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ORIGINAL ARTICLE

Evaluation of Effects of Clonidine Premedication on Changes Glucose Level in Insulin Dependent Diabetes Mellitus Type 1 during Ophthalmic Surgery under Intravenous General Anesthesia

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ABSTRACT
This study is aimed to design a randomized clinical trial with efficacy of Clonidine in comparison with premedication in reducing blood sugar in patients with diabetes type 1 who underwent vitrectomy surgery is examined. In this study, subjects were patients with diabetes type 1 hospitalized to viterctomy surgery in Rasol Akram Hospital during 2005-2006. Type 1 diabetics who referred to Rasol Akram Hospital aged between 20 to 60 years and were a candidate for eye surgery (vitrectomy) in case of corresponding to the inclusion and exclusion criteria's were randomly assigned into oral Clonidine groups (µg/kg 3) and placebo group, respectively. Serum glucose levels of patients before induction, two and four hours after induction was measured. In the Clonidine group patients compared with placebo, there is a significantly reduction after four and six hour induction of anesthesia. The study also showed that there was a significant effect between Clonidine and interaction time effect (p =007/0). This means that Clonidine during follow-up can lead to a significant reduction in blood glucose levels compared to placebo. This study showed that the use of Clonidine dose 3 µg / kg can prevent the increase in blood glucose levels in patients with diabetes type 1 who underwent vitrectomy eye surgery compared with the control group. However, in order to expand its use in other surgical cases complementary studies are needed.
Keywords*: diabetes Type 1, Clonidine, Randomized clinical trials, vitrectomy surgery, hyperglycemia*

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INTRODUCTION

Generally looking for any kind of stress, including induction and maintenance of anesthesia and surgery process, a set of responses under stress response is evoked in which different body systems, including the nervous system, endocrine, immunological and biochemical changes have been contributed to the cell surface [1].The endocrine system leading to activation of both, hypothalamic - pituitary - Adrenocortical and Sympathoadrenal pathways is also resulting in the increase or decrease in the number of hormones. These hormonal fluctuations, causing changes in the cardiovascular system - cardiovascular, respiratory and metabolism that would be problematic in a group of patients.

One of the most important hormones in this way is Catecholamines on patients with cardiovascular problems - especially patients with ischemic heart will impose adverse effects. The result contrasts the effects of various hormones (reducing insulin against the increase in glucagon, Catecholamines, Cortisol and growth hormone), which increases blood sugar interface control blood sugar levels in diabetics during surgery [2].

Since in addition to patient safety, reduction of complications is among the most important goals of anesthesiologist, if could be offered a way to minimize the effects it will facilitate the achievement of this goal somewhat. Given the high prevalence of Insulin Dependent Diabetes Mellitus type 1 in the population and given the prevalence of the disease in adolescence, and there is 80 to 90% of diabetic retinopathy in IDDM patients with a history of over 20 years, [3]. From this group of patients most of them need to eye surgery such as vitrectomy [4].

Thus it can be stated diabetes is the leading causes of eye disease that will require surgery. If the blood sugar of these patients can be controlled during eye surgery (vitrectomy) can be prevented complications such as hyperglycemia, ketoacidosis, dehydration and electrolyte abnormalities [5]. As was noted above, before and during surgery the human body due to physical and mental stress begin to secrete catecholamines, which increase blood sugar. Clonidine is one of A2-agonist drugs that will prevent the central release of catecholamines [6]. According to Clonidine as a safe drug for eye surgery to improve intraoperative hemodynamic status during surgery, reduces the intraocular pressure and as anesthetic requirements is used. With the assumption that oral Clonidine is used as premedication, blood sugar changes during surgery is reduced and complications as hyperglycemia, ketoacidosis, and so on is prevented [7]. Therefore, this study is aimed to design a randomized clinical trial with efficacy of Clonidine in comparison with premedication in reducing blood sugar in patients with diabetes type 1 who underwent vitrectomy surgery is examined.

METHODS

This study as a single-blind randomized clinical trial was designed and performed. Before implement the proposal approved by anesthesiology, Iran University of Medical Sciences and Research Council of Iran University of Medical Sciences. Subjects were patients with diabetes type 1 who are undergoing vitrectomy with intravenous anesthesia. In this study, subjects were patients with diabetes type 1 hospitalized to viterctomy surgery in Rasol Akram Hospital during 2005-2006. Sampling in this study is simple. This means that patients with were consistent with the to the inclusion and exclusion criteria's after take their consent were enrolled and were randomly assigned into oral Clonidine groups and placebo group, respectively. Inclusion criteria's included patients between 20 to 60 years with diabetes type I who was candidates for vitrectomy surgery and intravenous anesthesia. If the patient with bradycardia (heart rate less than 60), the presence of hypotension (systolic blood pressure less than 100) in the baseline and underlying other diseases were excluded. Before the study, a physician at all stages of the study explained to patients and obtain their written consent. After selecting patients based on the above criteria, patients were divided randomly into two groups: Group A (Clonidine) one hour before surgery oral Clonidine dose of 3 mg per kilogram of body weight was given to patients. The second group (control) one hour before surgery a multivitamin tablet given to patients. Blood sugar in both groups was check by hospital laboratory at morning (6 am). Then on the bed of operating room before induction of anesthesia, the blood glucose was measured by glucometer. To control blood glucose in both groups, non-light control method was used in the operating room. In the second method, patient is injected with insulin in the morning and then a dose of dextrose 5% 70 kg/h/cc 120 began. For general anesthesia, first ringer volume to 5 ml per kg of body weight was given to patients before induction of anesthesia. Anesthetic induction by using fentanyl (4μg / kg), propofol (1 /5-2 as Titreh) and atracurium (5 cc / kg within 30 minutes) was performed. For maintenance of anesthesia, propofol dose 100 μg / kg / min and remifentanil dose 1μg / kg / min was used.

The variables in this study were classified into two main sections: demographic characteristics of participants in the study included age, sex and blood glucose data. Patient's blood glucose before induction, two and four hours after induction was measured by trained personnel using a glucometer. It is worth noting that the staff did not notify the group type of the patients.

The data obtained using the statistical software SPSS 13 was analyzed. Quantitative data as mean and standard deviation and qualitative data as frequency is displayed. In order to comparison between qualitative and quantitative data in both groups in comply with the normal distribution two kind of tests chi-square test, student t-test were used. In order to investigate the influence of the time factor and its interaction with the intervention (Clonidine) in order to analysis Repeated Measurement of ANOVA was used. Significance in this study at level 0/05 is considered.

RESULTS

In this study, 96 patients in both Clonidine group (45 patients) and control group (51 patients) were enrolled. In the Clonidine group, 23 patients (51/1%) and in the control group 28 patients (54/9%) were males that were not statistically significant different between the two groups (p =0/710) in terms of statistical age distribution between the two groups were not significantly different from each another (p= 0/110). Time distribution of surgery in term of hour in both group's Clonidine and control are presented in Table 4 separately. As can be seen the mean duration of surgery in the Clonidine group than was equal to 4/2± 0/84 hours and in the control group was 4/06± 0/83 hours, which there was not statistically significant different between the two groups (p =0/846).

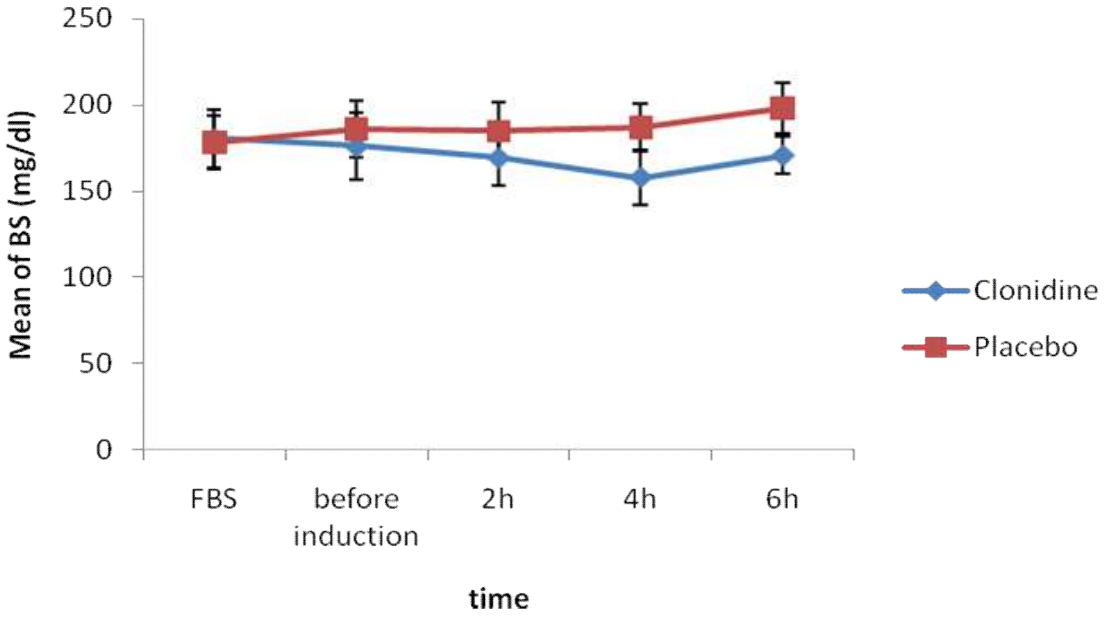
Patient's blood glucose levels were measured at five times, including fasting blood sugar in the morning of surgery, blood sugar before induction, two, four and six hours after the induction. Mean fasting serum

glucose levels compared between two groups and there was not a significant different (p =0/846). Table 6 is shown distribution of blood glucose in patients before induction. Mean blood glucose levels in patients who had received Clonidine was equal to 176/1±66/8 mg / dl and in the control group was equal to186/06±60/5 mg/dl, which there was statistically significant difference between the two groups this means that in the Clonidine group mean blood glucose levels in comparison with placebo, significantly reduced four and six hours after induction of anesthesia. The hemodynamic status including systolic and diastolic blood pressure and heart rate before induction and then compared the two groups during follow-up periods, there was not significantly differences at each desired time between two groups (p>0/05). To determine the effect of Clonidine in lowering blood sugar and observing the time effect and its interaction with drug effects Repeated Measurements of Analysis was used.

Accordingly, Clonidine could not reducing blood glucose over 5 period in comparison with placebo statistically (p =0/136).

In this model, the time effect was not statistically significant as well (p= 0/843). However, there was a significant relationship between time of interaction effect and Clonidine (p=0/007). This means that Clonidine during follow-up can lead to a significant reduction in blood glucose levels compared to placebo (Figure 1).

Figure 1: Distribution of blood glucose before and during vitrectomy surgery in both compared groups



DISCUSSION

This study, which was conducted as a randomized clinical trial on patients with diabetes type 1, indicated that Clonidine can reduce significantly blood glucose levels of follow up patients compared to control patients, and reduce hyperglycemia and its side effects. However, results of multivariate analysis demonstrated that effect of Clonidine intervenes with interval factor and these two factors intervention with the Clonidine group will cause significantly improvement in studied patients' glycemic status.

In general, following any stress, such as induction, maintenance of anesthesia, and surgical operation, a series of responses under stress response is stimulated, in which different systems of body contribute, including nervous system, endocrine, immunology system, and also biochemical changes at cellular level [1]. In stressful situations, especially in patients with diabetes mellitus, epinephrine and norepinephrine release results in increase hyperglycemia. This role of catecholamines results from Glycogenolytic and lipolytic effects, inhibits insulin activity, and stimulates the pituitary-adrenal axis [8].

In patients who undergo surgery, therapeutic strategy should imitate the normal metabolism as far as possible. Exogenous insulin prescription, which inhibits production of endogenous glucose (both glycogenolysis and gluconeogenesis) and stimulates use of glucose, intervenes with metabolic effects of hormonal changes of surgical stresses. However, insulin therapy may increase the risk of hypoglycemia in these patients whose occurrence has been reported between 5 to 10% in different studies [9]. Insulin infusion copes with metabolic effects of hormonal changes made during surgery (10) but insulin diets put individuals at risk of hypoglycemia reactions have no effect on resistance to insulin of released catecholamines [11]. Blood glucose may be controlled by adrenoreceptor agonists and decrease

sympathetic tone to the release of norepinephrine from nerve terminals [12]. This mechanism results from central α2 agonists that inhibit catecholamines release during activation of inhibitory α2 adreno receptors of central pre-synaptic. One of the frequently used drugs can be referred to Clonidine. Clonidine is considered as a receptor agonist of adreno receptors for improvement in metabolic status of diabetic patients in stressful situations such as surgery [13-14]. Yet, there is disagreement on pituitary – adrenal system; however, reduction in ACTH hormone and cortisol release has been reported by Clonidine in 15-16. In non-diabetic patients, the effect of α2 adrenoceptor agonists on blood concentration varies and depends on the type of surgery (18-17) and the consumed dosage [15-19]. Low doses of Clonidine may cause hyperglycemia while 4μg/kgdoses [17, 20] and more (15, 19) may inhibit hyperglycemia response.

In a study conducted in 2003, it was found that as a premedication, Clonidine reduces the need for insulin and improves blood glucose control during eye surgery. The improved metabolic control is related with lower concentrations of catecholamines [21]. This study indicated that higher doses of Clonidine adjust glycemic response to surgery. No hypoglycemic reaction was found in patients who received 375-225 μg Clonidine. Of course, authors of this study did not reject the potential risk of hypoglycemia when Clonidine was prescribed systemically with insulin.

In the present study, Clonidine dose used in patients was 3μg/kg, which was lower than doses used in previous studies; however, lowering effects of Clonidine on blood glucose is observedin comparison with the control group.

Clonidine stimulates releases of growth hormone and oral Clonidine is used in growth hormone stimulation test. It was found in a study that administration of oral Clonidine in diabetic patients who underwent eye surgery increases plasma levels of growth hormone but this increase does not influence control of patient' blood glucose [21]. This issue may be surprising but destructive effects of increased growth hormone on blood glucose levels in diabetic patients do not probably result from the effects of catecholamines or cortisol during surgery (19). However, this study indicated that increased growth hormone level is relatively short and researchers could not ignore the possibility that postoperative changes in glycemic control of patients occurred due to the growth hormone because growth hormone takes several hours to influence glucose homeostasis [8, 22].

On the other hand, it was found in another study that plasma peptide C concentration in patients who received Clonidine is lower [21]. Several explanations have been given for this issue. First, Clonidine inhibits insulin release through the effect of peripheralα2 pre-synaptic receptors (8). The second hypothesis is that lower concentration of blood glucose level results from stimulation of less powerful insulin release [21]. And lastly, the third hypothesis is that Clonidine reduces resistance against insulin through inhibition of catecholamines release. Thus, it reduces the need to endogenous and exogenous insulin [8].

Although, this study could demonstrate the positive effect of Clonidine on improvement of patients' metabolic status as control of blood glucose, it accompanied by some limitations. First, only changes in blood glucose were investigated in the study while if other hormonal changes such as of cortisol, growth hormone, and level Cpeptide were measured, it could show possible mechanism of the effect of Clonidine on patients' metabolic status well.

To recapitulate, this study showed that use of 3μg/kg Clonidine can prevents increase in blood glucose level in patients with diabetes type 1 who underwent vitrectomy in comparison to the control group. However, further supplementary studies are required in order to develop its application in other surgeries.

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