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Original Research Article

In Vivo Comparative Study Between Articaine and Mepivacaine on Hepatic and Pancreatic Function Using Diabetic Rat Model

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ABSTRACT

Local anaesthetics with amide bases are generally thought to be safe to use. However, there is little research on its safety in diabetic individuals. The current study aimed to assess two widely used amide-based local anaesthetics, articaine and mepivacaine, in the context of healthy and diabetic rats to determine their impact and safety. A total of 30 male rats divided into two groups (healthy and diabetic groups) were used for this study. The rats were injected with local anaesthetic agents (articaine or mepivacaine). The rats' biochemical parameters were compared in order to assess the impact of various medications. The study's findings showed that, in comparison to the effects of articaine, mepivacaine considerably raised the levels of blood sugar (BS), aspartate aminotransferase (AST), alanine transaminase (ALT), and amylase in healthy rats. In diabetic rats, mepivacaine significantly increased BS, AST, ALT and amylase levels compared with articaine (p<0.001).
In contrast, the increase in this group was higher than in healthy rats. However, the gamma-glutamyl transpeptidase (GGT) level showed non-significant differences compared to the control group in both groups. Articaine induced the least change in biochemical parameter levels in healthy and diabetic rats compared to mepivacaine.

Keywords: Articaine , Biochemical parameters, Diabetes, Mepivacaine , Wistar albino rats.

Introduction

Diabetes is a metabolic disorder with high blood sugar levels over a prolonged period that causes hyperglycaemia due to a defect in insulin secretion, action, or both.[1] The global percentage of adults with diabetes mellitus increased from 4.7% in 1980 to 8.5 % in 2014. The International Diabetes Federation (IDF) predicts diabetic patients will exceed 552 million by 2030. All types of diabetes (Type 1 and Type 2 diabetes) are characterised by elevated levels of glucose.[2–4] Type 2 diabetes mellitus (T2DM) represents (90-95%) of diabetic patients and is more common in people older than 45 years old as well as overweight adults[5], whereas Type 1 diabetes mellitus (T1DM) forms (5-10%) of diabetic patients.[6–8] Type 1 diabetes is most typical in children worldwide.[9–11] Diabetes is associated with microvascular and microvascular disease (atherosclerosis) and neuropathy. Together, these are leading causes of renal failure [12], limb amputation, myocardial infarction, and stroke.[13,14] Additionally, it is associated with non-vascular diseases such as cancers, especially liver cancer.[15,16] The role of liver enzymes in the prognosis of diabetes has received particular attention.

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Although numerous studies have linked higher liver enzymes with diabetes, the findings remain contradictory in this regard. Different studies have found a strong link between diabetes and elevated GGT (gamma-glutamyltransferase), AST (aspartate aminotransferase), and ALT (alanine aminotransferase) levels.[17,18] Amide-based local anaesthetics play a vital role in treating and preventing pain in patients. Medical practitioners prefer it because of its proven efficacy, low allergies, and minimal toxicity through clinical use.[19,20] A variety of amide-based local anaesthetics can have side effects, most of which are dose-related and occur mainly due to systemic administration or exposure. These side effects include neurological symptoms such as drowsiness, tinnitus, dizziness and twitching, and gastrointestinal effects.[21,22] At higher doses, ventricular arrhythmias, and cardiovascular depression are potentially possible side effects.[23–25] Most research on the adverse effects of amide-based local anaesthetics has mainly concentrated on their neurological effects. Therefore, the purpose of the current investigation was to assess the effects of mepivacaine and articaine, two commonly used amide-based local anesthetics, on rats that were both healthy and had been given diabetes.

Materials and method

Ethical Approval
The University of Jordan in Amman, Jordan's Department of Biology approved all experimental procedures, and all studies adhered to the standards established by the FIOCRUZ Committee on Ethics for the Use of Animals (CEUA LW16/14).

Experimental protocol
Thirty male Sprague-Dawley rats, weighing 190±10 g and eight weeks old, were taken from the animal laboratory. To prevent any inconsistencies, all rats were weighed at the beginning. The rats were housed in standard cages with 22±2 ℃ ambient temperature, 55% relative humidity, and 12 hours of daylight starting at 8:00 am. For five days, the rats were allowed unrestricted access to regular feed and water as they acclimated. The Guidelines for Laboratory Animal Care were followed when using and caring for rats.

Animals groupings
The rats were divided into two groups based on a simple random sampling method. Three subgroups were created from the first group (n = 15), which was the healthy group. There were three subgroups created from the second diabetes group (n = 15). The healthy subgroup 1 included the negative control (n=5), subgroup 2 treated rats with mepivacaine (n=5), and subgroup 3 treated with articaine (n=5) for 2hr and 4hr, respectively. The second diabetic rats' group was randomly divided into 3 subgroups: control diabetic rat (n=5) and treatment groups, with mepivacaine (n=5) and articaine (n=5) for 2hr and 4hr respectively.

Induction of diabetes
The experimental rats were given an intraperitoneal dose of 60 mg/kg body weight streptozotocin to induce diabetes. After three days, the On-call plus glucometer strips (Glucometer Asensia Contour Plus) were used to measure fasting blood glucose levels in order to analyze and confirm the emergence of diabetes. Diabetic animals were defined as those with more than 200 mg/dl of blood sugar.[16]
Mepivacaine and articaine were used with catalogue numbers (Pharamaffiliates, PA0259550, and PA 0175000, respectively). The rats were anaesthetised by ether inhalation. Two hours later, the initial blood samples were drawn so that blood sugar and liver enzyme levels, such as aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), and amylase, could be determined using ELISA kits. Then, the maximum dosages of the local anaesthetic drugs were given to the rats through the oral mucosa based on the pharmacological toxicity. The dosages of mepivacaine (5 mg/kg) and articaine (7 mg/kg) for each type of amide local anesthetic were used. Four hours after the initial blood samples, second blood samples were taken to assess liver enzyme levels, amylase, and blood sugar.

Statistical analysis
The two groups' data were analyzed using two-way ANOVA, and the data were expressed as mean ± standard error of the mean. The standards for statistical significance were $p < 0.05$*, $p < 0.01$**, and $p < 0.001$***. To conduct the analysis, GraphPad Prism 9.4.0 was used.

Results and Discussion

The results of the current study show the effects of the anaesthetic agents on the hepatic enzyme, amylase, and blood sugar levels (Table 1). All groups had an increase in biochemical parameter levels following the administration of anesthetics. Rats with induced diabetes showed a considerably greater degree of change in blood sugar, AST, ALT, and amylase levels compared to healthy rats ($p<0.001$).
The glucose level in healthy rats increased significantly ($p<0.001$) after treating the rats with mepivacaine and articaine. However, the blood sugar level significantly increased after the injection of the rats with both anaesthetics in the diabetic rats (Figures 1,2,4,5). The figures illustrated that the rat's blood sugar levels increased with the administration of mepivacaine more than those injected with articaine. Furthermore, the amylase level was increased in both groups of healthy and diabetic rats after administration of mepivacaine and articaine. In contrast, the amylase level in anesthetised diabetic rats was higher with mepivacaine than with articaine (Figures 3,6). Clinical trials that compare currently available local anaesthetics with articaine have a wide range regarding the study's approach and results.[26] In a previous study, 160 volunteers participated in a randomised controlled experiment to examine the effectiveness of articaine and lidocaine.[27] They found that the onset and duration of anaesthesia varied significantly between various local anaesthetic medications. Recent investigations have found that compared to other anaesthetics, articaine is more effective at various sites of action. Certain studies have shown that articaine was more effective in producing anesthesia and extending the duration of the anesthetic effect.[28]
Furthermore, the findings demonstrated that both the diabetic and the healthy groups of rats had considerably ($p<0.001$) different changes in the amount of AST level alteration brought on by the administration of each anesthetic medication (Table 1).
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Figure 1. Effect of mepivacaine on biochemical parameters in healthy rats. Data are expressed as mean±SEM were n=5. *** significant $p<0.001$ compared to healthy control.

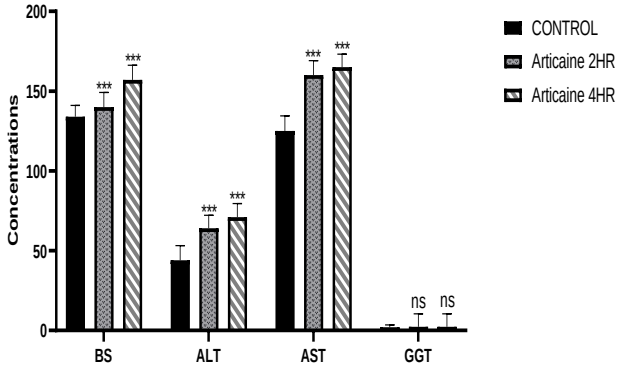

Figure 2. Effect of articaine in biochemical parameters in healthy rats. Data are expressed as mean±SEM were n=5. *** significant $p<0.001$ compared to healthy control.

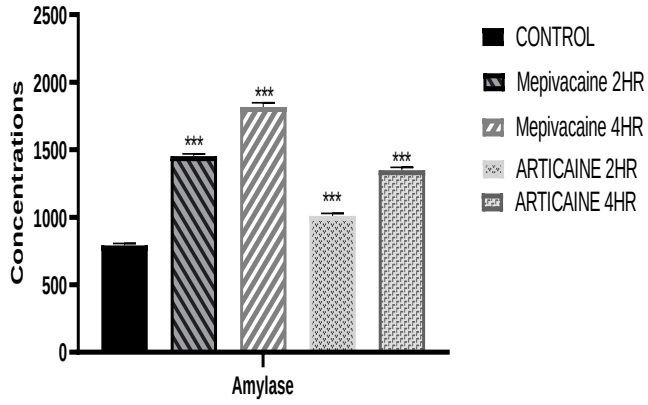

Figure 3. Effect of mepivacaine and articaine in the level of amylase in healthy rats. Data are expressed as mean±SEM were n=5. *** significant $p<0.001$ compared to healthy control.

Table 1. Biochemical parameters in the serum of rats (healthy and diabetic) anaesthetised by mepivacaine and articaine. Data are expressed as mean±SEM were n=5.

Groups	Biochemical parameters	Control	Mepivacaine		Articaine	
			2hrs	4hrs	2hrs	4hrs
Healthy rats	BS	134±12	142±10.1	165 ±8.1	140±9.11	157±9.18
	AST	125±9.45	135±9.1	195 ±9.17	160±9.06	165±8.16
	ALT	44±9.23	74±9.2	94 ±7.52	64±8.13	71±8.52
	GGT	2±1.48	3.2±2.07	3.25 ±2.16	2.3±8.07	2.25±1.16
	Amylase	792±14.4	1452±17.55	1817±12.18	1010±19	1349±20.46
Diabetic rats	BS	300±12.68	581±10.2	808 ±12.1	497±8.11	600±9.18
	AST	240±15.76	499±12.06	561 ±11.70	262±8.01	478±6.16
	ALT	94±30.82	153±11.30	177 ±12.25	104±9.1	121±8.52
	GGT	7±5.86	9±6.07	8 ±5.16	8±4.7	9±4.16
	Amylase	943±30	2083±66	2296 ±70	1938±40	1973±50

AST levels changed more when mepivacaine was given in diabetic rats than when articaine was used in other groups. The results for ALT in both healthy and diabetic rats were consistent with AST results, as the ALT for healthy and diabetic rats after anaesthetic administration was significantly higher than the negative control (untreated group). In comparison, the level of ALT in diabetic rats after administration of mepivacaine and articaine exhibited a higher level than in healthy rats. However, the level of ALT by using mepivacaine was higher than articaine in diabetic rats. Significant changes were not detected in the GGT level in healthy and diabetic rats treated with mepivacaine and articaine compared to untreated rats (Figures 1,2,4,5).

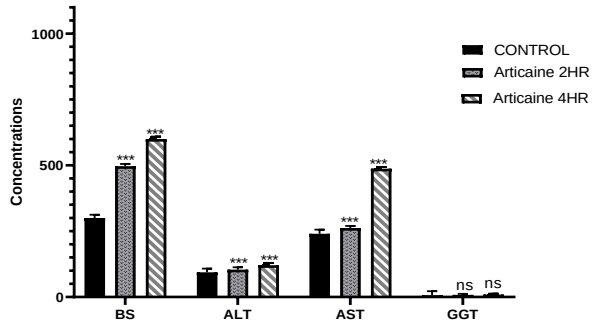

Figure 4. Effect of articaine in biochemical parameters in diabetic rats. Data are expressed as mean±SEM were n=5 .*** significant p<0.001 compared to diabetic control.

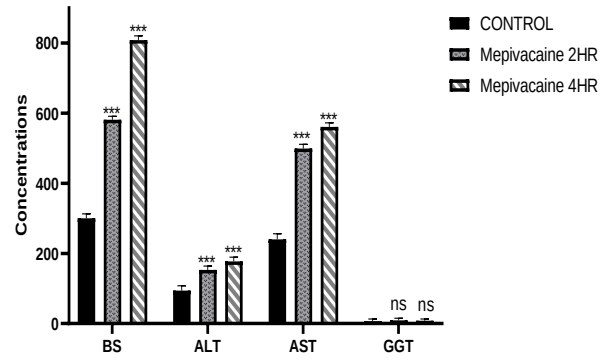

Figure 5. Effect of mepivacaine in biochemical parameters in diabetic rats. Data are expressed as mean±SEM were n=5 .*** significant P<0.001 compared to diabetic control.

In the current investigation, rats with induced diabetes showed minimal alterations in metabolic markers due to articaine. Our results agreed with the study conducted by Alizadeh which showed that articaine induced lesser change in liver enzymes (ALT, AST, GGT) than mepivacaine. The success of articaine may be attributable to the smaller size of the thiophene ring used instead of the benzene ring and the presence of an intramolecular hydrogen bond that facilitates easier bone absorption.[29] In this study, the biochemical parameters level was elevated after treating the diabetic rat with mepivacaine compared to articaine because the articaine has lesser systemic toxicity and a wider therapeutic range than other amides and rapid metabolism of about 90% into inactive metabolites. Additionally, it has an ester ring, which allows the liver's hepatic microsomal enzymes and plasma esterase to hydrolyse articaine in the blood. These properties make Articaine's hard and soft tissue diffusion potential better than other local anaesthetics.[30] Nonetheless, mepivacaine is frequently used in uncomfortable clinical settings due to its increased compatibility with inflammatory tissues, quicker onset, and longer-lasting analgesic effects.[31]

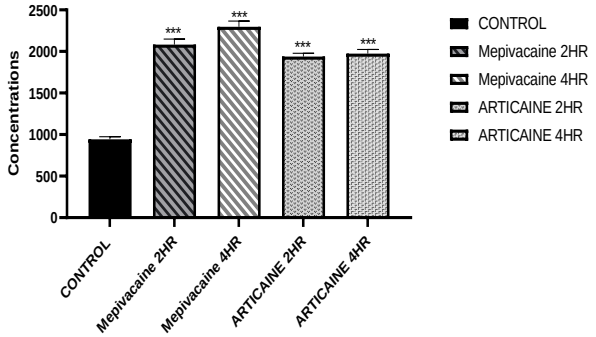

Figure 6. Effect of mepivacaine and articaine in the level of amylase in diabetic rats. Data are expressed as mean±SEM were n=5. *** significant p<0.001 compared to diabetic control

However, several investigations have demonstrated that patients receiving repeated dosages or infusions of local anesthetics ought to be cautious, as liver P450 enzyme first-pass metabolizes aminoamide local anesthetics, with the specific drug's pharmacological properties determining this process.[32] This demonstrates the significance of our discovery that various local anesthetics altered liver enzyme levels and other biochemical markers to varying degrees. In the rats with induced diabetes, articaine showed fewer liver alterations. A small amount of the drug is excreted in urine, contributing to decreased hepatic toxicity. The remainder is eliminated through the liver and kidneys. Finally, to our knowledge, no study has contrasted articaine and mepivacaine effects on liver enzyme and biochemical parameters.

Conclusion

Local anaesthesia with articaine caused less change in the levels of biochemical parameters in normal and diabetic rats than mepivacaine.

However, mepivacaine should be used less than other anaesthetics in dental surgery.

Conflict of interest

There is no conflict of interest disclosed by the authors.

Authors' declaration

The authors hereby attest that the work presented in this article is entirely original to them and that they will be held accountable for any claims relating to its content.

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