

## Study of the anesthetic activity of Novocaine-containing metal complexes

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### Abstract

The study of the biological activity of metal coordination compounds is a crucial area of research in chemistry, pharmacology, and medicine. The ability of metal complexes to influence biological systems has led to their exploration in various therapeutic contexts. We have previously studied the complexes of the local anesthetics at various times. Additionally, other researchers have conducted studies on their structure and coordination properties. Some of them have a biological activity, but almost nothing is known about the biological activity of novocaine-containing compounds.

Based on the above, the aim of our work is to study the local anesthetic activity of the novocaine-containing metal complexes. In particular, complex compounds, designated as Nov 1 and Nov 2, were studied. For comparison, a solution of novocaine hydrochloride with an equivalent novocaine concentration was used. The experiment was conducted on male rats weighing 250-370 g.

Both substances we studied have local anesthetic property. In particular, Nov 1 is superior to novocaine hydrochloride in all respects at all concentrations studied (0.25%, 0.5%, and 1%). The anesthetic effect of Nov 2 immediately after injection is lower compared to novocaine hydrochloride, after 10 minutes these values equalize, and then Nov 2 prevails over novocaine hydrochloride in strength and duration of anesthesia, especially at low concentrations. The tested substances are promising as new local anesthetics.

**Keywords:** Local anesthetics; Metal complexes; Biological activity; The depth and the duration of anesthesia

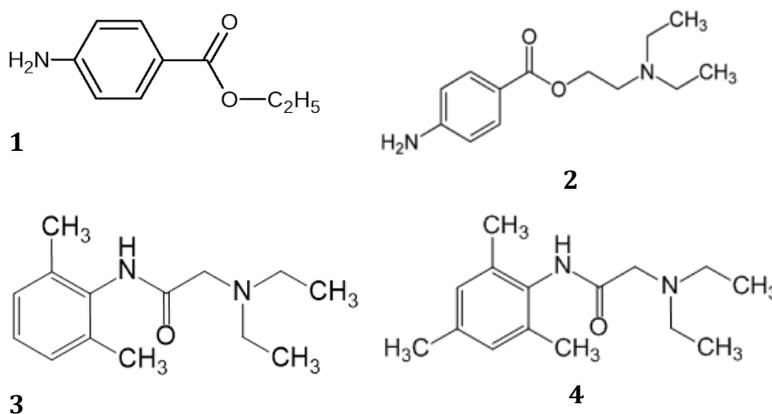
### 1. Introduction

The study of the biological activity of metal coordination compounds is a crucial area of research in chemistry, pharmacology, and medicine. This research plays a dual role: on one hand, it fosters the development of these scientific fields by enhancing our understanding of the behavior and reactivity of metal complexes; on the other hand, it is essential for elucidating the biochemical processes that occur within living organisms. Furthermore, this line of investigation is vital for the design and creation of novel therapeutic agents that can target specific biological mechanisms. The ability of metal complexes to influence biological systems has led to their exploration in various therapeutic contexts [1-14]. Many recent studies have highlighted the significant potential of these coordination compounds in the development of drugs aimed at treating diseases such as diabetes, cancer, and other complex health conditions [15-18].

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Among the broad category of metal coordination compounds, those involving local anesthetics (hereafter referred to as LAC) are of particular interest. The integration of metal ions into the structure of local anesthetic compounds changes their biological properties, making them distinct from their parent ligands. These metal-LAC complexes exhibit a variety of unique properties, including the prolongation of anesthetic effects, which is crucial for improving the efficacy of anesthesia [19, 20]. Additionally, these compounds have shown promising antitumor activity, opening up new avenues for cancer treatment [15]. These distinctive properties suggest that metal-containing LAC may serve as versatile therapeutic agents not only in the realm of anesthesia but also in the treatment of diseases such as cancer and in managing conditions related to metal deficiencies.

Local anesthetics, which are widely used in clinical medicine, are generally classified as either esters or amides based on their chemical structure. Esters, such as anesthesin (1) (ethyl-4-aminobenzoate), and novocaine (2) (2-(diethylamino)ethyl-4-aminobenzoate), amines as lidocaine (3) (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) and trimecaine (4) (2-(diethylamino)-N-(2,4,6-trimethylphenyl)acetamid) are among the most commonly employed compounds. They work by temporarily blocking nerve signal transmission, providing pain relief during medical procedures. The modification of these anesthetic agents through metal coordination may significantly alter their pharmacokinetic and pharmacodynamic properties, making them more effective and versatile in clinical applications. By extending the duration of anesthesia and potentially adding other therapeutic effects, such as antitumor activity or the ability to correct metal imbalances in the body, these metal-enhanced LAC represent a promising area of research in the design of new and improved medical treatments.

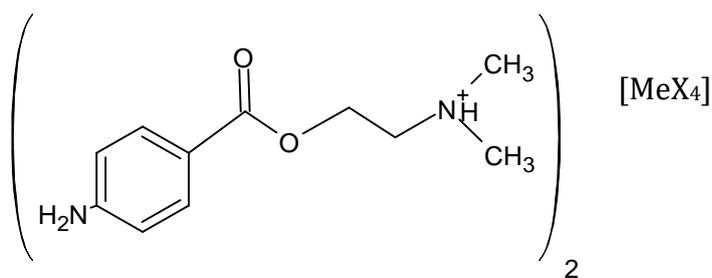


All four substances [anesthesin (1), novocaine (2), lidocaine (3), and trimecaine (4)] listed above are potential ligands because they contain groups, capable of forming coordination bonds, such as primary and tertiary amino-, secondary amide- and carbonyl groups.

Based on the above, the synthesis and study of metal complexes involving biologically active substances, including local anesthetics, holds both theoretical and practical significance. Theoretically, it enhances our understanding of metal-drug interactions, molecular mechanisms, and drug design principles. Practically, it opens up avenues for the development of more effective, stable, and targeted therapeutic agents, including local anesthetics with improved properties. These advances could lead to the design of safer and more efficient drugs, particularly in the areas of pain management, drug delivery, and metal-related diseases, making this area of research crucial for the future of medicinal chemistry and clinical practice.

We have previously studied the complexes of the aforementioned substances at various times [19-21]. Additionally, other researchers have conducted studies on their structure and coordination properties [15, 22]. It has been established that lidocaine (Lid) and trimecaine (Tm) form two types of complexes: (LH)<sub>2</sub>[MeX<sub>4</sub>] (1), where M = Mn<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, L = Tm or Lid, and X = Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, NCS<sup>-</sup>; and MeLX<sub>2</sub> (2), where M = Co<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Cd<sup>2+</sup>, L = Tm or Lid, and X = Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>. Of these, (LidH)<sub>2</sub>[ZnCl<sub>4</sub>] and (TmH)<sub>2</sub>[ZnCl<sub>4</sub>] exhibit local anesthetic activity [19,20], while (TmH)<sub>2</sub>[CuCl<sub>4</sub>] is noted for its antiarrhythmic activity [19].

Novocaine-containing compounds have been described in the literature since the 1960s [23]. These complexes exist in various forms, including (NovH)<sub>2</sub>[MeX<sub>4</sub>], where M = Fe<sup>2+</sup>, Co<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, Hg<sup>2+</sup>, and X = Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>. The nitrogen atom of the tertiary amino group in novocaine is protonated. Accordingly, their structural formula is following:



## 2. Experimental part

- Materials and Methods:** The novocaine-containing complex compounds, designated as Nov1 and Nov2, were studied. For comparison, a solution of novocaine hydrochloride (Nov · HCl) with an equivalent novocaine concentration was used. The experiment was conducted on male rats weighing 250-370 g, following the methodology described in the literature [24].

Animal experiments were conducted in accordance with the laws of the United States, the European Union and Japan for the protection and use of animals in experiments rules (Guide for the Care and Use of Laboratory animals, Washington, D.C., 1996, Standards Relating of the Care and Management. Etc. of Experimental Animals (Notification #6), March 27, 1980; Animal Welfare Act Regulations; Title 9 Code of Federal Regulations, Part 1, 2 and 3).

- Description of the Experiment:** The anesthetic activity of the metal novocaine-containing complexes (Nov1 and Nov2) synthesized in our study was experimentally assessed, specifically focusing on the duration and depth of anesthetic action. For this purpose, the test animals were divided into groups of three rats. In total, 19 groups were examined, with two groups for each specific concentration of each substance, corresponding to 12 parallel determinations. One of these groups served as a control group and was not anesthetized. In the remaining groups, four points were marked on the back of each rat, on both sides of the spine, forming the vertices of a square with a side length of 3 cm [24]. A solution of novocaine hydrochloride was injected on one side of the spine, while the test substance was administered on the opposite side. A total of 0.5 ml of the injection solution was administered into two points (0.25 ml per point).

At the beginning of the experiment, 1% solutions of the test substances were administered, followed by concentrations of 0.5% and 0.25%. Accordingly, the injection solutions contained 10, 5, and 2.5 mg/ml of the substance, calculated as novocaine hydrochloride. Thus, the injection doses were as follows: for the 1% solution, 14 mg/kg; for the 0.5% solution, 7 mg/kg; and for the 0.25% solution, 3.5 mg/kg. To assess the anesthetic effect of the test substances, a solution of novocaine hydrochloride with the same concentrations was used for comparison. The onset and duration of anesthesia were monitored by pricking the injection sites with the tip of the needle, applying equal force and frequency (6 pricks at each point). To calculate the infiltration anesthesia index, the rats were observed at 5, 10, 15, 20, 25, and 30 minutes post-injection [24]. The results are presented in Table 1.

**Table 1** Infiltration anesthesia index for test solutions of different concentrations

Compound	Concentration <sup>1</sup> of LAC, in % and mmol/L	Point <sup>2</sup>	Minutes after the injection/number of pricks that do not cause pain						Infiltration anesthesia index
			5	10	15	20	25	30	
Nov · HCl	1 36.6	1	4	6	6	6	6	4	32
		2	4	6	6	6	6	5	33
		1	3	6	6	6	6	4	31
		2	4	6	6	6	6	5	33
		1	4	6	6	6	6	4	32

		2	4	6	6	6	6	5	33
		1	4	6	6	6	6	5	33
		2	5	6	6	6	6	5	34
		1	3	6	6	6	6	4	31
		2	4	6	6	6	6	5	33
		1	3	6	6	6	6	4	31
		2	5	6	6	6	6	4	33
									32.42 ± 0.9966
	0.5 18.3	1	3	6	6	6	6	4	31
		2	4	6	6	6	6	4	32
		1	4	5	6	6	6	4	31
		2	4	6	6	6	6	4	32
		1	3	6	6	6	6	4	30
		2	4	6	6	6	6	3	31
		1	3	6	6	6	6	3	30
		2	4	6	6	6	6	4	32
		1	3	6	6	6	6	4	31
		2	4	6	6	6	6	4	32
		1	3	6	6	6	6	3	30
		2	3	6	6	6	6	4	31
									31.08 ± 0.7592
	0.25 9.15	1	2	5	5	5	5	3	25
		2	2	5	5	5	5	2	24
		1	2	5	5	6	5	3	24
		2	3	5	5	5	4	2	24
		1	3	5	6	5	4	2	25
		2	2	5	6	5	5	3	26
		1	2	5	6	5	4	2	25
		2	2	5	6	5	4	3	25
		1	2	4	6	6	4	2	24
		2	3	5	6	5	4	2	25
		1	3	5	5	6	4	2	25
		2	3	5	6	5	4	2	25
									24.75 ± 0.5951
Nov 1	1 36.6	1	5	6	6	6	6	6	35
		2	5	6	6	6	6	5	34
		1	6	6	6	6	6	6	36
		2	5	6	6	6	6	6	35

		1	4	6	6	6	6	6	34
		2	5	6	6	6	6	6	35
		1	5	6	6	6	6	6	35
		2	6	6	6	6	6	6	36
		1	5	6	6	6	6	6	35
		2	5	6	6	6	6	5	34
		1	5	6	6	6	6	6	35
		2	5	6	6	6	6	6	35
									34.92 ± 0.6401
	0.5 18.3	1	4	6	6	6	6	4	32
		2	5	6	6	6	6	4	33
		1	4	6	6	6	6	4	32
		2	5	6	6	6	6	4	33
		1	6	6	6	6	5	4	33
2		6	6	6	6	5	5	34	
		1	6	6	6	6	5	4	33
		2	6	6	6	6	5	5	34
		1	5	6	6	6	6	4	33
		2	5	6	6	6	6	5	34
		1	6	6	6	6	6	4	34
		2	6	6	6	6	6	5	35
									33.33 ± 0.8498
	0.25 9.15	1	4	5	6	6	6	5	32
		2	4	6	6	6	6	4	32
		1	3	5	6	6	6	4	30
		2	4	5	6	6	5	4	30
		1	3	5	6	6	6	4	30
		2	4	5	6	6	6	5	32
		1	4	5	6	6	6	4	31
2		4	5	6	6	6	4	31	
1		4	5	6	6	6	4	31	
2		5	5	6	6	6	4	32	
1	4	5	6	6	6	5	32		
2	5	5	6	6	6	4	32		
								31.25 ± 0.8292	
Nov 2	1 36.6	1	3	5	6	6	6	4	30
		2	4	6	6	6	6	4	32
		1	4	5	6	6	6	4	31

		2	4	5	6	6	6	5	32
		1	4	5	6	6	6	4	31
		2	3	5	6	6	6	5	31
		1	3	6	6	6	6	5	32
		2	4	6	6	6	6	5	33
		1	3	6	6	6	5	5	31
		2	3	6	6	6	6	5	32
		1	3	6	6	6	6	5	32
		2	5	6	6	6	6	4	32
									31.58 ± 0.7592
	0.5 18.3	1	3	6	6	6	6	4	31
		2	4	6	6	6	6	4	32
		1	4	5	6	6	6	4	31
		2	4	6	6	6	6	4	32
		1	3	5	6	6	6	4	30
		2	4	5	6	6	6	3	30
		1	3	6	6	6	6	3	30
		2	4	6	6	6	6	4	32
		1	3	6	6	6	6	4	32
		2	4	6	6	6	6	4	32
		1	3	6	6	6	6	3	30
		2	3	6	6	6	6	4	31
									31.08 ± 0.8620
	0.25 9.15	1	3	5	5	5	5	3	26
		2	3	5	6	5	5	2	26
		1	3	5	6	6	5	4	29
		2	3	5	5	5	5	3	26
		1	2	5	6	5	4	3	25
		2	2	5	6	5	6	3	27
		1	3	5	6	6	5	2	27
		2	3	5	6	6	5	3	28
		1	3	5	6	6	5	3	28
		2	3	5	6	6	5	3	28
		1	2	5	5	5	5	3	25
		2	3	5	6	6	5	3	28
									26.91 ± 0.9841

Note: The composition and molar mass of novocaine hydrochloride and the complex compounds differ; therefore, the percentage and molar concentrations presented in the table are calculated with respect to novocaine hydrochloride; Point 1 refers to the area on the neck side of the rat, while Point 2 refers to the area on the tail side.

The table shows that both complexes we studied exhibit anesthetic activity. The anesthetic effect was observed within 5 minutes of injection and was maintained for 30 minutes in all rats.

As a result of the experiment, we determined (Table 2) that the anesthetic effect of Nov1 exceeds that of Nov·HCl. In contrast, the anesthetic effect of Nov2 at a 1% concentration is slightly inferior, but at a 0.5% concentration it is nearly equivalent, and at a 0.25% concentration it surpasses the anesthetic effect of novocaine hydrochloride. In all cases, changing the concentration of the injection solution did not produce any visible toxic effects (Table 2).

**Table 2** Dependence of the Infiltration anesthesia average index on the nature and concentration of the tested solutions

Compound	Concentration <sup>1</sup> of LAC, in % and mmol/L	Infiltration anaesthesia average index
Nov· HCl	1	32.42 ± 0.9966
	36.6	
	0.5	31.08 ± 0.7592
	18.3	
	0.25	24.75 ± 0.5951
	9.15	
Nov 1	1	34.92 ± 0.6401
	36.6	
	0.5	33.33 ± 0.8498
	18.3	
	0.25	31.25 ± 0.8292
	9.15	
Nov 2	1	31.58 ± 0.7592
	36.6	
	0.5	31.08 ± 0.8620
	18.3	
	0.25	26.91 ± 0.9841
	9.15	

To determine the onset time and duration of complete anesthesia, observations were conducted for 2 to 90 minutes following the injection in the second series of experiments (Table 3).

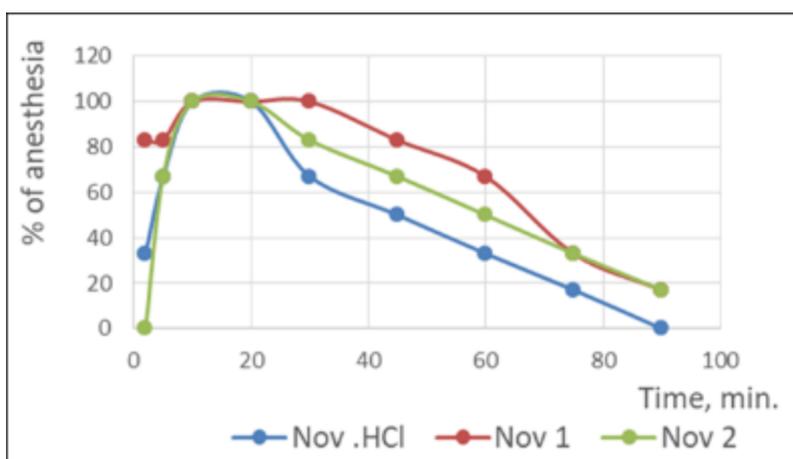
The experimental results (Table 3) indicated that in cases Nov • HCl and Nov 1 signs of anesthesia appeared within 2 minutes of injection. The duration of anesthesia extended in all 3 cases (Table 3.).

**Table 3** The depth and the duration of anesthesia

Compound	Concentration %	Minutes after the injection/ average number of pricks that do not cause pain and % of anesthesia									
		2	5	10	20	25	30	45	60	75	90
Nov • HCl	1.0	2	3.91	6	6	6	4.5	3	2	1	-
		33	65.2	100	100	100	75	50	33	17	0
	0.5	1	3	6	6	6	4.33	2	2	-	-
		17	50	100	100	100	72.16	33	33	0	0

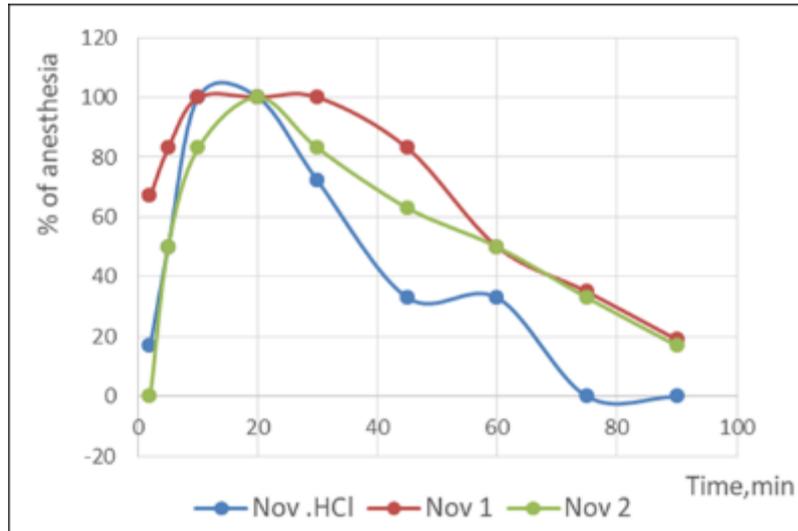
	0.25	1	2.42	4.91	5.42	5	3.75	2	1	-	-
		17	40	81.83	90	87.5	62.5	33	17	0	0
Nov 1	1.0	5	5	6	6	6	6	5	4	2	1
		83	83	100	100	100	100	83	67	33	17
	0.5	4	5	6	6	6	6	5	3	2	1
		67	83	100	100	100	100	83	50	33	17
	0.25	3	4	5	6	6	5	4	3	1	-
		50	67	83	100	100	83	67	50	17	0
Nov 2	1.0	-	4	6	6	5	4.58	4	3	2	1
		0	67	100	100	83	76	67	50	33	17
	0.5	-	3	5	6		5	3.16	3	2	1
		0	50	83	100	83	83	52.7	50	33	17
	0.25	-	2	5	6	5.25	4	3	2	1	-
		0	33	83	100	87.5	66.7	50	33	17	0

In particular, in the case of novocaine-hydrochloride 1% solution, partial anesthesia is established in 2 minutes, full in 10 minutes and lasts for 15 minutes. When using a 1% solution of Nov 1, partial anesthesia is established in 2 minutes, complete - in 10 minutes, lasts for 20 minutes, and then decreases much more slowly than in the case of novocaine-hydrochloride solution. In the case of 1% solution of Nov 2, partial anesthesia is established in 5 minutes, complete - in 10 minutes, lasts for 10 minutes, and then decreases much more slowly than when using novocaine-hydrochloride solution. In all three cases, signs of anesthesia persisted for 90 minutes (Figure 1).



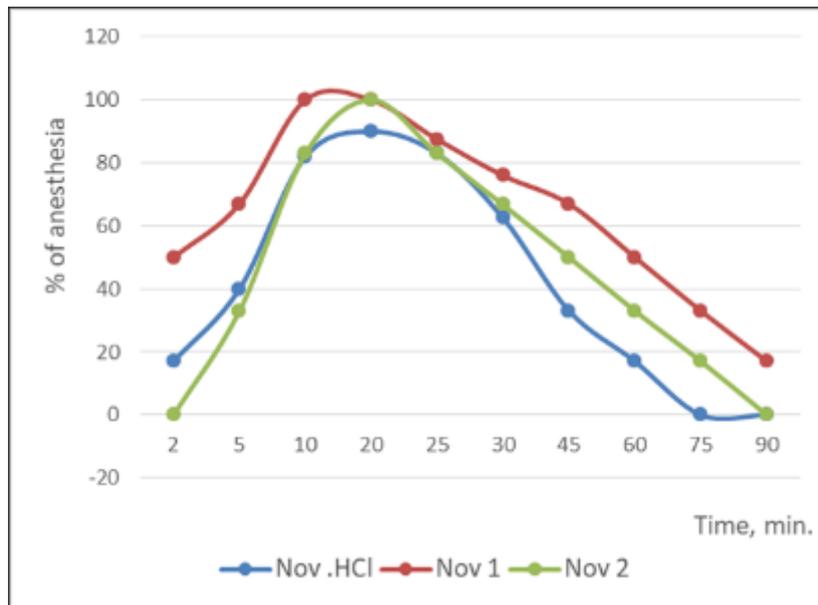
**Figure 1** The anesthetic effect of 1% solutions

With a 0.5% solution of novocaine hydrochloride, partial anesthesia occurs within 2 minutes, complete anesthesia within 10 minutes, and lasts for 15 minutes. The signs of anesthesia are observed within 75 minutes. When using a 0.5% solution of Nov 1, partial anesthesia occurs within 2 minutes, complete anesthesia within 10 minutes, with a duration of 20 minutes, after which the effects diminish more slowly compared to the novocaine hydrochloride solution. With a 0.5% solution of Nov 2, partial anesthesia occurs within 5 minutes, complete anesthesia within 10 minutes, lasting for 10 minutes, and the effects diminish more slowly than with the novocaine hydrochloride solution. In the last two cases signs of anesthesia persist for up to 90 minutes (Figure 2).



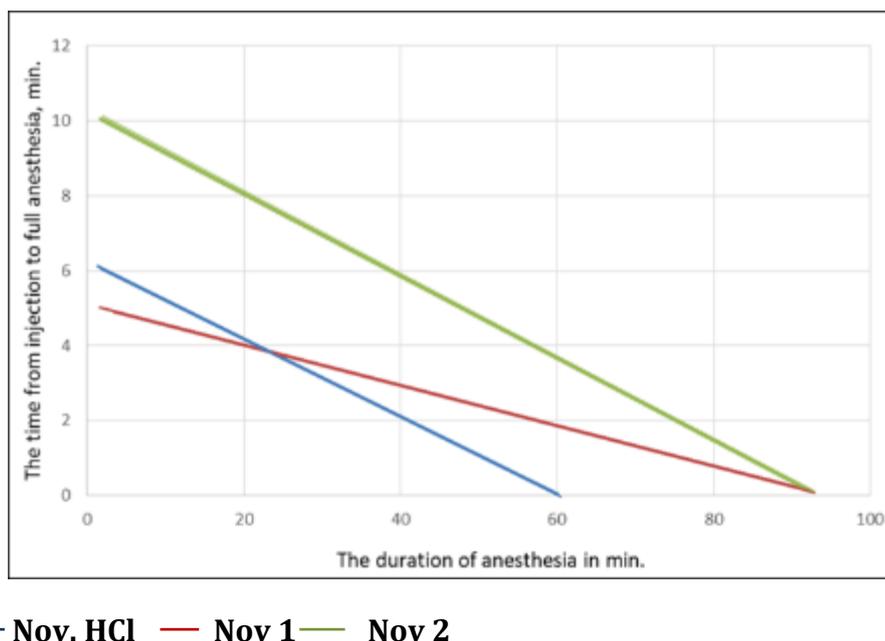
**Figure 2** The anesthetic effect of 0.5% solutions

With a 0.25% solution of novocaine hydrochloride, partial anesthesia occurs within 2 minutes, but complete anesthesia does not develop. Signs of anesthesia are observed for 60 minutes. When using a 0.25% solution of Nov 1, partial anesthesia occurs within 2 minutes, complete anesthesia within 10 minutes, lasting for 10 minutes, after which the effects diminish more slowly compared to the novocaine hydrochloride solution. Signs of anesthesia are maintained for up to 90 minutes. With a 0.25% solution of Nov 2, partial anesthesia occurs within 5 minutes, complete anesthesia within 20 minutes, lasting for 8-10 minutes, and the effects decrease more slowly than with the novocaine hydrochloride solution. Signs of anesthesia persist for 75 minutes (Figure 3).



**Figure 3** The anesthetic effect of 0.25% solutions

These findings are summarized in Figure 4, which illustrates the relationship between the duration of local anesthesia and the time elapsed from injection to the onset of complete anesthesia.



**Figure 4** The relationship between the duration of local anesthesia and the time from injection to full anesthesia

### 3. Discussion

Thus, Nov 1 demonstrates significantly greater anesthetic activity compared to both Nov 2 and novocaine hydrochloride within the first 90 minutes following injection. This difference in efficacy is particularly notable in the initial stages of the anesthetic effect. Between the 10th and 20th minutes after injection, however, the anesthetic activity of novocaine hydrochloride aligns closely with that of both test substances, indicating a temporary overlap in their effects. This observation holds consistently across all three concentrations tested (0.25%, 0.5%, and 1%).

For Nov 2, the onset of anesthetic activity is delayed by approximately 3-5 minutes when compared to novocaine hydrochloride, indicating a slower initial response. However, once the anesthetic effect is established, Nov 2 provides a significantly longer duration of action, lasting an additional 15-30 minutes compared to novocaine hydrochloride. This extended duration of action is particularly evident when the concentration of the solution is reduced, further highlighting the relative effectiveness of Nov 2, especially at lower doses.

### 4. Conclusion

Based on the above, we can conclude that both substances we studied have local anesthetic property. In particular, Nov 1 is superior to novocaine hydrochloride in all respects at all concentrations studied. The anesthetic effect of Nov 2 immediately after injection is lower compared to novocaine hydrochloride, after 10 minutes these values equalize, and then Nov 2 prevails over Nov • HCl in strength and duration of anesthesia, especially at low concentrations. The tested substances are promising as new LAC.

### Compliance with ethical standards

#### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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