis-atracurium 1 mg/ kg at the beginning and then 1 mg every 30 mins. The anesthesia was maintained by using 2% isoflurane. The reversal was performed using prostigmine 1.25 mg and atropin 0.75 mg.

After completion of intubation and assurance of its security, operation was started immediately.

A blood sample was obtained immediately before induction for measurement of pre-operative glucose level. An anesthesia technician, who was unaware of patient allocation, obtained blood samples every 30 minutes from the time that operation started and then in the recovery room after extubation (the post-operative blood sample) for measurement of blood glucose levels. Blood samples were sent to Cancer Institute Central Laboratory and analyzed by the routine way. All data were recorded in a standard data form by the same technician.

RESULTS

In this study 60 patients were randomly allocated to two arms. There were no loss and no deviation from protocol and 30 patients remained in each study arm.

There were 14 males in halothane arm (46.7%) and 15 males in isoflurane arm (50%) (p value = 0.79). The mean age in halothane and isoflurane groups were 59.84 and 60.28 years, respectively (p value=0.860). Table 1 summarizes other characteristics of two arms which were not different significantly. Disease stage and operation type between the two arms also were not different significantly (Table 2). The mean operation time in halothane and isoflurane arms were 156 and 144 minutes, respectively (p value=0.481). The initial, pre-anesthesia blood glucose level in halothane and isoflurane arms were 129.96 and 138.97 mg/dl, respectively (p value=0.322).

Table 3 summarizes the main objectives in two arms. In both arms an increase in blood glucose level could be detected 30 minutes after induction of anesthesia, and this increase was higher in the halothane arm. This increase was maintained for the next 30 minutes as well as through the rest of duration of the anesthesia. Both arms had higher blood glucose levels after operation compared to initial, pre-anesthesia state, and this increase was more prominent in the halothane arm. No Halothane toxicity was detected during hospitalization.

DISCUSSION

This study shows that anesthesia with halothane causes a greater degree of hyperglycemia compared to isoflurane in diabetic patients. In both arms, induction of anesthesia and the stress of surgery increased the blood glucose level.

Surgery evokes the ‘stress response’, resulting in secretion of catecholamines, cortisol, growth hormone and in some cases, glucagon. These hormones oppose glucose homeostasis, as they have ‘anti-insulin’ and hyperglycemic effects, where gluconeogenesis is stimulated and peripheral glucose uptake decreases (7). Although the occurrence of hyperglycemia can be partly explained by these phenomena, the anesthetic agents may also have some effects. In the halothane arm, the mean intra-operative blood glucose levels as well as post-operative blood glucose level were significantly higher than those of isoflurane arm.

The inhibitory effects of halothane on glucose-induced insulin secretion has long been known through in vitro and in vivo animal studies (8,9). This effect is exerted in a reversible and dose-dependent fashion, and has not been shown to be due to interference with glucose oxidation, and as a result a reduction in glucose metabolism (10).

Similar inhibitory effects of isoflurane have been reported as the result of in vitro and in vivo animal studies. Effects of isoflurane on insulin secretion on the rat isolated islands of langerhans have been reported as a significant, dose-related and reversible inhibition of insulin secretion (11). Isoflurane's effect on intravenous glucose tolerance and insulin secretion in six Yucatan minipigs has been reported. The glucose disappearance rate, baseline plasma insulin concentration, and the area under the insulin response curve were significantly lower in the anesthetized animals than in controls (12).

Several human studies have also reported similar effects for isoflurane (13, 14). Other studies have shown the effect of isoflurane-air anesthesia on glucose tolerance in human using two successive intravenous glucose tolerance tests. Isoflurane seemed to induce glucose intolerance partly due to a decreased glucose induced insulin response (14). In another human study (15), impairment of glucose tolerance during isoflurane anesthesia was compared with sevoflurane anesthesia, and it has been found that the latter impairs glucose tolerance to the same degree as isoflurane anesthesia. However glucose intolerance during sevoflurane or isoflurane anesthesia is independent of the type of anesthetic agent and

Table 1. Patients' characteristics of two arms

Variable	Arm		P Value
	Halothane	Isoflurane	
Hypertension	8 (26%)	12 (40%)	0.09
Hypercholesterolemia	11 (36%)	9 (30%)	0.4
Hypertriglyceridemia	13 (40%)	7 (23%)	0.06
Coronary artery disease	8 (26%)	11(36%)	0.1
Chronic lung disease	4 (13%)	2 (6.5%)	0.085
ASA class I	11 (36%)	12 (40%)	0.3
ASA class II	19 (64%)	18 (60%)	0.3

A.S.A (American society of Anesthesiologists)

Table 2. Disease stage and type of the operation of two arms.

Variable	Arm	
	Halothane	Isoflurane
TNM Stage I	2 (6%)	0
TNM stage II	18 (60%)	21 (70%)
TNM Stage III	10 (34%)	9 (30%)
Right hemicolectomy	3 (10%)	4 (13%)
Transverse colectomy	1 (3%)	0
Left hemicolectomy	6 (20%)	9 (30%)
Sigmoid colectomy	10 (33%)	7 (23%)
Low anterior resection	6 (20%)	7 (23%)
Abdomino-perineal resection	4 (13%)	3 (10%)

Table 3. Result of two study arms.

Blood glucose level mg/dI	Arm		P Value
	Halothane	Isoflurane	
30 minutes after operation started	172.4	147.36	0.002
60 minutes after operation started	169.68	144.34	0.005
Increase, 30 minutes after operation started	42.43	8.44	<0.001
Increase, 60 minutes after operation started	38.51	6.80	<0.001
The mean intra-operative	171.73	142.27	0.001
The mean Post-operative	169.93	143.06	0.002

dosage up to 1.5 MAC (Minimal Alveolar Concentration).

To the best of our knowledge, no previous human study has been performed to compare the effect of halothane and isoflurane anesthesia on blood glucose levels in the diabetic patients. The greater effect of halothane in increasing the blood glucose level may be due to its higher degree of glucose-induced insulin secretion inhibition, or may be secondary to different stress hormone release profile, as it has been shown that epinephrine levels were lowered by isoflurane anesthesia (14).

However ,serum levels of various stress hormones in the two arms, which may be important was not determined in this study.Although the operation time was similar in the two arms, the operation types were not exactly similar, and this may influence the magnitude of surgical stress. This study has produced preliminary results that certainly require further evaluation.

We did not know the standard deviations of our outcomes, but to detect a difference of one standard deviation among the two arms with a significance level of 0.05, the total number of 30 patients would translate into a power of more than 80 percent (6).

This study was designed to evaluate the hypothesis that halothane causes a higher increase in intra-operative blood glucose level compared to isoflurane.The main study outcomes were blood glucose level after 30 and 60 minutes of induction of anesthesia, mean intra-operative blood glucose level, and post-operative blood glucose level.

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