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Effect of local anesthetics on renal function: An animal study in Iran

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ABSTRACT

Background: Although most of the metabolism of local anesthetics (LAs) takes place in the liver, no study has investigated the effect of these anesthetics on the kidney function of single-kidney humans or animals. The present study was conducted to examine the effect of LAs on renal function in single-kidney rats.

Materials and Methods: The present experimental animal study with two control groups was done in an animal laboratory. Forty-two rats were randomly assigned to seven groups of six rats, including two control groups and five experimental groups. The experimental groups underwent intraperitoneal anesthesia with 2% lidocaine, 2% lidocaine with 1:80,000 epinephrine, 4% articaine, 3% prilocaine with 0.03 IU Felypressin, and 3% mepivacaine, respectively. Unilateral nephrectomy was done. After 24 h, the rats' blood urea nitrogen (BUN), serum creatinine (Cr), and blood specific gravity (BSG) were measured. A standard dose of anesthetics was injected into the peritoneum for 4 days afterward. Then, these indices were measured again 24 h after the last injection. Data were analyzed using IBM SPSS (version 21.0). One-way analysis of variance, Tukey's honestly significant difference *post hoc*, and paired *t*-tests were used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results: The results indicated significant differences among groups in the rats' BUN and serum Cr 24 h after nephrectomy ($P < 0.05$). However, there were no significant differences in BUN, BSG, and Cr among groups after the interventions.

Conclusion: LAs did not affect renal function in single-kidney rats. Therefore, dentists can use the anesthetics in single-kidney people.

Key Words: Articaine, kidney function test, lidocaine, local anesthesia, mepivacaine, prilocaine, single kidney

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INTRODUCTION

Congenital abnormalities of the kidney and urinary tract occur in 4/1000 births in Russia and some Asian and European countries.[1] About 30,000 live donor kidney transplant surgeries are performed worldwide every year.[2] Although most donors have the same life expectancy and quality of life as healthy people with two kidneys, living kidney donation is associated with a low but increased risk (<0.5% over 15 years)

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of developing end-stage renal disease.[3] The donor's remaining kidney typically becomes hypertrophic and adjusts its function with the increased kidney plasma flow (F_p) and glomerular filtration rate (GFR), and this partial compensation may cause renal disease.[4] This compensatory mechanism begins within the first few hours after nephrectomy. Some studies have found that GFR reaches 66% of its prekidney donation level within 8 h of transplantation.[5] In dental surgeries, renal function is assessed indirectly by measuring serum creatinine (Cr).[6]

Dental clinicians prefer to use amide local anesthetics (LAs) because amide drugs can achieve the effect of surgical anesthesia faster and more reliably and have fewer allergic reactions than ester anesthetics.[7] Various formulations are used in dentistry, including lidocaine, mepivacaine, articaine, bupivacaine, and prilocaine.[8] LAs are the safest and most effective pain control and prevention medications; however, they have certain side effects that clinicians should identify and control.[9] Amide LAs are mainly excreted through metabolization in the liver,[5] and their unaltered residue is excreted through urination.[10]

Lidocaine is a LA that is almost exclusively metabolized in the liver[8] and excreted through the kidneys, 10% unchanged and 80% as their metabolites.[11] Mepivacaine is an amide structure that is rapidly metabolized and excreted through the liver, and its unchanged amount excreted through the liver is also 1%.[12] Prilocaine is metabolized in two stages. The first stage occurs in the kidneys and lungs, which creates metabolites that are easily broken down by the liver in the second stage.[13] Consequently, liver and kidney dysfunction may change the kinetics of prilocaine,[11] and its excessive amount in the blood can cause cardiovascular impairments, nervous system diseases, liver and kidney toxicity, and methemoglobin formation.[14]

Articaine, an amide LA widely used in dentistry, is inactivated by plasma carboxylesterase-induced cleavage of a methyl ester on the aromatic ring. Articaine has a serum half-life of 20–30 min, shorter than the other amide LAs due to the more rapid hydrolysis of the ester group within the plasma.[15] A total of 75% of articaine acid is excreted unaltered, and the rest is glucuronidated before excretion through the kidney. LAs and their metabolites can accumulate in patients with acute renal failure and cause systemic LA poisoning.[11,14] However, patients with kidney dysfunction are at a higher risk of adverse responses. This may lead to an increase in side effects due to LAs, and a lower-than-usual dose of LAs may be adequate to produce a similar anesthetic effect.[16] They may be life-threatening if the patient has an uncontrolled systemic disease.[17]

There is conflicting evidence regarding the effects of anesthetics on the renal function of patients with renal damage or failure.[18-21] Some studies have shown that the administration of certain anesthetics during surgery can affect renal function.[18,19,21] However, others have shown that some anesthetics have anti-necrotic and anti-apoptotic effects and protect the individuals against acute renal damage.[21-23]

On the other hand, although the effect of anesthetics on the kidney function of patients with kidney failure has been investigated, to the best of the researchers' knowledge, there are no reports in the literature about the effect of LAs on the renal function of healthy people or single-kidney animals. Thus, the present animal study aimed to determine the effect of LAs on kidney function in single-kidney rats. The research hypothesis was "LAs would have no effects on renal function in single-kidney rats."

MATERIALS AND METHODS

The present experimental animal study was done in an animal laboratory. A total of 42 male Sprague–Dawley rats weighing between 250 and 350 g were procured from the animal house of Shiraz University of Medical Sciences. The study protocol was approved by the ethics committee of the university (IR. SUMS. REC.1397.312). The rats, were divided into seven groups of six each using simple random sampling, as follows:

- Group one (Control Group 1): Six healthy rats receiving no intervention
- Group two (Control Group 2): Six single-kidney rats receiving no LAs
- Group three: Six single-kidney rats receiving lidocaine LA
- Group four: Six single-kidney rats receiving lidocaine LA plus epinephrine
- Group five: Six single-kidney rats receiving articaine LA
- Group six: Six single-kidney rats receiving prilocaine LA plus felypressin

- Group seven: Six single-kidney rats receiving mepivacaine LA.

The rats were kept in alternating 12-h light-dark cycles (6 am–6 pm) throughout the experiment at 23°C ± 2°C without food or water limitations. The left kidneys of all groups (except the control group) were removed by a veterinarian under general anesthesia with 40 mg/kg ketamine and 10 mg/kg xylazine.[24] Then, 24 h later, 1 ml of blood was taken from the rats' hearts in all groups to measure blood urea nitrogen (BUN), serum Cr, and blood-specific gravity (BSG). A standard dose of anesthetics was then injected into the peritoneum daily at 9 am for 4 days, and rats had free access to standard chow and water. The dosages for each type of LA included 2% lidocaine, 5 mg/kg (Pasteur Institute of Iran); 2% lidocaine with 1:80,000 epinephrine, 7 mg/kg (Persocaine-E; Darou Pakhsh Pharmaceutical Manufacturing Co., Tehran, Iran); 4% articaine, 4 mg/kg (Septocaine; Septodont, New Castle, DE); 3% prilocaine with 0.03 IU felypressin, 8 mg/kg (Dentanest; Darou Pakhsh Pharmaceutical Manufacturing Co., Tehran, Iran); and 3% mepivacaine, 5 mg/kg (Novocol Pharmaceutical of Canada, Inc., 25 Wolseley Court Cambridge, ON N1R 6 × 3 519-623-480).[8,9,25,26] Then, 24 h after the last injection, second blood samples were taken to assess BUN, Cr, and BSG. Before and after the intervention, data were recorded in a data collection form. A person with a bachelor's degree in laboratory sciences performed all the pretests and posttests using a calibrated device.

Statistical analysis

The Shapiro–Wilk test was employed to assess the normality assumption. Given the normal distribution of the data, one-way analysis of variance and Tukey's honestly significant difference *post hoc* test were used to perform the intergroup comparisons of BUN, Cr, and BSG. The paired *t*-test was used to compare BUN, Cr, and BSG before and after the administration of the medications in each of the intervention and control groups. The results obtained were analyzed using IBM SPSS for Windows version 21.0 (Armonk, NY, USA, IBM Corp). $P < 0.05$ was considered statistically significant.

Ethical considerations

This research was approved by the Ethical Committee of Shiraz University of Medical Sciences with the ethical code of IR. SUMS. REC.1397.312. The use of and care for rats were based on the Guidelines for Laboratory Animal Care.[27].

RESULTS

Of the 42 rats, two did not survive after the surgery. There was a significant difference among the 7 groups before the intervention in BUN and Cr, which means the 7 groups were not homogeneous before the intervention. Therefore, to compare the groups after the intervention, the differences before and after the intervention were used. The intergroup comparison indicated the difference among groups in BUN was significant before the intervention (injection of LAs) ($P < 0.001$) [Table 1]. The *post hoc* test results showed a significant decrease in BUN between group one (without nephrectomy) and all other groups. However, the difference in BUN changes was not significant after the intervention among the study groups [Table 2]. The intragroup comparison showed, although BUN had decreased in groups 2–7 after the intervention, the difference was only significant in group two with nephrectomy (which had not received anesthetics) ($P = 0.04$) and group 3 (which had received lidocaine) ($P = 0.04$) [Table 3]. However, BUN did not change in the group without nephrectomy.

The difference in Cr level among the study groups was significant before the intervention ($P < 0.009$) [Table 1]. The *post hoc* test results also showed a significant decrease in serum Cr in group 1 (without nephrectomy) compared to groups 5 and 7 before the intervention. However, the difference in changes was nonsignificant among the study groups after the intervention [Table 2].

No significant differences were also observed among the groups before the intervention in mean BSG [Table 1] as well as BSG changes [Table 2]. The results showed a significant difference in BSG after the intervention in group 6 ($P = 0.04$), However, there was no significant difference in the BSG of other study groups before and after the intervention [Table 3].

DISCUSSION

The present study was conducted to evaluate the effect of LAs (lidocaine, lidocaine plus epinephrine, articaine, prilocaine, prilocaine plus felypressin, and mepivacaine) on renal function in single-kidney rats.

Table 1: Comparing mean serum level of blood urea nitrogen, creatinine, and specific gravity before the intervention among study groups

Factors	Time	1	2	3	4	5	6	7	*P*
BUN	Before	16.50±1.87	27.60±1.82	26.33±1.75	27.50±2.07	22.83±3.82	22.83±3.82	26.17±6.08	0.001
Cr	Before	0.55±0.05	0.67±0.52	0.66±0.08	0.66±0.05	0.73±0.10	0.66±0.08	0.72±0.09	0.009
SPG	Before	1.04±0.01	1.04±1.01	1.04±0.01	1.03±0.01	1.03±0.01	1.03±0.01	1.03±0.01	0.290

One-way ANOVA. 1: Control 1: Without nephrectomy and anesthesia; 2: Control 2: With nephrectomy and no local anesthetics; 3: Lidocaine; 4: Lidocaine plus epinephrine; 5: Articaine; 6: Prilocaine plus felypressin; 7: Mepivacaine. BUN: Blood urea nitrogen (mg/dL); Cr: Creatinine (mg/dL); SPG: Specific gravity (IU/mg); ANOVA: Analysis of variance

Table 2: Comparisons of change (Δ) in the blood factors between the groups

Group	ΔBUN	ΔCr	ΔSPG
Control 1	0.00±1.26 (−0.5)	0.00±6.32 (0.0)	−0.50±0.55 (−0.5)
Control 2	−10.00±3.32 (−9.0)	−6.00±0.5.48 (−10.0)	−1.60±1.14 (−2.0)
Lidocaine	−6.83±2.79 (−7.0)	3.33±10.33 (0.0)	−1.17±2.64 (−0.5)
Lidocaine + epinephrine	−5.33±6.05 (−7.0)	1.67±7.53 (0.0)	−0.17±2.04 (−0.5)
Articaine	−5.67±6.47 (−5.0)	0.00±10.95 (0.0)	−0.67±1.63 (−0.5)
Prilocaine + felypressin	−5.33±5.92 (−6.0)	−5.00±3.67 (0.0)	−2.67±1.51 (−3.0)
Mepivacaine	−6.20±9.18 (−4.0)	−6.00±−11.40 (−10.0)	−1.40±2.88 (−3.0)
P	0.15	0.37	0.25

Δ: The difference between measurements before and after intervention (after−before). For ease of presentation, data were multiplied by 100. One-way ANOVA. BUN: Blood urea nitrogen (mg/dL); Cr: Creatinine (mg/dL); SPG: Specific gravity (IU/mg); ANOVA: Analysis of variance

Table 3: Comparing mean serum level of blood urea nitrogen and creatinine before and after intervention in each group

Factors	Time	1	2	3	4	5	6	7
BUN	Before	16.50±1.87	27.60±1.82	26.33±1.75	27.50±2.07	22.83±3.82	22.83±3.82	26.17±6.08
	After	16.50±1.52	17.60±2.30	19.50±1.76	22.17±4.26	17.50±3.27	17.50±3.27	20.20±3.56
	P	0.999	0.042	0.027	0.116	0.075	0.078	0.223
Cr	Before	0.55±0.05	0.67±0.52	0.66±0.08	0.66±0.05	0.73±0.10	0.66±0.08	0.72±0.09
	After	0.62±0.04	0.62±0.04	0.70±0.06	0.68±0.04	0.73±0.05	0.62±0.04	1.03±0.01
	P	0.999	0.083	0.414	0.564	0.999	0.180	0.257
SPG	Before	1.04±0.01	1.04±1.01	1.04±0.01	1.03±0.01	1.03±0.01	1.03±0.01	1.03±0.01
	After	1.03±0.01	1.03±0.01	1.03±0.01	1.03±0.01	1.03±0.01	1.03±0.0001	1.03±0.01
	P	0.157	0.066	0.336	0.783	0.336	0.041	0.257

Paired *t*-test. For ease of presentation, data were multiplied by 100. 1: Control 1: Without nephrectomy and anesthesia; 2: Control 2: With nephrectomy and no local anesthetics; 3: Lidocaine; 4: Lidocaine plus epinephrine; 5: Articaine; 6: Prilocaine plus felypressin; 7: Mepivacaine. BUN: Blood urea nitrogen (mg/dL); Cr: Creatinine (mg/dL); SPG: Specific gravity (IU/mg)

The results indicated a significant difference in Cr and BUN among the study groups 24 h after nephrectomy (before the administration of LAs). However, no significant difference was observed in these indicators after the intervention.

Twenty-four hours after nephrectomy, significant differences were observed among the study groups in terms of Cr and BUN. This difference was most striking between group 1 (without nephrectomy) and the other groups with unilateral nephrectomy. Similar to the results of the present study, Goldfarb *et al*. reported a significant increase in Cr 24 h after unilateral nephrectomy.[28] Moreover, in a study by Mehta *et al*., an average of 26 months after kidney donation,[5] and in another study by Kasiske *et al*., 36 months after kidney donation, Cr and BUN increased significantly in the kidney donor groups compared to the controls, but this increase was within the normal range.[29] However, in the present and above studies, there was no abnormal increase in renal function indices. Another study reported improved renal function a week after nephrectomy.[30] Therefore, future studies are recommended to carry out the intervention at least a week after unilateral nephrectomy to assess the effect of anesthetics on renal function so that the single kidney can be adjusted to glomerular filtration.

Considering the significant difference between the groups in BUN and serum Cr indexes before the intervention, the difference in intragroup changes

after the intervention was used to show the effect of the anesthetics. The results showed no significant differences in BUN, serum Cr, and BSG between the study groups after the intervention. Similar to the present study, Lobetti *et al*. conducted a study on dogs under general anesthesia for ovariohysterectomy and indicated no significant change in urine-specific gravity, BUN, and Cr.[31] This study was performed on healthy dogs under general anesthesia, but the present study measured the effect of LAs on the function of single-kidney rats. Furthermore, Pere *et al*. showed that renal dysfunction has no effect on the pharmacokinetics of ropivacaine. In this study, blood samples were used to assay the concentrations of ropivacaine and α_1-acid glycoprotein, and ropivacaine was administered intravenously.[20] However, in the present study, BUN, Cr, and BSG were measured to assess renal function in single-kidney rats. Yet, in both the present and the above studies, LAs had no effect on the kidney function.

Some anesthetic drugs induce anti-necrotic, anti-inflammatory, and anti-apoptotic effects with different mechanisms.[22] In a systematic review, some researchers had hypothesized that lidocaine might protect the kidney against perfusion and necrosis by preventing miRNA dysregulation.[21] Furthermore, Deng *et al*. reported riluzole, lidocaine, and lamotrigine had anti-ischemic effects on the rats' kidney, and the degree of DNA fragmentation was significantly reduced in all of them.[23] Moreover, Peker *et al*. indicated that ketamine and lidocaine injection significantly reduced the high levels of lactate associated with skeletal muscle ischemia-reperfusion injury.[32] In the present study, in the single-kidney group receiving lidocaine, BUN decreased significantly after the interventions. Perhaps due to the anti-inflammatory, anti-necrotic, and anti-apoptotic effects of anesthesia, kidney function impairment was not observed in single-kidney rats after the intervention. Further, investigation of miRNA dysregulation and antitoxins and histological tests were not done in the present study, and this result cannot be confirmed with high confidence.

Inconsistent with the results of the present study, Lee *et al*. showed that LAs, including continuous 1% bupivacaine epidural infusions and chronic infusions of either 5% lidocaine or 2.5% tetracaine, worsened renal function in rats following damage-induced ischemia, which increased both necrotic and apoptotic cell death in the kidney and significantly increased Cr. However, the injection of LAs alone with no prior renal damage or low dose did not affect the renal function.[33] Moreover, in a study by De Martin *et al*., the intravenous injection of lidocaine changed the kinetics of renal parameters in nonhemodialysis patients proportional to the extent of failure, and the difference was only significant in the patients with severe failure. Further, Cr clearance was half of that in the control group, but no changes were observed in renal parameters in the hemodialysis patients compared to the control group following the injection of lidocaine.[18] Uppal *et al*. mentioned that renal function recovery after partial nephrectomy is strongly related to the quality and quantity of conserved kidney.[4] Therefore, the subjects in the present study who also developed nephrectomy despite their renal health and showed no abnormalities in their renal indices before anesthetic injection did not experience any renal dysfunction after the injection.

The above studies were conducted on patients with renal damage or failure or on healthy ones, and the anesthetics led to conflicting results, but in the present study, LAs did not cause renal dysfunction in single-kidney rats. This difference in the results of the above studies can be due to differences in the type of anesthetics, injection method, dose and frequency of administration, measurement time, type of disease, number of samples, and diagnostic tests. However, none of the mentioned studies have been performed on patients or animals with a single kidney.

In the present study, BUN was improved in all the groups with nephrectomy after the interventions (6 days after nephrectomy), however, this reduction was significant only in group 2 (single-kidney rats receiving no anesthetics) and group 3 (single-kidney rats receiving lidocaine). The adaptation of glomerular filtration after 6 days can be another reason for the lack of the effect of LAs on renal function in single-kidney rats, as in a study by Zaky *et al*., renal function improved a week after nephrectomy.[30] In addition, BSG was significantly reduced in group 6 (prilocaine plus felypressin) after the intervention. Yet, considering the lack of significant difference between the control groups and this group, this difference may not be related to the intervention. BSG is used to identify volume depletion and urine concentration and indicate dehydration. Given that the rats received water during the study, this lack of increase can be a good sign of the rats' hydration and even a reduction in BUN,

although there was equal access to water and food in the cages.

In the present study, LAs were expected to have no effects on renal function due to their metabolism in the liver. Therefore, the research hypothesis "LAs would have no effects on renal function in single-kidney rats" was confirmed. Amide LAs are mainly excreted through metabolization in the liver and also through urination.[4] Moreover, Kambakamba *et al*. showed that the patients who had received epidural analgesia with ropivacaine after major liver resection had a higher risk of developing acute kidney injury.[19] If the results of the present study are confirmed in human studies, the injection of LAs in single-kidney cases can be safe. Van der Weijden *et al*. suggested that patients with severe renal insufficiency not only have hyperdynamic circulation and decreased local anesthesia clearance but also show an increase in α1-acid glycoprotein concentration. Therefore, the concentration of these LAs in plasma remains largely unchanged, and no dose reduction is required.[34]

The present study had some limitations. One limitation was the short interval between unilateral nephrectomy and intervention, although based on the studies, this interval is probably appropriate. Given the impossibility of taking urine samples from all rats due to the limited equipment available at Shiraz University of Medical Sciences, it was impossible to measure the estimated GFR (eGFR) in the present study. Although Cr is a good marker for assessing renal function in dentistry, histological diagnostic tests could also help to diagnose kidney tissue damage, but they were not considered in this research.

CONCLUSION

LAs had no effect on the rats' renal function. Dentists can use these results for dental interventions in single-kidney patients. They can carry out dental procedures with greater assurance in single-kidney patients without any concern about renal complications and having to change the dose of anesthetic administered.

However, it is better to first conduct a clinical trial on an adequate human sample. Besides, future studies are recommended to perform the intervention at least a week after unilateral nephrectomy and measure eGFR in addition to Cr. Moreover, future research is required to carry out histological diagnostic studies to measure the renal tissue damage.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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