THE STUDY OF HEMODYNAMIC CHANGES OF PATIENTS UNDER GENERAL ANESTHESIA WITH DIFFERENT RATES OF INJECTION OF REVERSE

Sohrab Kochaki¹, Dr. Kaveh Behaeeën², Dr. Kamran Mahmodi³, Mostafa Fatahi³*, Hossein Rahmani¹

¹Department of Anesthesia, Paramedical School, Jundi Shapur University of Medical Sciences, Ahvaz, Iran.
²Department of Anesthesia, Faculty of Medicine, Jundi Shapur University of Medical Sciences, Ahvaz, Iran.
³Department of Perfusion, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran.

ABSTRACT

Background and Purpose: Neostigmine is used to reverse the neuromuscular block, and Atropine is used to antagonize the muscarinic effects of Neostigmine. This study aims to investigate hemodynamic changes of patient under general anesthesia with different rates of reverse injection. Methods: This applied study was performed on 64 ASA1 patients under general anesthesia. In both group, premedication was done by Midazolam, Fentanyl and induction was done by thiopental and Atracurium. Then, the patient was reversed by mixture of Neostigmine and Atropine. The injected rate of reverse in group A was 5s and in group B was 15s. One minute before injection of reverse and in minutes 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 after injection of reverse, hemodynamic changes were recorded in both groups. Results: Findings show that group A had initial increase in heart rate till third minute after injection of the reverse and then heart rate changes descended along with fluctuations. In group B, the initial increase in heart rate continued to 3 minutes after reverse and heart rate changes had steady descent and other variables of hemodynamic changes didn't have significant differences. Conclusion: Based on
these results, it is recommended to have a better stability of the hemodynamic changes after injection of reverse, it should be injected within 15 seconds.

KEYWORDS: Neostigmine, Atropine, Reverse, Heart rate, Neuromuscular relaxants.

INTRODUCTION

Neuromuscular blockers are used to induce the anesthesia in order to safe airway intubation.\[1\]

The use of neuromuscular blockers also prepare condition for Anesthesiologists to keep the airway open during long-term operations, eliminate muscle reflex function and moderate patient position during surgery. Neuromuscular blockers are divided into two categories: non-depolarizing and depolarizing. And are related to acetyl choline. Depolarizing substances act as acetylcholine agonists and non-depolarizing compete directly with acetyl choline on nicotinic receptors. Reverse of neuromuscular block takes place by one of two methods: 1 - Increase Acetylcholine release from pre-synaptic 2 - reduction in acetylcholine metabolism.\[2\]

Today, anti-choline esterase is used to reverse of neuromuscular block. Although, anti-choline esterase has effect of releasing increase of pre-synaptic acetylcholine. It is believed that the main mechanism of their reverse is to avoid performance of acetylcholine esterase in synaptic cleft.\[3\]

Adequate recovery of neuromuscular relaxants in order to preserve the laryngeal reflexes (to prevent aspiration of gastric contents) and maintain the respiratory muscle function is vital which is done by spontaneous rejection of neuromuscular relaxants from the junction of neuromuscular and also their metabolism and elimination are done. This practice will be promoted by reverse medications including anti-choline esterase.\[4,5\] Anticholinesterase cause bradycardia, arrhythmia, nausea and vomiting, increased the secretion of salivary glands, abdominal pain, and bronchoconstriction by stimulating the Muscarinic receptors, and bronchoconstriction is caused by anti-choline esterase and resolved by atropine.\[6-8\]

Today, the mixture of anti-cholinergic and anti-choline esterase is used to reverse of non-depolarizing relaxants.\[9\] The most common anti-choline esterase are Neostigmine, edrophonium and pirydostigmine. Among the mentioned drug, Neostigmine is the most common anti-choline esterase that its main mechanism is inhibition of choline esterase enzyme function and cause to acetyl choline molecules increasing.\[10,11\] And the most
common anti-cholinergic used in anesthesia is atropine.\textsuperscript{12} Neostigmine is used to reverse the residual neuromuscular block during anesthesia and atropine is used to antagonize the muscarinic effects of Neostigmine with Neostigmine.\textsuperscript{13,14}

However, simultaneous use of these drugs cause to bradycardia because of para- Sympathetic function increasing and Sympathetic function decreasing. Many researchers have studied the effect of atropine and Neostigmine on hemodynamic changes and recovery from neuromuscular block in anesthetized patients. Nevertheless, there isn't same agreement about the rate and dose of atropine and neostigmine in order to reverse of neuromuscular block.\textsuperscript{15-17} According to Tetzlaff's statements, some changes is created in heart rate during the reverse of neuromuscular block drugs with a combination of anticholinergic and anti-choline esterase.\textsuperscript{18} It has been explained in other researches that the slow injection of mixture of atropine and neostigmine reduce heart rate. It has been tried in this research that reverse velocity impact (Atropine and neostigmine) on hemodynamic changes of patient will be studied.\textsuperscript{19,20} Then this study was done aims to investigate hemodynamic changes of patient under general anesthesia with different rates of reverse injection.

**METHODS**

This study has been conducted on 64 patients of class ASA 1 in two 32 individual groups in Imam Khomeini hospital of Ahvaz with Courtesy from Ethics Committee of JondiShapoor medical university and obtaining informed consent from patients. This study includes patients with 1-3 hour general anesthesia, 50-85 kg weight range and 18-65 age range. All patients with systemic disease (cardiovascular, respiratory, hypertension, diabetes), liver disorders, kidney disease, COPD (chronic obstructive pulmonary disease) (likelihood of postoperative respiratory depression), neurological and psychiatric disorders which intercostal blocks and ancillary space was used, cardiac arrhythmias before anesthesia induction, known diseases would affect the autonomic system and patients who used drugs affecting the cardiovascular system, anti-depressant, anticonvulsant, sedative, and also in patients with difficult laryngoscopy and intubation for more than 30 seconds, apparent deformity in upper airway and addiction to drugs and alcohol were excluded.

The study was performed on all patients undergoing general anesthesia. After placing the patient on the operating table, necessary monitoring was connected and premedication was done with 0.02 mg/kg midazolam, 2 Microgram/kg fentanyl and induction was done with 4 mg\(\text{kg}\) thiopental and 0.5mg/kg atracurium. During anesthesia, after every half an hour, 0.25
of initial dose of atracurium and after every hour, 1 microgram/kg fentanyl was injected. Obtained fluid in all Ringer patients was 10 ml/kg and in order to maintenance of anesthesia, mixture of O2 + N2O (50%) plus propofol(50-100 microgram/kg/hr) was used. after anesthesia, all anesthetic gases were closed and by returning the respiration, patients were reversed with a mixture of 0-0.04 mg/kg neostigmine and 0.02 mg/kg atropine. Patients were divided into two groups, A and B. the velocity of reverse injection was 5 s in group A and in group B was 15 s. after operating and minute before reverse injection, hemodynamic changes such as Heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and arterial oxygen were recorded in both groups.

After reverse injection with mentioned velocity, in both group, hemodynamic changes of patients were recorded at minutes 1, 2, 3, 4, 5, 10, 15, 20, 25, 30 by ECG monitoring in Lead II. Then all the information about patients in both groups were classified separately in the tables and were analyzed by SPSS 19 software and repeated measures test. The difference in each point between data (0.05> P) was considered significant.

**RESULTS**

According to the results of two group, sex, age, weight, and surgery time didn't have significant difference(p>0.05).

**Table 1. The comparison of the mean of ± SD in patient demographic**

<table>
<thead>
<tr>
<th>Reverse within 5s</th>
<th>Weight (Kg)</th>
<th>Age (years)</th>
<th>Sex (m/f)</th>
<th>Surgery duration (minutes )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse within 15s</td>
<td>63.7±12.9</td>
<td>45.1±15.2</td>
<td>22/10</td>
<td>125±21</td>
</tr>
<tr>
<td>p.value</td>
<td>0.438</td>
<td>0.685</td>
<td>0.840</td>
<td>0.756</td>
</tr>
</tbody>
</table>

Repeated measures test was used in order to investigating data in groups A and B and the following result are obtained.

According to the obtained results in table 2 between the obtained measures for heart rate between 2 groups before reverse injection, there isn't significant difference (P=0.854). After reverse injection till minute 3, significant increasing is observed in both group and the heart rate comparison between 2 groups in this 3 minutes show significant difference (P=0.001). From minute 3 after reverse injection till minute 30 after reverse injection, heart rate changes decreased in group A and it was with fluctuations. In group B which reverse was injected within 15 s, initial increasing in heart rate continued till minute 3 after reverse and from
minute 3 after reverse injection till minute 30 after reverse injection, heart rate changes decreased but it was monotonic. (Chart 1).

![Chart 1](image)

**Chart 1.** In this diagram, vertical axis shows heart rate and the horizontal axis shows registration time of heart rate in before and after reverse. (Zero number is the heart rate before reverse injection).

**Table 2.** Mean and SD of heart rate changes in both groups A and B

<table>
<thead>
<tr>
<th></th>
<th>Reverse within 15s(B)</th>
<th>Reverse within 5s(A)</th>
<th>p.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before reverse</td>
<td>87.62±27.84</td>
<td>84.06±22.28</td>
<td>0.854</td>
</tr>
<tr>
<td>1 minute before reverse</td>
<td>95.53±27.59</td>
<td>109.09±21.50</td>
<td>0.001</td>
</tr>
<tr>
<td>2 minutes before reverse</td>
<td>96.59±19.07</td>
<td>110.18±27.32</td>
<td>0.001</td>
</tr>
<tr>
<td>3 minutes before reverse</td>
<td>99.21±20.21</td>
<td>113.93±26.93</td>
<td>0.001</td>
</tr>
<tr>
<td>4 minutes before reverse</td>
<td>90.42±18.85</td>
<td>92.53±22.72</td>
<td>0.596</td>
</tr>
<tr>
<td>5 minutes before reverse</td>
<td>88.46±17.01</td>
<td>96.71±22.37</td>
<td>0.146</td>
</tr>
<tr>
<td>10 minutes before reverse</td>
<td>79.31±15.84</td>
<td>84.21±21.37</td>
<td>0.748</td>
</tr>
<tr>
<td>15 minutes before reverse</td>
<td>77.37±14.90</td>
<td>86.06±18.90</td>
<td>0.385</td>
</tr>
<tr>
<td>20 minutes before reverse</td>
<td>74.87±15.48</td>
<td>79.37±19.80</td>
<td>0.984</td>
</tr>
<tr>
<td>25 minutes before reverse</td>
<td>73.81±14.30</td>
<td>80.96±18.77</td>
<td>0.476</td>
</tr>
<tr>
<td>30 minutes before reverse</td>
<td>71.68±12.25</td>
<td>78.90±22.66</td>
<td>0.852</td>
</tr>
</tbody>
</table>
Chart 2. In this diagram, vertical axis shows the systolic blood pressure and horizontal axis shows the registration time of the systolic blood pressure in before and after the reverse. (Zero is the systolic blood pressure before reverse injection).

According to obtained results in chart 2, there isn't significant difference of systolic blood pressure between both groups before reverse injection (p=0.098). After reverse injection till second minute in both groups, notable increasing is observed in systolic blood pressure but systolic blood pressure comparison between both groups at this 2 minutes doesn't show significant difference. From minute 2 after reverse injection till minute 30 after reverse injection, systolic blood pressure changes decreased in group A and it was with fluctuations. In group B which reverse was injected within 15 s, initial increasing in systolic blood pressure continued till minute 2 after reverse and from minute 2 after reverse injection till minute 30 after reverse injection, systolic blood pressure changes decreased but it was monotonic.(chart 2).

According to obtained results in chart 3, there isn't significant difference of diastolic blood pressure between 2 groups before reverse injection (p=0.568). After reverse injection at first minute, notable increasing is observed in diastolic blood pressure in both groups but diastolic blood pressure comparison doesn't show a significant difference between both groups at first minute (p=0.847). From 2 minutes after reverse injection till minute 30 after reverse injection, diastolic blood pressure changes decreased in group A and it was with fluctuations just between minutes 5 till 10.
DISCUSSION

Accidental death has been observed by using atropine and neostigmine in order to reverse the residual neuromuscular relaxant. The reason is related to bradycardia formed by neostigmine, especially when a few dose of atropine along with neostigmine is use.\[21-24\] It seems unlikely that decreasing the heart rate by neostigmine cause to cardiovascular clops.\[25\] During reverse, dangerous dysrhythmia occur by atropine injection to patients who doesn't ventilate adequately or in presence of cyclopropane.\[26\] Retardation of heart rate is sometimes observed by presynaptic central function of atropine that it is along with bradycardia due to neostigmine. But if adequate and proper dose of atropine is used along with neostigmine, heart rate increasing is created before bradycardia.\[27\]

The effect of residual neuromuscular block reverse by neostigmine mostly depends on the amount of residual block during injection, dose of neuromuscular relaxant and the time of the last injection of neuromuscular relaxant.\[28\]

As long as we use the least possible dose of relaxant, and the residual relaxant reverse is done at proper time, no problem will happen during residual relaxant reverse.\[15\]
Most of the performed studies related to atropine and neostigmine have concentrated on the amount of injection dose. In one investigation, Sirirat et al concluded that using atropine 1.2 mg and neostigmine 2.5 mg to residual neuromuscular block reverse in adults cause tachycardia.\textsuperscript{[29,30]} This dose may be dangerous for old patients\textsuperscript{[31]}, patients with cardiovascular disease, patients with thyrotoxicosis and also patients with hypovolemia due to tachycardia.\textsuperscript{[32-34]}

According to the performed search by Pooler, if reverse injection is done slowly, atropine cannot counter with created bradycardia by neostigmine. Probably, it is due to the effects of pre-sympathetic acetylcholine block of sympathetic autonomic neural by atropine.\textsuperscript{[35]}

This investigation showed that heart rate changes and systolic blood pressure had better hemodynamic stability in group B in comparison with group A. at first 3 minutes after reverse injection initial heart rate increasing in group A is more than group B. It may be dangerous in elderly people, people with cardiovascular diseases and also heart rate changes after the injection of reverse in Group B has less intensity and changes than reverse injection during 5 seconds.

According to the obtained results, it seems that slow reverse injection is better and according to the better hemodynamic stability in reverse injection during 5 second, hemodynamic stability is an important principle in anesthesia.

Furthermore, since other Hemodynamic variables (systolic and Diastolic blood pressure) have no significant difference as like as the results of similar researches\textsuperscript{[9,36]}, it is recommended to prescript reverse within 15s in order to prevent high increase of hemodynamic changes with lower fluctuations of patients after injection of reverse.

In a research carried out by Harper and his colleagues on the changes of heart rate with slow injection of mixture of Atropine and Neostigmine, they concluded that minimum decrease of heart rate is followed by injection of reverse more than 3 minutes.\textsuperscript{[15]}

Regarding to the fact that, slower injection of reverse can be effective on the incidence of tachycardia, it is recommended to study reverse injection for 30s, 1m, 2m, 3m, in further researches in order to investigate the effects of these different velocities.
ACKNOWLEDGEMENT
I really appreciate students' researches committee of medical University of Jondi Shapoor in Ahwaz, and I also thank Mrs. Alboghbish, Raki, and all kind persons who helped us in this project.

REFERENCES


