

A comparative study of certain pharmacological effects of lidocaine and ropivacaine

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Abstract—In order to study the safety and efficacy of lidocaine and ropivacaine some of their actions were compared using the parameters namely local anaesthetic effect on rabbit cornea, local anaesthetic effect on the reflex movements of the nostrils of rabbit, analgesic effect on rat, cardiac effect on frog heart and the effect on the blood vessels of frog.

The local anaesthetic effect on rabbit cornea and reflex movements of the nostrils of rabbit had longer duration with ropivacaine but there were differences in the onset of action.

By rat tail flick method, ropivacaine proved to be more potent and longer acting in its analgesic action.

Ropivacaine took longer time to produce bradycardia. There was less number of missed beats of the frog heart with ropivacaine.

While lidocaine produced vasoconstriction of frog blood vessels, ropivacaine produced initial vasoconstriction followed by vasodilatation.

In all the parameters used, ropivacaine proved to be more potent, longer acting and safer when compared to lidocaine.

Keywords—Lidocaine, ropivacaine, local anaesthetic effect, analgesic effect, bradycardia, vasoconstriction.

I. INTRODUCTION

Though the pharmacological effects of lidocaine and ropivacaine are well established individually, there are conflicting reports of the comparison of actions between these two drugs both experimentally and clinically (Raffi Kapitanyan 2010). While lidocaine is a well established local anaesthetic, ropivacaine is a new aminoamide local anaesthetic agent with a greater margin of safety than other local anaesthetics for cardio toxicity and central nervous system toxicity (McClure J H, 1996; Knudsen K, et al, 1997). Hence, it was thought to further explore experimentally certain pharmacological actions of these drugs and try to assess the safety and efficacy of the two drugs to be helpful for further experimental and clinical studies to establish safe use of lidocaine and ropivacaine.

Materials and Methods:

The parameters used for this study were the local anaesthetic effect on the rabbit cornea, the local anaesthetic effect on the reflex movements of the nostrils in rabbit, analgesic effect on the rat, cardiac effect on the frog heart, and the effect on the blood vessels of frog.

The experiment was approved by the Institutional Animal Ethics Committee, Mamata Medical College, Khammam, Andhra Pradesh, India.

Lidocaine and ropivacaine (Neon Laboratories Ltd, Mumbai) were procured from Institution's Pharmacy.

Animals used in these experiments were male Wister albino rats weighing 150-180 g, albino rabbits weighing 1.5 Kg, and frogs purchased from the Institutional breeding stock. The animals were housed at $25 \pm 2^\circ\text{C}$ in clean polypropylene cages. They had access to food and water *ad libitum* throughout the duration of the study. All efforts were made to minimise both the suffering and the number of animals used.

1. Local anaesthetic effect on corneal reflex in rabbits (Yao-Tseng Huang, et al 1946):

The object of the study was to demonstrate and compare the local anaesthetic effect of lidocaine and ropivacaine on rabbit by corneal reflex method. The method described by Yao-Tseng Huang (1946) was followed with slight modification. Three groups of rabbits with five animals in each group were taken. The first group was taken as control. The second group of animals was administered 50 μg of each lidocaine and

ropivacaine by injecting into the limbus of the left eye and right eye respectively. The second and third groups were given 100µg and 200µg each of lidocaine and ropivacaine respectively by the same route of administration. The local anaesthetic effect was studied before and after the administration of the drugs by eliciting the corneal reflex with the help of a pointed cotton swab. The onset of action was noted when the corneal reflex was lost and the duration of action was noted when the corneal reflex was recovered.

2. Local anaesthetic effect on the reflex movements of nostrils in rabbit:

A modified Regniers method was followed, introduced by Hotovy in 1956 (Hans G Vogels, 2007). This method also helps in demonstrating and comparing the local anaesthetic effect of lidocaine and ropivacaine. This involves the absence and presence of movements of the nostrils in rabbit by the use of the test drug. The first group was kept as control.

The second group was administered 2.5µg of lidocaine and ropivacaine by injecting the drug into the mucosa of any one of the nostrils on separate animals. The third group was administered 5µg of lidocaine and ropivacaine by injecting the drugs by the method mentioned above. The local anaesthetic effect was studied by testing the reflex movements of nostrils when stimulated by using a fine tipped pencil. The onset of action was noted when the movement of nostrils due to stimulation was absent after injecting the test drug. The duration of action was noted when reflex was regained.

3. Analgesic effect on albino rats by tail-flick method (D'Amour F E, et al, 1941):

The object of the study was to demonstrate and compare the analgesic effect of lidocaine and ropivacaine on albino-rats by tail-flick method (D'Amour F E, and Smith D L, 1941). Six groups of animals, with six animals in each group were taken. The first, second, and third groups were administered 6.25 µg, 12-25 µg, and 25 µg of lidocaine subcutaneously, respectively near the base of the tail. The fourth, fifth, and sixth groups were administered 6.25 µg, 12.5 µg, and 25 µg of ropivacaine subcutaneously, respectively. The analgesic effect was studied by noting the tail-retaining time on the analgesiometer, ie, the absence of tail-flick was taken as the start of analgesic effect. Each animal was tested for the tail-flick before administering the test drugs, which served as the control. The duration of action was noted as the tail-flick was regained.

4. Cardiac effect on the frog heart:

The object of the study was to demonstrate and compare the cardiac toxic effect of lidocaine and ropivacaine using frog heart perfusion (G K Pal and Pravati Pal-I, 2005). Twelve groups of frogs with 3 animals in each group were used. In group one, after taking the normal graph of the myocardial contractions 6.25 µg lidocaine was added to 500ml of perfusing Ringer and the perfusion was continued. In group two, the same method was followed as in group one but with a dose of 12.5 µg lidocaine. In group three, with the same method, 25 µg of lidocaine was used. In group four, five, and six, the same method was used as in group one but lidocaine was replaced with ropivacaine in the doses of 6 µg, 12.5 µg, and 25 µg respectively.

5. Effect on the blood vessels of frog (S S Gambhir, et al 1970):

The object of the study was to demonstrate and compare the vasoconstrictor or vasodilatory effect of lidocaine and ropivacaine. The method described by G K Pal and Pravati Pal-II (2005) was followed with slight modification. The aorta was cannulated after cutting off a major portion of the ventricle. Through the cannulation the perfusion of the vessels of the body of the animal was started as the fluid passed from the reservoir. The perfusion rate was established by counting drops falling in the i.v. set used for perfusing the blood vessels. Reduction in the number of drops indicated vasoconstriction and increase in the number of drops indicated vasodilatation.

II. RESULTS

1. In group 2,3, & 4, 50 µg, 100 µg, and 200µg of lidocaine produced the onset of action of loss of corneal reflex in 11.6min, 10.8min, and 8min respectively. 50 µg, 100 µg, and 200 µg of ropivacaine produced the onset of action of loss of corneal reflex in 2min, 2min, and 1min respectively (Table 1; Fig.1). 50 µg, 100 µg, and 200 µg of lidocaine produced the duration of action of regain of corneal reflex in 12.4min, 22.8min, and 40.0min respectively (Table 2; Fig.2). Again 50 µg, 100 µg, 200 µg of ropivacaine produced the duration of action of regain of corneal reflex in 26.0min, 38.4min, and 80.0min respectively (Table.2; Fig.2).

Table 1: Effects of Lidocaine and Ropivacaine on corneal reflex in rabbits

Drug	Onset of Action in minutes in different doses		
	50mg	100mg	200mg
Lidocaine	11.6±0.74	10.8±0.48	8.4±0.4
Ropivacaine	2.0	2.0	1.0
P-value	0.00	0.00	0.00

All values are expressed as Mean ± SD

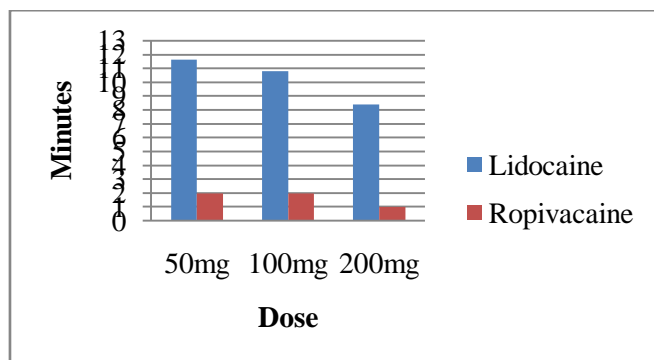


Fig 1: Comparison of onset of Action of Lidocaine and Ropivacaine on corneal reflex in rabbits

Table 2: Effects of Lidocaine and Ropivacaine on corneal reflex in rabbits

Drug	Duration of Action in minutes in different doses		
	50mg	100mg	200mg
Lidocaine	12.4±1.16	22.8± 0.8	40.4±0.4
Ropivacaine	26.0±1.09	38.4±0.4	80.0±0.63
P-value	0.00	0.00	0.00

All values are expressed as Mean ± SD

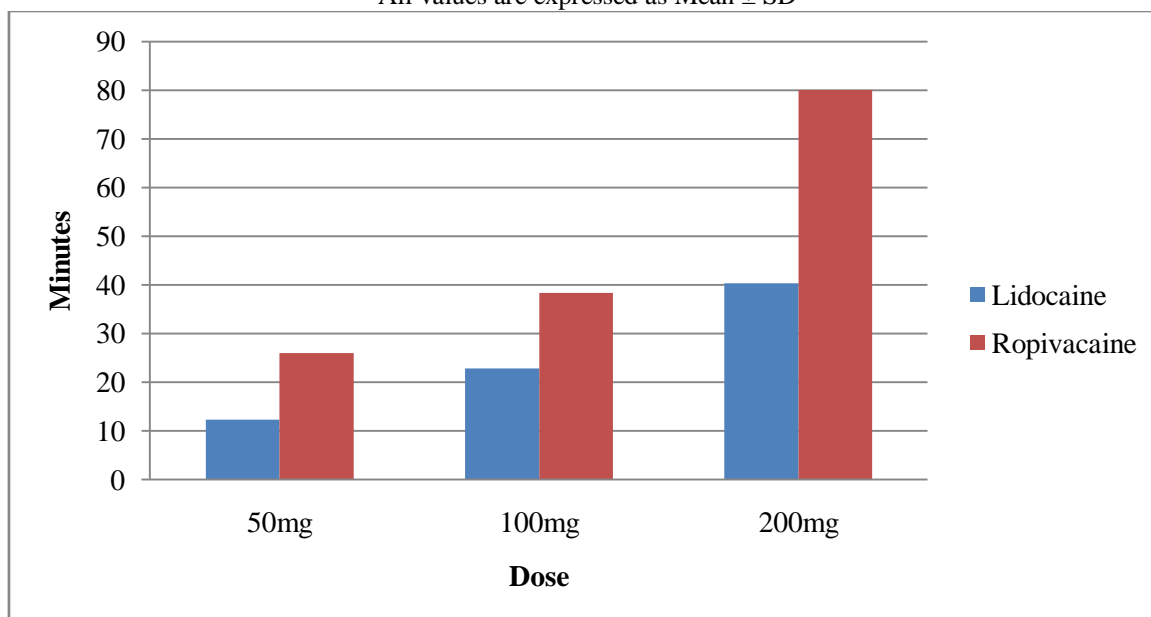


Fig 2: Comparison of duration of Action of Lidocaine and Ropivacaine on corneal reflex in rabbits

2. In groups 2 and 3, 2.5 µg and 5.0 µg of lidocaine produced the onset of action of loss of movement of nostrils in 11.0min, and 20.0min respectively. 2.5 µg and 5.0 µg of ropivacaine produced the onset of action of loss of movement of nostrils in 17.0min, and 38.0min respectively (Table 3; Fig.3). In groups 2 and 3, 2.5 µg and 5.0 µg of lidocaine produced the duration of action of regain of movements of nostrils in 45.0min and 94.0min respectively. 2.5 µg and 5.0 µg of ropivacaine produced the duration of action of regain of movement of nostrils in 80.0min and 163.0min respectively (Table 4; Fig.4).

Table 3: Effect of Lidocaine and Ropivacaine on the reflex movements of nostrils in rabbits

	Onset of Action in minutes in different doses	
	2.5 µg	5.0 µg
Lidocaine	11.0 ± 1.21 min	20.0 ± 2.99 min
Ropivacaine	17.0 ± 1.21 min	38.0 ± 2.82 min
P-value	<0.0001	<0.0001

All values are expressed as Mean ± SD value

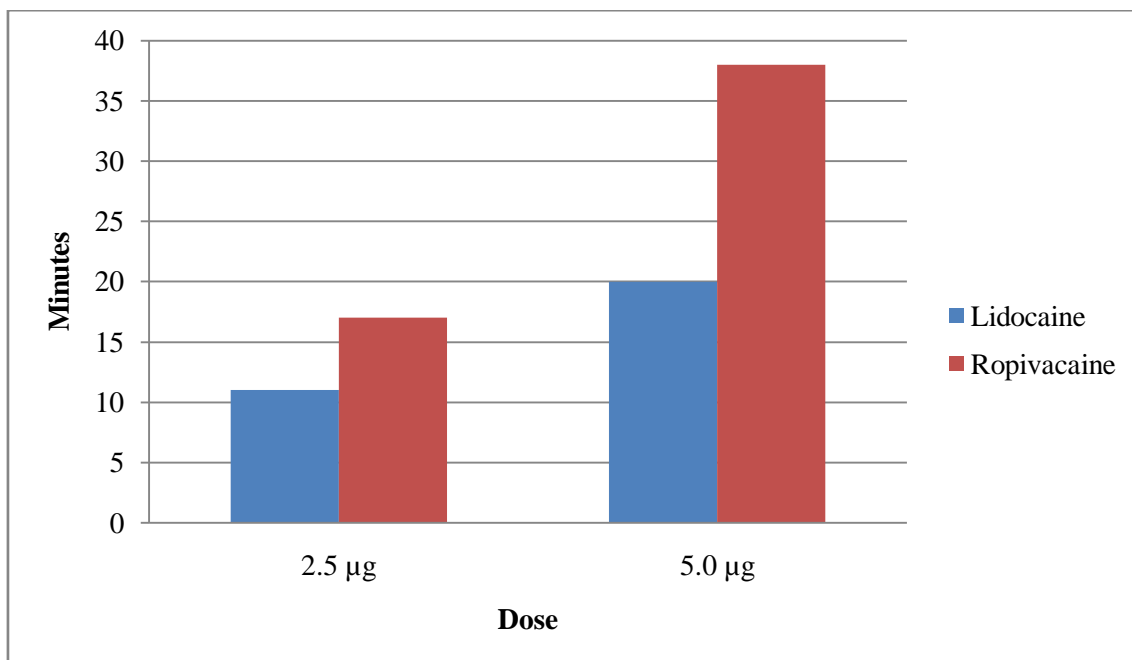


Fig 3: Comparison of onset of action of Lidocaine and Ropivacaine on the reflex movements of nostrils in rabbits

Table 4: Effect of Lidocaine and Ropivacaine on the reflex movements of nostrils in rabbits

Drug	Duration of Action in different doses	
	2.5 µg	5.0 µg
Lidocaine	45.0 ± 2.73 min	94.0 ± 6.28 min
Ropivacaine	80.0 ± 4.32 min	163.0 ± 4.91 min
P-value	<0.0001	<0.0001

All values are expressed as Mean ± SD value

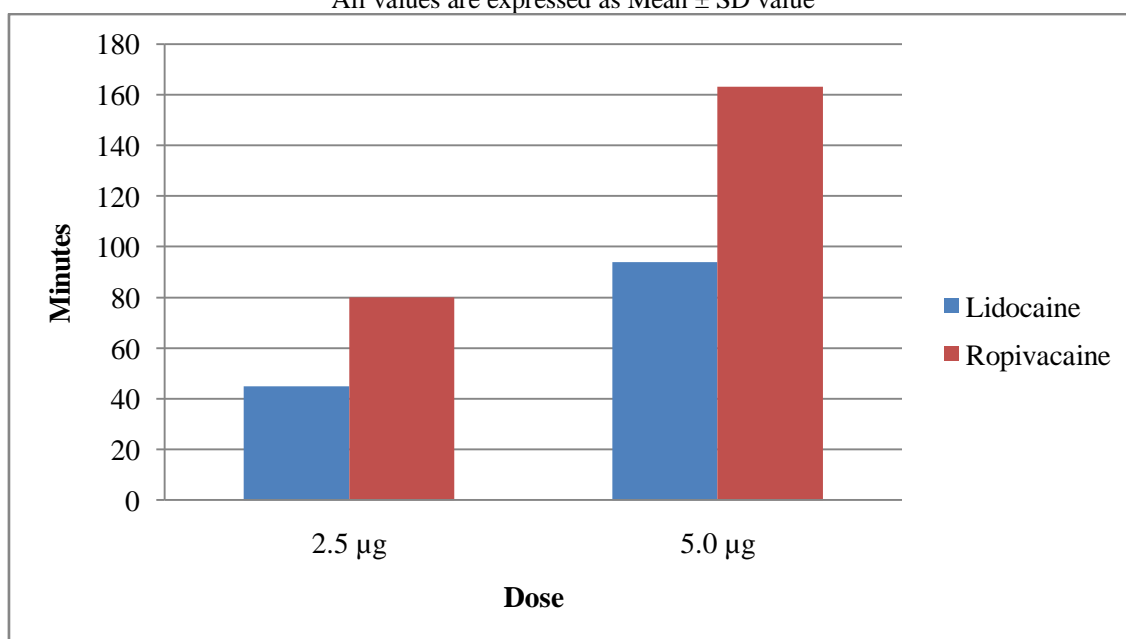


Fig 4: Comparison of duration of action of Lidocaine and Ropivacaine on the reflex movements of nostrils in rabbits

3. In group 1, where 6.25 µg of lidocaine was added the onset of action was reduced to 2.25min and 1.5min respectively. In group 4, where 6.25 µg, 12.5 µg, and 25.0 µg of ropivacaine were added, the onset of action was uniformly the same with 3min for all the three doses (Table 5; Fig.5). In group 1, where 6.25 µg, 12.5 µg, and 25.0 µg of lidocaine were added, the durations of action of action were 60.0min, 80.0min, and

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120.0min respectively. In group 4, where 6.25 µg, 12.5 µg, and 25.0 µg of ropivacaine were added the durations of action were 145min, 175min, and 210min respectively (Table 6; Fig.6).

Table 5: Analgesic effect of Lidocaine and Ropivacaine on rats by tail-flick method

Onset of action in minutes			
Dose (in mcg)	6.25	12.5	25.0
Lidocaine	4.33±1.03	2.33±0.51	1.41±0.49
Ropivacaine	3.0±0.0	3.0±0.0	3.0±0.0
P-value	0.00	<0.01	0.00

All values are expressed as Mean ± SD value

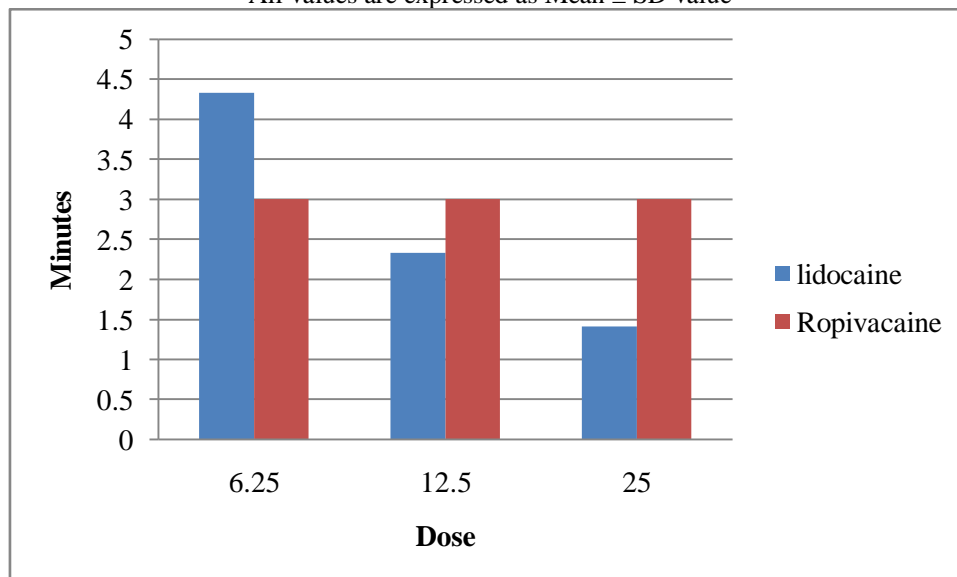


Fig 5: Comparison of onset of analgesic effect of Lidocaine and Ropivacaine on rats by tail-flick method

Table 6: Analgesic effect of Lidocaine and Ropivacaine on rats by tail-flick method

Duration of action in minutes			
Dose (in mcg)	6.25	12.5	25.0
Lidocaine	55.67±1.03	86.17±2.56	118.4±0.66
Ropivacaine	147.0±0.0	177.0±0.0	207.0±0.0
P-value	0.00	0.00	0.00

All values are expressed as Mean ± SD value

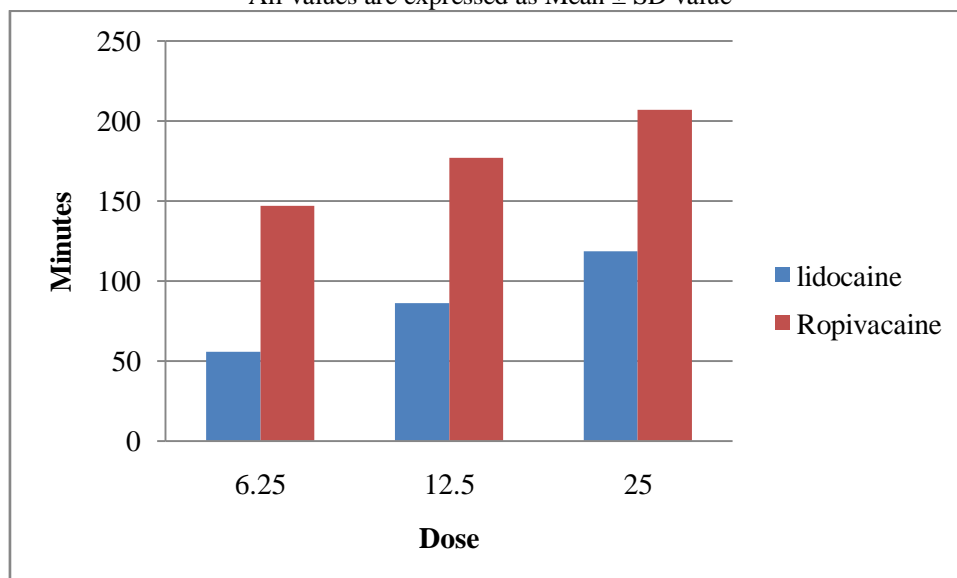


Fig 6: Comparison of duration of analgesic effect of Lidocaine and Ropivacaine on rats by tail-flick method

4. On perfused frog heart, lidocaine reduced the force of contraction progressively when the drug was added to the perfusion fluid in increased doses. There was also bradycardia, and the heart stopped in systolic arrest. When compared to lidocaine ropivacaine increased the force of contraction initially with bradycardia but the cardiac arrest was produced one and half times later than that of lidocaine. The missed beats were less for ropivacaine when compared to lidocaine (Table 7; Fig.7).

Table 7: Effect of Lidocaine and Ropivacaine on perfused frog heart

	Number of heart beats / min					
Dose	0.4mcg	0.8mcg	1.68mcg	3.36mcg	6.72mcg	13.4mcg
Control	50.66	56.33	44.0	30.7	37.5	44.66
Lidocaine	34.03	24.13	31.39	21.67	21.24	24.58
Ropivacaine	42.16	37.73	37.93	25.21	34.64	32.95

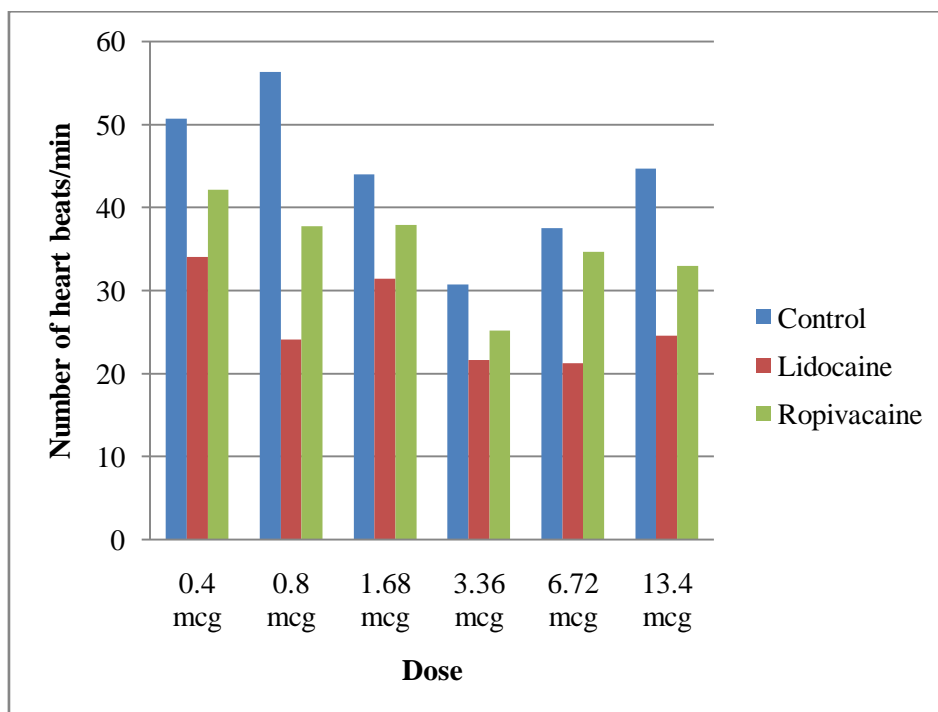


Fig 7: Comparison of toxicity of Lidocaine and Ropivacaine on perfused frog heart

5. On perfused blood vessels of frog, lidocaine produced vasoconstriction. Ropivacaine produced lesser initial vasoconstriction followed by vasodilation (Table 8; Fig.8).

Table 8: Effect of Lidocaine and Ropivacaine on the perfused blood vessels of frog

	Number of drops/ min			
Dose	6.72mcg	13.44mcg	26.88mcg	53.76mcg
Control	113.12	102.66	82.16	56.0
Lidocaine	81.51	85.42	75.33	17.24
Ropivacaine	96.74	118.86	129.98	79.51

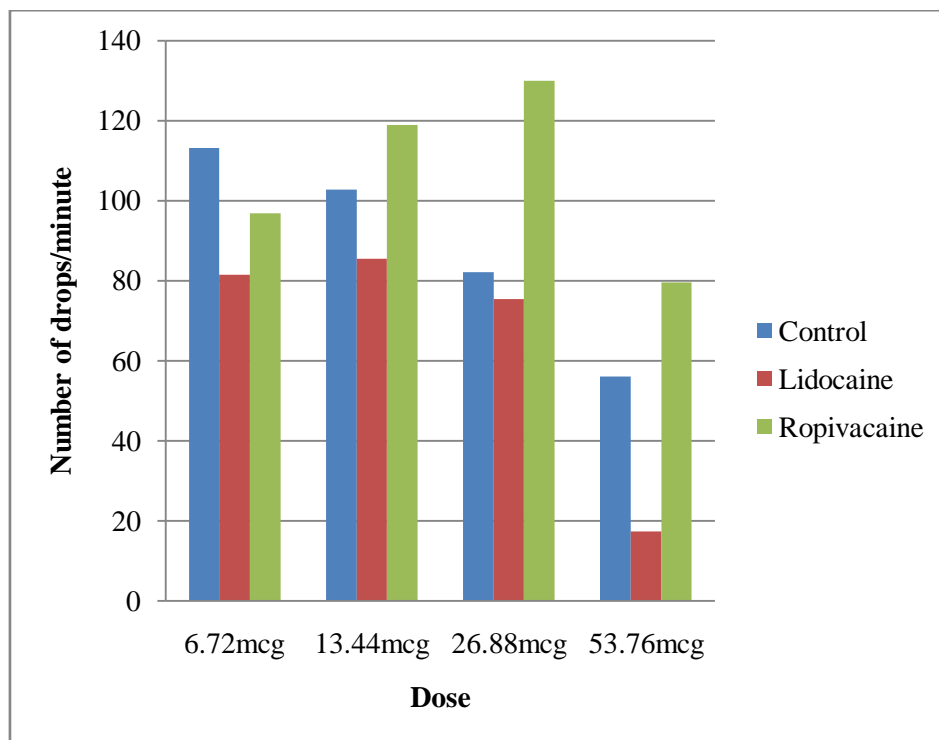


Fig 8: Comparison of Lidocaine and Ropivacaine on the perfused blood vessels of frog
For all parameters used, the observations were statistically significant as shown in the respective tables.

III. DISCUSSION

1. In the rabbit corneal reflex experiments the onset of action for ropivacaine was earlier than that of lidocaine in the same doses of 50 μg , 100 μg , and 200 μg . Similarly, the duration of action of ropivacaine was twice longer than lidocaine in the same doses. Both the results were statistically significant. Nicholson, et al (2000) has stated that lidocaine produces faster onset of action than ropivacaine, in contrast to our observation. However, it should be noted that they had used different concentrations of lidocaine (2%) and ropivacaine (1%). But we used the same concentrations of both the local anaesthetics. This may be the reason for the faster onset of ropivacaine. The findings of Borazan, et al (2007) also coincide with our results regarding the longer duration of action of ropivacaine than lidocaine.

They claim that long acting local anaesthetics like ropivacaine can be used safely in order to provide topical anaesthesia in cataract surgery and to avoid the necessity for repeated instillation doses.

2. In the other study of local anaesthetic effect of lidocaine and ropivacaine on the reflex movement of nostrils in rabbit, we got different results regarding the onset of action of lidocaine and ropivacaine when compared to the results of rabbit corneal reflex experiments. In spite of the same doses given for both the local anaesthetics, lidocaine yet produced faster onset of action when compared to ropivacaine. Though the species of animal used was same, the difference in the tissue/organ used might be the cause for the different results (Borazan, et al 2007). And yet, there was no difference in results regarding the duration of action of lidocaine and ropivacaine on the reflex movements of the nostrils in rabbits. Ropivacaine still produced twice the duration of time when compared to lidocaine in different doses.

3. In the comparative study of the analgesic action of lidocaine and ropivacaine on rats by tail flick method, ropivacaine proved to be more potent and longer acting in its analgesic action when compared to lidocaine. Ropivacaine increased the duration of action in both low dose and high dose. Peng Philip, et al (2002) have also made similar observations in their experiments in humans.

4. In comparing the effects of lidocaine and ropivacaine on the perfused frog heart ropivacaine took a longer time in producing bradycardia and finally the cardiac arrest in systole. The force of myocardial contraction by ropivacaine was greater than lidocaine. The missed beats produced by ropivacaine were less in number when compared to lidocaine. This observation is supported by the reports of Gheradini, et al (1995).

5. On the perfused blood vessels of frog lidocaine produced vasoconstriction. On the other hand ropivacaine produced initial vasoconstriction followed by vasodilatation. This observation is also supported by

the findings of Gherardini et al (1995). Hence, if it is true in case of humans, use of ropivacaine may require the addition of adrenaline in order to avoid systemic adverse effects when high doses are given.

IV. CONCLUSION

Our study using different parameters clearly demonstrates that ropivacaine has rapid onset and longer duration of action; it is more potent but less cardiotoxic and produces delayed vascular effects when compared to lidocaine (Mc Clure J H, 1996; Knudson K, et al 1997).

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