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RESEARCH ARTICLE

ASSESSMENT OF THE POTENTIALLY TOXIC EFFECT OF 2% AND 4% ARTICAINE ON THE PATIENTS' CARDIOVASCULAR SYSTEM DURING TOOTH EXTRACTION

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ABSTRACT

Aim: The purpose of this study was to conduct a comparative analysis of the potential toxicity of 2% and 4% articaine on the cardiovascualar system of patients during tooth extraction, as well as to assess the risk of complications associated with the use of anesthetics. As part of the study, the tasks were set to assess the toxicity of articaine on cell cultures and analyze hemodynamic changes in patients during the tooth extraction procedure.
Materials and Methods: The determination of the half-life concentration (LC50) in an in vitro study was used to assess cytotoxicity.Monitoring of the cardiovascular and respiratory systems was carried out using Mindray ePM 10.
Results: A cell culture study confirmed that the 2% drug has significantly lower cytotoxicity than the 4% drug. The monitoring results showed that systolic blood pressure was normal before surgery, with no statistically significant differences between the groups ($p>0.05$). 2 minutes after the injection of the anesthetic, the pressure remained normal, but after 4 minutes it increased, while in the 2% articaine group it was 3 mmHg lower than in the 4% group ($p<0.05$). By 8 minutes, the pressure returned to normal values. Dynamics analysis showed a significant increase in systolic blood pressure in both groups by 2 and 4 minutes, followed by a decrease by 8 minutes ($p<0.001$). Diastolic pressure and pulse also did not show significant differences between the groups, but their dynamics increased in both groups by 4 minutes, followed by a decrease by 8 minutes ($p<0.001$). Saturation remained normal, but it decreased by 4 minutes with recovery by 8 minutes ($p<0.001$).
Conclusion: The revealed results confirm that 2% articaine is a safe alternative to 4% articaine, especially for patients with concomitant pathologies. The study highlights the need for careful choice of anesthetics in clinical practice to minimize the risk of complications.

Keywords: Articaine; Cardiovascular system; Cytotoxicity; Tooth extraction; Dentistry

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INTRODUCTION

One of the most common operations in surgical dentistry is dental extraction. This manipulation requires knowledge from the doctor not only in the field of manual skills, but also an understanding of the risks of life-threatening complications that occur during the anesthesia stage. Undesirable reactions may occur due to violations of the anesthesia technique and may also be associated with the anesthetic itself in case of incorrect choice of its dosage and not careful collection of medical history.[1]

In addition, the lack of consideration of individual anatomical features of patients can also lead to complications during the work of a dental surgeon.[2] Increasingly, dentists prefer articaine-based local anesthetics. Articaine is a local anesthetic belonging to the amide group of anesthetics. Good solubility in water leads to rapid penetration through the membrane of a nerve cell or axon and creates intracellularly high concentrations, which is due to a short latency period of 1-3 minutes. Systemic toxicity is prevented by the high value of binding to plasma proteins[3]

Articaine does not cross the placental and blood-brain barriers, unlike other amide anesthetics. This is due to the relatively poor permeability of the vascular endothelium to arrhythmia, therefore the drug penetrates poorly into the bloodstream and lingers longer at the injection site .[4,5]

Adverse reactions occur quite rarely, which allows it to be used in pregnant women and children.[6]

Therefore, articaine is the optimal anesthetic for anesthesia in pregnant and lactating women due to its high degree of binding to plasma proteins – 95%.[7] Studies prove that articaine-based anesthetics are recommended for use in the treatment of pregnant women who have not been diagnosed with extragenital and obstetric pathology .[8]

Articaine-based drugs are the recommended choice of local anesthesia in children from 5 years of age due to their low toxicity and wide range of therapeutic effects [9]. And according to O.V. Gulenko's research, articaine can also be used in the treatment of children under 4 years of age [10]

Articaine, among other things, is a suitable alternative for patients with a true allergy to lidocaine. No cross-reactivity has yet been reported between lidocaine and articaine .[11]

For various somatic diseases, you also need to know how to choose the right anesthetic. For example, lidocaine and mepivacaine have a sedative effect, therefore, if a patient has central nervous system diseases, it is recommended to use articaine, since it does not affect the central nervous system.[12]

Articaine is used in dental practice more and more often, and previously it was compared with the "gold standard" in the form of lidocaine. But research does not stand still, the effectiveness of articaine has been proven, and now the topic of reduced concentration of local anesthetics in solution is relevant.

The novelty of the proposed topic on literary sources and patent documentation is determined by the fact that there are currently no comprehensive studies in the domestic and foreign scientific literature devoted to the study of indications for the use of 2% articaine.

The aim of the study was to compare the use of 2% and 4% articaine during tooth extraction and reduce the risk of complications with the use of anesthetics.

To achieve this goal, the following tasks were set:

1. To evaluate the potential toxicity of 2% and 4% articaine on human cell culture (epitheliocytes).
2. To evaluate the stress response of the patient's body during tooth extraction and indirectly the toxic effect of the anesthetic by recording changes in hemodynamics (blood pressure, pulse).

MATERIALS AND METHODS

Assessment of the potential toxicity of 2% and 4% articaine in human cell culture (epitheliocytes)

To substantiate the reason for the use of 2% articaine in clinical practice, especially in patients with concomitant pathology, children and the elderly, a comparative analysis of the cytotoxicity of 2% and 4% articaine in an in vitro study was performed, namely, the determination of the half–life concentration (LC_{50}).

The study was conducted based on the Laboratory of Molecular and Cellular Technologies and Experimental Research of the Institute of Physics and Technology of the National Research Nuclear University MEPhI.

The experiment was conducted on the primary culture of epithelial cells of the human oral cavity (Human oral epithelial primary cell culture, Celprogen Inc., USA). This cell culture was chosen due to its proximity to the conditions during infiltration anesthesia.

Subcultivation protocol:

1. The vial was thawed, stirring gently, in a water bath at 37°C.
2. The contents of the vial were transferred to a sterile centrifuge tube with a volume of 15 ml and carefully preheated medium was added for the primary culture of epithelial cells of the human oral cavity. The cells were centrifuged at 100 g for 5 minutes. The supernatant was removed, and the cellular precipitate was re-suspended in 500 µl of medium.
3. 500 µl of cell suspension was transferred to a 25 cm^2 culture vial with 10 ml of medium.
4. The cells were incubated at 37°C in a humidified incubator in an atmosphere of 5% CO2. The medium was changed every 2-3 days, cultured to a confluent of

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70%, and then the cells were transplanted for the experiment.

The cells were planted in 96-well plates with a density of $5*10^3$ cells/well. The cells were counted and viability was determined by staining with trypan blue (Invitrogen, USA) in a dye–suspension ratio of 1:1, with a total volume of 20 µl and measuring in a LUNA II Brightfield Cell Counter (Biolab, USA). After reaching 100% confluence, a cytotoxicity study was performed. The cells were washed with a phosphate buffer and the studied preparations dissolved in the culture medium in the following concentrations were added: 100, 50, 25, 12,5, 6,25, 3,13, 1,56 and 0.78%. A medium without the addition of a drug was used as a control.

The study was carried out in three repetitions. After 7 days, the culture reaches a confluent of 100%.

After 3 hours of incubation, cell viability was determined according to the MTT protocol:

1. The medium was removed from the wells of the tablet and washed with phosphate buffer.
2. 50 ml of serum-free medium and 50 ml of MTT (dimethyl sulfoxide) solution were added to each well.
3. The tablet was incubated at 37°C for 3.5 hours.
4. After incubation, 150 µl of MTT solvent was added to each well.
5. The tablet was wrapped in foil and shaken in an orbital shaker for 15 minutes until the MTT formazane was completely dissolved.
6. Light absorption was measured at a wavelength of 590 nm in an XMark spectrophotometer (Bio-Rad Laboratories, USA).

Visual control of proliferation was performed in an inverted Nexcope NIB600-FL microscope.

According to the obtained optical density values, cell viability was determined with normalization to control values (wells without the addition of the drug were taken for viability of 100%), graphs of the dependence of viability on the concentration of drugs were plotted, and the half-year concentration (LC_{50}) was determined.

Assessment of the stress response of the patient's body by recording changes in hemodynamics

To assess the stress level for the body and the potential reaction to the anesthetic, the cardiovascular and respiratory systems were monitored.

These measures were carried out using the Mindray ePM 10 device, a medical device designed to monitor the patient's condition during dental procedures. This compact and lightweight monitor provides reliable and accurate display of vital signs of the patient, such as blood pressure, pulse rate, oxygen saturation in the blood and respiratory function.

During the monitoring, blood pressure (systolic and diastolic), pulse, and saturation were measured before surgery, 2, 4, and 8 minutes after administration of the anesthetic.

Pulse oxygen saturation (SpO2) monitoring is a non–invasive method used to measure the amount of oxygenated hemoglobin and pulse rate by measuring the absorption of selected wavelengths of light. The light generated on the side of the probe emitter is partially absorbed when passing through the controlled tissue.

The amount of transmitted light is determined on the detector side of the probe. When examining the pulsating part of the light signal, the amount of light absorbed by hemoglobin is measured, and pulse oxygen saturation can be calculated. This device is calibrated to display functional oxygen saturation.

The monitor uses an oscillometric method to measure noninvasive blood pressure (NIBP). The measurement of NIBP is based on the principle that the pulsating blood flow through an artery creates fluctuations in the arterial wall. An oscillometric device uses a blood pressure cuff to sense these fluctuations, which manifest as tiny pulsations of cuff pressure. Oscillometric devices measure the amplitude of pressure changes in the occlusal cuff when the cuff deflates from pressure above systolic. The amplitude suddenly increases when the pulse breaks through the occluded place in the artery. As the cuff pressure decreases further, the pulsations increase in amplitude, reach a maximum (which approaches the average pressure), and then decrease. The oscillometric method measures average blood pressure and determines systolic and diastolic blood pressure.

RESULTS

Assessment of the potential toxicity of 2% and 4% articaine in human cell culture (epitheliocytes)

As a result of the study, viability values were obtained (Table 1) and graphs of the dependence of viability on the concentration of the studied drugs in the medium were constructed (Fig. 1 and 2). The images of epitheliocytes after incubation with drugs (Fig. 7) show that the destruction of the monolayer under the action of the drug is observed at lower concentrations for the drug of 4% than for 2%. Based on the experimental data on the effect of drug concentrations on cell viability, the half-life concentration (LC_{50}) values were determined, which for drugs of 2% and 4% were 65.7% and 17.5%, respectively.

The results obtained allow us to conclude that the 2% drug has significantly lower cytotoxicity than the 4% drug.

Table 1. The average values of epithelial cell viability for different concentrations of drugs are 2% and 4%.

The concentration of the drug in the medium, %	Viability, %	
	2%	4%
100,00	9,6%	10,3%
50,00	77,5%	7,2%
25,00	91,3%	8,7%
12,50	91,6%	86,0%
6,25	99,8%	96,8%
3,13	88,9%	92,0%
1,56	101,6%	96,0%
0,78	101,7%	99,8%

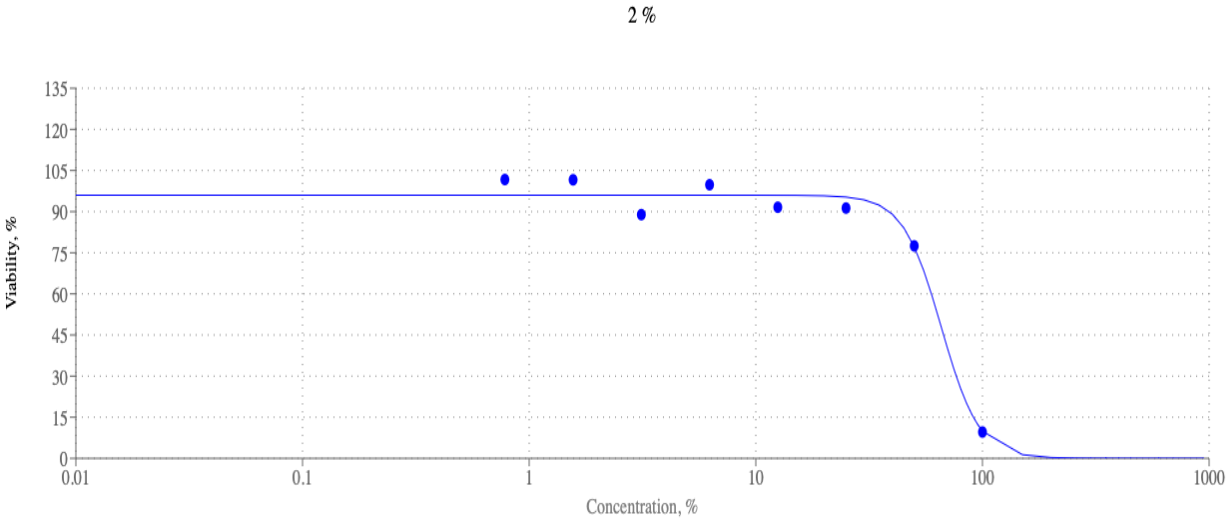

Figure 1. The dependence of epithelial cell viability on the concentration of the drug 2% in the medium.

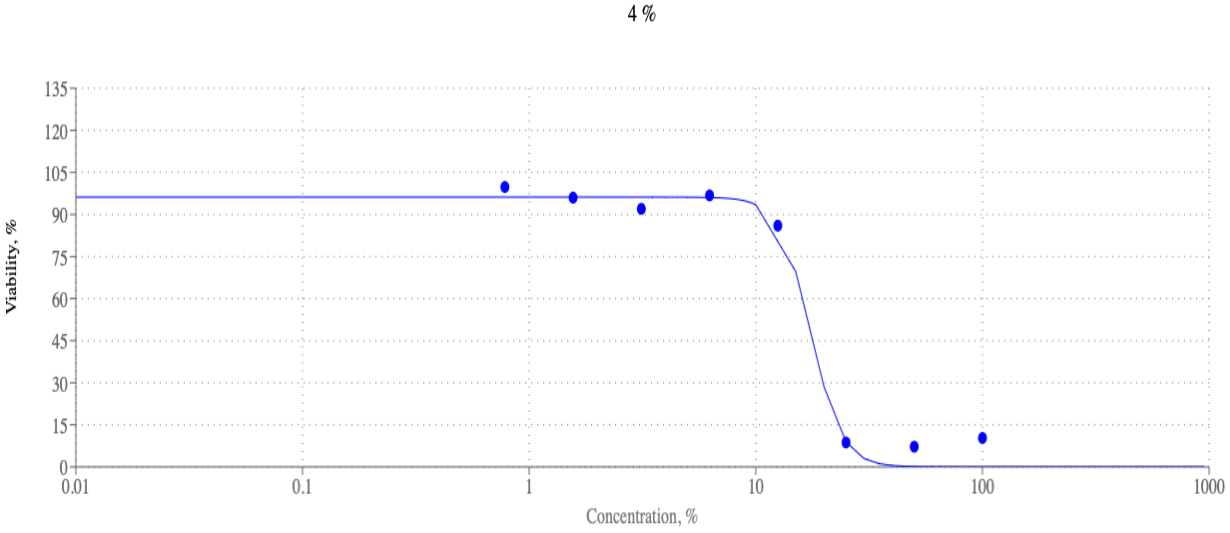

Figure 2. The dependence of epithelial cell viability on the concentration of the drug 4% in the medium.

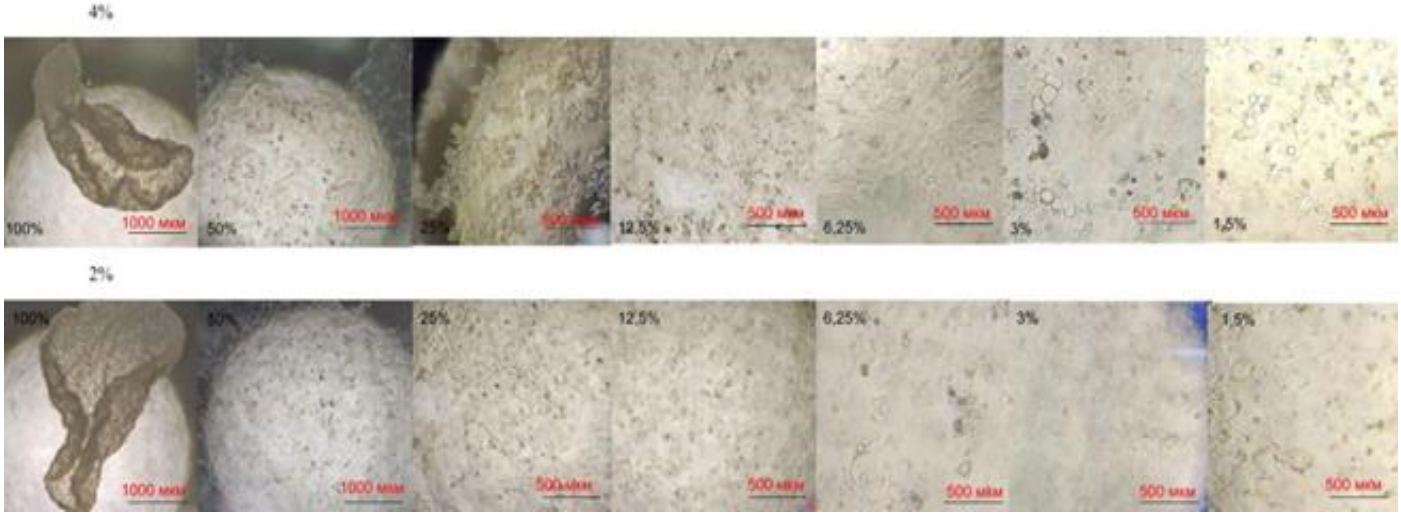

Figure 3. Images of the cell monolayer of epitheliocytes after incubation for 3 hours with different concentrations of 2% and 4% preparations.

Assessment of the stress response of the patient's body by recording changes in hemodynamics

According to the standards of the European Society for the Study of Hypertension and the recommendations of the Ministry of Health of the Russian Federation of 2020, the following ranges of figures are set for blood pressure (BP) [13]:

- Normal –120-129/80-85 mmHg;
- High normal – 130-139/85-89 mmHg;
- 1st degree – 140-159/90-99 mmHg;
- 2nd degree – 160-179/100-109 mmHg;
- 3rd degree – more than 180/110 mmHg.

For the pulse of an adult, the norm is 60-80 beats per minute, but under certain conditions, the norm can be 50 beats (for trained people) and 90 (for women and young people).

When measuring the average oxygen saturation rate in adults, when measuring with a pulse oximeter, the normal oxygen saturation level in an adult is more than 95%. Saturation from 94% to 90% indicates respiratory failure of the 1st degree. With respiratory failure of the 2nd degree, saturation decreases to 89%-75%, and hypoxemic coma is less than 60% .[14]

The results of monitoring are given in Tables 2-5.

Table 2. The results of monitoring systolic blood pressure in the study groups in dynamics (n=56). Each cell contains: mean±the standard error of the mean, the median, and the range from minimum to maximum values.

Measurement period	Group 1 (n=28) Articaine 2%	Group 2 (n=28) Articaine 4%	p
Before the operation	112,4±10,8 123,5 99-140	124,2±7,7 123,5 110-138	>0,05
2 minutes after the injection of the anesthetic	126,6±11 129 99-145	127,1±8,3 127 110-140	>0,05
4 minutes after the injection of the anesthetic	125,3±7,2 126,5 110-140	130,6±5,6 130 114-145	**<0,05 (0,028)**
8 minutes after the injection of the anesthetic	119±8,8 120 100-131	119,3±6,5 121 109-132	>0,05
p	**<0,001**	**<0,001**	

Before surgery, on average, all patients had normal systolic blood pressure, and there were no statistically significant differences between the groups (p>0.05).
After 2 minutes in both groups, blood pressure remained normal without statistically significant differences (p>0.05).
4 minutes after administration of the anesthetic, systolic blood pressure increased, but remained within the normal or high normal range, and 3 mmHg less in the 2% articaine group compared to 4% (p<0.05).
After 8 minutes, the pressure decreased by 5-6 mmHg and reached normal values in both groups. There were no statistically significant differences (p>0.05).
When assessing the dynamics of systolic blood pressure within each group, there was a significant increase by 2 minutes with a gradual decrease by 8 minutes with the administration of 2% articaine and a significant increase by 4 minutes with a decrease by 8 minutes with the use of 4% articaine (p<0.001).

Table 3. The results of monitoring diastolic blood pressure in the study groups in dynamics (n=56). Each cell contains: mean±the standard error of the mean, the median, and the range from minimum to maximum values.

Measurement period	Group 1 (n=28) Articaine 2%	Group 2 (n=28) Articaine 4%	p
Before the operation	70,25±7,3 70 56-89	71,1±7,8 71 56-88	>0,05
2 minutes after the injection of the anesthetic	73,71±5,9 74 62-88	72,18±7,6 72 60-90	>0,05
4 minutes after the injection of the anesthetic	72,9±5,6 71,5 60-88	73,9±6,2 74 62-91	>0,05
8 minutes after the injection of the anesthetic	67,5±5,3 69 58-80	67,9±4,7 68 60-78	>0,05
P	**<0,001**	**<0,001**	

When comparing diastolic blood pressure between the 2% and 4% articaine groups, no statistically significant differences were found at all registration periods (p>0.05). However, when assessing the dynamics of the indicator within the groups, a statistically significant increase in blood pressure was revealed by 4 minutes with a decrease by the eighth in both groups (p<0.001).

Table 4. The results of pulse monitoring in the study groups in dynamics (n=56). Each cell contains: mean±the standard error of the mean, the median, and the range from minimum to maximum values.

Measurement period	Group 1 (n=28) Articaine 2%	Group 2 (n=28) Articaine 4%	p
Before the operation	70,2±7,8 70 49-88	69,7±8,1 72 48-81	>0.05
2 minutes after the injection of the anesthetic	74,6±8,2 75,5 56-90	71,6±7,6 74 50-82	>0,05
4 minutes after the injection of the anesthetic	76,1±7,4 76 60-90	75,7±6,4 78 60-85	>0,05
8 minutes after the injection of the anesthetic	67,7±6,7 68 51-86	67,6±8,3 70 50-80	>0,05
p	**<0,001**	**<0,001**	

When comparing the pulse rate between the 2% and 4% articaine groups, no statistically significant differences were found at all registration periods (p>0.05). However, when assessing the dynamics of the indicator within the groups, a statistically significant increase in heart rate was revealed by 4 minutes with a decrease by the eighth in both groups (p<0.001). At all registration dates, the indicator remained normal.

Table 5. The results of saturation monitoring in the study groups in dynamics (n=56). Each cell contains: mean±the standard error of the mean, the median, and the range from minimum to maximum values.

Measurement period	Group 1 (n=28) Articaine 2%	Group 2 (n=28) Articaine 4%	P
Before the operation	96,1±2,1 96 92-99	95,9±2 96 92-99	>0,05
2 minutes after the injection of the anesthetic	95±1,9 95 90-98	94,3±1,2 94 92-97	**<0,05 (0,049)**
4 minutes after the injection of the anesthetic	94,1±1,8 94 90-98	93,5±1,9 94 90-96	>0,05
8 minutes after the injection of the anesthetic	97,1±1,6 98 94-99	97,3±1,4 98 94-99	>0,05
p	**<0,001**	**<0,001**	

When comparing saturation between the 2% and 4% articaine groups, no statistically significant differences were found at all registration periods (p>0.05). However, when assessing the dynamics of the indicator within the groups, a statistically significant decrease was revealed by 4 minutes with a return to normal by the eighth minute in both groups (p<0.001).

Other correlations may also be indicative, for example, saturation with blood pressure and pulse, since its decrease by even 1% can lead to noticeable changes in hemodynamics (Table 6).

Table 6. The relationship of saturation with hemodynamic parameters in the study groups.

Relationship of indicators	Group 1 (n=28) Articaine 2%	Group 2 (n=28) Articaine 4%
Saturation/Systolic blood pressure	**r= (-)0,27, p<0,05**	**r=(-)0,39, p<0,001**
Saturation/Diastolic blood pressure	**r=(-)0,23, p<0,05**	**r=(-)0,27, p<0,05**
Saturation/Pulse	**r=(-)0,29, p<0,05**	**r=(-)0,27, p<0,05**

Weak reliable inverse relationships were found between the saturation level in both groups and hemodynamic parameters – with a decrease in saturation, a reversible increase in blood pressure and pulse occurred in both study groups (p<0.05).

DISCUSSION

The results of the study showed that at the initial stages of the procedure (before and 2 minutes after the injection of the anesthetic), systolic blood pressure remained within the normal range, which indicates the stability of hemodynamic parameters in both groups. However, 4 minutes after the injection of the anesthetic, a significant increase in systolic blood pressure was recorded, which was more pronounced in the 4% articaine group. This indicates that a higher concentration of anesthetic may have a more pronounced effect on the cardiovascular system, which requires special attention when choosing anesthetics for patients with a predisposition to cardiovascular diseases.

Analysis of the dynamics of blood pressure, pulse, and saturation also confirmed that when using 2% articaine, a less pronounced hemodynamic reaction is observed, which makes it the preferred choice for patients requiring anesthesia. Even though temporary fluctuations in the parameters were noted in both groups, they did not exceed the normal values, which indicates that the anesthetics used in the studied concentrations do not lead to serious disorders.

In addition, the results of the study emphasize the importance of monitoring hemodynamic parameters during anesthesia, which can help in the timely detection of possible complications and reduce the risk of adverse outcomes. The inverse relationship between saturation level and hemodynamic parameters also indicates the need for an integrated approach to assessing the patient's condition during anesthesia.

Articaine, produced in concentrations of 2% and 4%, is widely used due to its effectiveness and rapid action. However, the potential toxic effects on the cardiovascular system, especially in patients with concomitant somatic diseases, remains a serious problem that requires careful study.

Studies have shown that various classes of drugs, including local anesthetics such as articaine, can cause cardiovascular toxicity.[15] Cardiovascular toxicity can manifest itself in different ways, including changes in blood pressure, heart rate, and heart contractility. In a detailed review by Mladěnka et al. The need for careful monitoring of cardiovascular parameters during procedures using local anesthetics is emphasized.

Despite the results obtained in the course of current research, significant knowledge gaps remain. There is a lack of comprehensive studies on the effect of 2% and 4% articaine solution on the cardiovascular system in patients with various somatic diseases. Most existing studies either study a healthy population or insufficiently represent patients with concomitant diseases, which limits the applicability of the results to risk groups.[16]

According to Anisimova et al., the use of a 2% articaine solution with 1:200,000 epinephrine administered by infiltration or a modified periodontal method registered an increase in the threshold of electrical excitability of the pulp by 95.93% and 93.58%, respectively. There were no statistically significant hemodynamic changes in the studied patient groups,[17] which is consistent with our data.

The purpose of the study is Kämmerer et al. The anesthetic efficacy of 2% and 4% articaine solution was compared in case of blockage of the inferior alveolar nerve for the extraction of mandibular teeth. The local anesthetic effect of a 4% articaine solution is not significantly better than that of a 2% solution . [18]

When studying the pharmacokinetics of articaine, it was proved that the maximum concentrations of articaine in the blood serum when using a 2% solution of articaine are lower. It was also noted that the plasma half-life of a 2% solution of articaine is shorter than that of a 4% solution: 18.54 minutes versus 23.62 minutes, which is beneficial if the patient has a concomitant pathology. [19, 20]

Future research should aim to fill in these gaps by conducting studies focusing on the effects of 2% and 4% articaine on the cardiovascular system in various patient groups, especially those with pre-existing cardiovascular diseases. Randomized controlled trials evaluating hemodynamic changes in these patients can provide valuable information about the safety of these anesthetics.

In addition, it would be useful to conduct long-term studies that would monitor cardiovascular parameters in patients receiving multiple doses of articaine. This study could help develop recommendations for safe use in patients with cardiovascular diseases, which would ultimately improve patient safety and the quality of medical care in dental clinics.

CONCLUSION

In the course of the study, a comprehensive assessment of the potential toxicity of 2% and 4% articaine on the cardiovascular system of patients undergoing tooth extraction was carried out. Taking into account the results obtained, indicating adequate anesthesia of the surgical area up to and including the 8th minute, 2% articaine demonstrated no less effectiveness than 4% articaine.

Thus, the data obtained confirm that 2% articaine can be a safe alternative to 4% articaine, which is especially important for patients with concomitant diseases, children and the elderly, who may have a higher risk of complications.

Articaine shows good anesthetic efficacy and low toxicity, so it can be recommended for use with short-term tooth extraction, especially in patients with

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concomitant diseases or conditions such as pregnancy.

The study highlights the need for careful choice of anesthetics in clinical practice. It is important to take into account the individual characteristics of the patient, including the presence of concomitant diseases, age and general physical fitness. Recommendations for the use of 2% articaine can help reduce the risk of complications and improve the quality of medical care, which is an important aspect of modern dental practice.

In the future, it is advisable to conduct additional studies aimed at studying the long-term effects of using different concentrations of articaine, as well as their effect on different groups of patients. This will make it possible to more accurately determine the optimal approaches to anesthesia and improve the safety of dental procedures.

DECLARATION

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