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Original Article

Investigating and Comparing the Effect of Articaine with Epinephrine 1:200000 in Type 2 Diabetic and Non-Diabetic Patients: A Clinical Trial

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Abstract

Introduction: Diabetes is highly prevalent in modern society. There are many controversies regarding the use of epinephrine in type 2 diabetic patients. This study aimed to examine and contrast the effects of articaine with epinephrine 1:200,000 in type 2 diabetic and non-diabetic patients referred to the Toubi Dental Clinic in Sari City.

Methods: This clinical trial involved two parallel groups. 30 patients with diabetes (whose diabetes has been confirmed by an internist) and 30 systemically healthy patients were selected. The baseline state was used to measure the blood sugar levels in both groups. Then, blood sugar concentration was measured on two occasions, one after 5 minutes of 2 doses of articaine injection with epinephrine 1:200000, and the other after 15 minutes of injection. Mann-Whitney, Chi-square, and GEE non-parametric tests were used.

Results: In each of the three instances, the average blood glucose level in the diabetic group was noticeably greater than that in the non-diabetic group. The average blood glucose at 15 minutes was significantly different from that at zero time, but the scale at 5 minutes did not have a substantial difference with zero time.

Conclusion: Despite a considerable increase in blood glucose levels in diabetic patients 15 minutes after injection, the administration of two articaine capsules with epinephrine 1:200,000 remained deemed safe.

Keywords: Diabetes mellitus, Local anesthesia, Pain control, Blood sugar, Articaine, Epinephrine

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Introduction

Diabetes mellitus is a diverse collection of metabolic illnesses marked by increased blood glucose levels due to impairments in insulin secretion, insulin action, or both. The global prevalence of diabetes continues to rise steadily)1, 2(. Diabetes is categorized into various kinds, including type 1 diabetes, type 2 diabetes, puberty-onset diabetes, gestational diabetes, and secondary diabetes resulting from exocrine gland dysfunction or steroid use (3). Type 2 diabetes is one of the types of diabetes that increases the resistance of cells to absorb glucose and reduces the effectiveness of secreted insulin (4). Due to their heightened susceptibility to periodontal illnesses, diabetic patients necessitate regular invasive treatments that demand specific strategies for stress management, as endogenous catecholamines released during stress-elevated heart rate, blood pressure, and blood glucose levels (5). Most dental procedures are stressful and painful (6,7). And preventing and eliminating pain during dental treatment is beneficial for patients, doctors, and dental hygienists. One of the main components of dental pain management strategies is local anesthetic. One of the safest and best medications for managing and preventing these problems is a local anesthetic (8).

Because of the ester group in its structure, articaine is a short-acting amide local anesthetic with a quick metabolism. This material works well in dentistry through a peripheral nerve block or local infiltration (9).

Adrenaline, a vasoconstrictor, is used in local anesthetic solutions to delay systemic absorption of the anesthetic agent, limit the anesthetic effect of the agent at the injection site, control bleeding, reduce toxicity, prolong the anesthetic effect, and reduce the dose of local anesthetic (10). Epinephrine (adrenaline) is involved in

processes, such as gluconeogenesis and glucogenolysis, both of which are very important in patients with diabetes mellitus. There are many controversies about the use of epinephrine in type 2 diabetic patients, so that in a series of studies, the use of anesthetics without epinephrine is suggested for type 2 diabetic patients, and in another series of studies, epinephrine is contraindicated in this type of diabetes (5).

Considering the complications of diabetes and its effect on wound healing and oral health, this study aimed to compare the impact of two types of local anesthetics, articaine 4% with epinephrine 1:200,000, on blood glucose levels in diabetic and non-diabetic patients.

Methods

Study design

This study is a clinical trial with two parallel groups. The study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1401.532). Inclusion criteria include Patients who, according to their report, either do not have any underlying disease or only have type 2 diabetes, patients who need an anesthetic injection in the form of infiltration, patients from whom written consent has been obtained, in the group of diabetic patients, patients whose diabetes is controlled (minimum: 70 mg/dl and maximum: 180 mg/dl) (11). Exclusion criteria include patients unwilling to participate (12), patients having an allergy to amide anesthetics (12), and patients with uncontrolled diabetes (11, 13).

Sample size calculation

To determine the sample size, the information from the Kalra study was used, in which the average blood sugar after 20 minutes of injection in two groups was obtained as 242.5 ± 32.9 and 205.6 ± 29.3, respectively. Considering a significance level (α) of 1% and the test power (1-β) of 90%, using the following formula and considering the probability of a 20% reduction, 27 samples were deemed necessary in each group. This number was increased to a total sample size of 30 in each group (10).

$$n = \frac{(Z_{1-a/2} + Z_{1-\beta})^2 * (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Treatment methods and effect evaluation

Patients with diabetes were included in the intervention group, while those without the disease were included in the control group. In this study, an intervention was performed in both groups; people were placed in two predetermined groups, and there was no randomization or blinding. This study was conducted at the Dental Clinic (Toba), Mazandaran University of Medical Sciences. First, the medical and dental histories were obtained from both groups of patients. In the group of diabetic patients (whose diagnosis of diabetes was confirmed by an internist using the HbA1c test), before any intervention, it was asked whether the blood sugar concentration was controlled and measured. In both groups of patients, blood sugar concentration in the baseline state was measured using a glucometer device (AGM01, Avan company/Iran). Then, while the patient was in a semi-supine position, two capsules of articaine 4% with epinephrine 1:200,000 (Exir Company/Iran) were injected using the infiltration method. In total, for each patient, an amount of 3.6 ml of articaine anesthetic solution, containing 0.01 mg of epinephrine, was injected. For this purpose, the needle was inserted from the depth of the vestibule, and the injection was performed in the apex area of the desired tooth root. The blood sugar concentration was measured twice; for the first time, it was measured after 5 minutes of anesthetic injection; for the second time, it was measured after 15 minutes.

Statistical analysis

Descriptive indices such as mean, standard deviation, frequency, and percentage were used. For inferential analysis, the hypothesis of normality of the variables was checked using the Shapiro-Wilk test, and non-parametric Mann-Whitney, Chi-square, and GEE tests were used.

SPSS software version 22 was used for the statistical calculations, and the level of statistical significance was set at 0.05.

Results

A total of 60 people participated in this study, with a mean and standard deviation age of 40.75 ± 12.85 years. In Table 1, the descriptive information of age in the two groups is reported and compared. According to the findings, the age of the diabetic group was considerably higher than that of the non-diabetic group ($P < 0.001$).

Women made up 51.7% of the participants in this study. In Table 2, the frequency information of gender in the two groups is reported and compared. The comparison of gender in the two groups showed that the distribution of gender in the two groups was not significantly different from each other and that they were homogeneously distributed ($P = 0.071$).

According to the findings, the average blood glucose level in the diabetic group was consistently greater than that in the non-diabetic group ($P < 0.001$).

Due to the significant interaction between group and time, the results are presented separately for the two groups in Table 3. In the diabetic group, age and time had a significant relationship with the blood glucose concentration. As the patient's age increased, the average blood glucose concentration increased by 1.27 units. In addition, the average blood glucose at 15 minutes was 7.20 units higher than at zero time and had a significant difference with zero time ($P = 0.005$). The average blood glucose in 5 minutes was 0.77 units higher than at zero time and had no significant difference with zero time ($P = 0.514$).

In non-diabetic patients, age had a significant relationship with blood glucose concentration. As the age of patients increased, the average concentration of blood

Table 1. Comparison of age and gender in two treatment groups

Variable		Total	Group		*P* value
			Diabetic	Non-diabetic	
Age[a]		40.75±12.85	11.49±46.67	11.67±35.03	<0.001[c]
Gender[b]	Female	31 (51.7)	19 (63.3)	12 (40.0)	0.071[d]
	male	29 (48.3)	11 (36.7)	18 (60.0)	

a: mean±sd b: N (%) c: independent t-test d: chi-square test

Table 2. Comparison of blood glucose concentrations at different times between the two groups.

Time	Group				*P* value[d]
	Diabetic		Non-diabetic		
	Mean±SD	Mean Rank	Mean±SD	Mean Rank	
0	142.47±25.20	42.25	101.70±19.35	18.75	<0.001
5 min	143.23±27.16	41.97	101.97±19.47	19.03	<0.001
15 min	149.67±30.86	41.78	102.23±23.63	19.22	<0.001

d: Mann-whitney U test

Table 3. Factors investigated on blood glucose level using the GEE method, separated into two diabetic and non-diabetic groups

group	variables		B	SE	%95 CI	*P*-value
diabetic	gender	male	-			
		female	2.70	8.13	-13.24, 18.6	0.740
	age		1.27	0.24	0.79, 1.74	0.001>
	time	0	-			
		5 min	0.77	1.17	-1.53, 3.07	0.514
		15 min	7.20	2.57	2.16, 12.24	0.005
Non-diabetic	gender	male	-			
		female	0.44	6.89	-13.06, 13.94	0.949
	age		0.64	0.29	0.07, 1.20	0.027
	time	0	-			
		5 min	0.23	0.57	-0.89, 1.36	0.684
		15 min	0.60	1.90	-3.13, 4.33	0.753

glucose increased by 0.64 units. In addition, the average blood glucose in 15 minutes was 0.60 units higher than at zero time and had no significant difference with zero time ($P=0.753$). The average blood glucose in 5 minutes was 0.23 units higher than that at zero time and was not significantly different from zero time ($P=0.684$).

Discussion

There is limited research on the effects of local anesthesia on the metabolic and cellular functions of the human body. In this clinical trial, two capsules of articaine were administered via infiltration to two groups: Those with diabetes (experimental group) and those without (control group). Before the injection, as well as five and fifteen minutes later, blood glucose levels were assessed. The results indicated that the average blood glucose concentration in the diabetic group was significantly higher than in the non-diabetic group at all three time points. Additionally, the average blood glucose at 15 minutes showed a statistically significant increase compared to baseline, whereas the change at 5 minutes was not significant.

A study by Ridder et al. on the contraindications of articaine was conducted and stated that the contraindication of articaine for patients with diabetes is based on a warning against the use of large amounts of epinephrine. It opposes the action of insulin and converts it into a hyperglycemic hormone. Their study also stated that the probability of complications is different in the population; for example, insulin-dependent diabetics or uncontrolled diabetics are at an increased risk for complications such as acidosis and hyperglycemic coma. However, this is unlikely to occur at the low doses used in dentistry (14). In addition, Dionne et al. measured circulating epinephrine levels in two groups of patients undergoing oral surgery—one receiving local anesthesia without epinephrine and the other with epinephrine—and it was found that injected epinephrine increased the adrenal response to preoperative stress (15).

Another potential issue for insulin-dependent diabetic patients is that they often delay eating for several hours after a dental visit due to the lingering numbness from anesthesia. This disruption of their normal eating schedule increases the risk of hypoglycemia, which is why insulin doses may need to be adjusted in advance (16).

In contrast to our findings, the study by Diaconu et al. showed a significant decrease in blood glucose concentration before surgery in patients who received 4% articaine with epinephrine 1:200,000. However, in the present study, a mild increase in blood glucose was observed in diabetic patients following the injection. This slight postoperative hyperglycemia was attributed to the endogenous release of catecholamines, which can cause a transient rise in blood glucose levels (17). Additionally, even though stress always causes the body to release endogenous adrenaline, exogenous epinephrine has a considerable impact (18).

The study by Madan et al. showed that blood glucose levels in people with controlled diabetes significantly increase when local anesthetics and adrenaline are used together (19). In contrast, the study by Santos examined the effects of pure lidocaine and lidocaine combined

with epinephrine in diabetic patients and found no significant differences in blood glucose levels between the groups at any time point. It's interesting to note that over time, blood glucose levels significantly decreased in both groups. Furthermore, there were no appreciable variations in the groups' hemodynamic metrics or anxiety levels (20). Differences in patient characteristics and glucose level measurement techniques may be the cause of variations seen among studies. Epinephrine can stimulate glucose production even without an increase in circulating glucagon levels or a reduction in peripheral insulin concentration. This suggests that epinephrine exerts a direct effect on the liver and may serve as a physiological regulator of hepatic glucose production in humans. Furthermore, while transient elevations in epinephrine temporarily enhance glucose production, persistent hyperepinephrinemia leads to a sustained reduction in glucose clearance, which may significantly contribute to its overall hyperglycemic effect (21).

Articaine has become popular in dentistry over the last 20 years. One distinctive structural characteristic of this amino-amide substance is that it has a thiophene ring rather than a benzene ring. Furthermore, articaine's thiophene ring has an ester group that is quickly hydrolyzed by plasma esterases; this results in a very short plasma half-life (20 minutes) and less systemic toxicity (neurological and cardiac).

In the present study, no significant association was found between participants' gender and changes in blood glucose levels. Similarly, Tily et al. conducted a study on 60 healthy and diabetic individuals and reported no significant relationship between gender and blood glucose variations. However, they did observe a significant difference in glucose level changes between diabetic patients who had taken their hypoglycemic medication and those who had not (22). Furthermore, their investigation highlighted the correlation between the blood glucose level and the number of anesthetic capsules injected, which was not significant for up to six capsules. To alter blood glucose levels, however, a number of additional factors must be taken into account, either raising or lowering them. This study sought to examine the association between patients' blood glucose levels and age, gender, psychological characteristics, time interval measurement (post-injection and tooth extraction), type of hypoglycemic medication, and degree of surgery.

The present study demonstrated a statistically significant increase of 7 units in blood glucose concentration in diabetic patients 15 minutes after the injection. However, this increase does not constitute a contraindication for the use of this anesthetic. Therefore, the administration of two carpules of articaine containing epinephrine 1:200,000 (0.04 mg) is considered safe for these patients (23). In general, as long as the condition and diet of diabetic patients are under control, vasoconstrictor drugs can be used for most patients (14). As with all at-risk populations, the lowest effective dose should be administered to minimize potential risks. However, it is essential to identify patients with uncontrolled diabetes, as they may be at a higher risk for complications.

The limitation of this study was the scarcity of existing research in this area, highlighting the need for further studies with larger sample sizes.

Conclusion

According to the findings of the study, the blood glucose concentration in diabetic patients increased significantly 15 minutes after the injection; however, this increase in glucose did not create a contraindication for the use of this anesthesia, and the use of 2 articaine capsules containing epinephrine 1:200,000 was allowed in these patients.

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Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interest.

Data Availability Statement

All necessary data will be available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the Ethics Committee of the Mazandaran University of Medical Sciences, Sari (Ethical code: IR.MAZUMS.REC.1401.532).

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