



The Effect of Gentamicin on the Action of Atracurium in Adult Patients

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Abstract

The aim of the trial was to study the effect of Gentamicin as an aminoglycoside on Atracurium as a neuromuscular blocker. Forty patients (20-60 years old) who had minor surgical procedures were enrolled in the study. All the patients were with the American Society of Anaesthesiologists (ASA) physical status I-II with elective surgery in supine position. Patients were represented to full history, clinical examination and laboratory tests at Beni suef University Hospital to be sure that they met the criteria. Patients were divided into two equal groups. Group I (atracurium-gentamicin) and Group II (atracurium alone). Group I received gentamicin at dose of 2 mg/kg 5 minutes before starting the general anesthesia. The degree of muscle relaxation was monitored by using peripheral nerve stimulator with recording of Train of Four (TOF) ratio every 10 minutes, clinical duration ($p=0.89$), onset time ($p=0.76$), time to spontaneous recovery T4/T1 ratio(0.84) and occurrence of recurrence of the neuromuscular blockade were assessed. At the end of anesthesia it was noticed that there was no significant difference according to onset time, clinical duration or time to spontaneous recovery. Hence, there was no effect of using gentamicin preoperatively on the action of the atracurium.

Key Words: Gentamicin, atracutium, neuromuscular blocker

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Introduction

Anesthesiologists use a few medications during anesthesia of a patient. Those medications include inhaled anesthetics, adrenergic agonists, adrenergic antagonists, intravenous anesthetics, opioids, muscle relaxants, cholinesterase inhibitors, anticholinergic drugs, blood pressure lowering agents, local anesthetizing agents and many other adjunct drugs. Antibiotics can be used for diminishing or prevention of incidence of infections after surgery or for treatment of existed infections. Regularly the anesthesiologist use already prescribed antibiotics for the patient before surgery. The optimal use of the antibiotics and also the precision of the responsibility of its use between the anesthesiologist and the surgeon, their side effects and drug interactions are somehow controversial among different scientific organizations. Anesthesiologist face difficulties knowing all information about the use of the antibiotics, their side effects, allergic reactions and also the prolongation of action of muscle relaxants as every organization has its own scheme which is regularly adapted [1]. Anesthesiologists' main attention is about the effect of antibiotics on the neuromuscular system [2]. A neuromuscular blockage can occur by antibiotics even if they were used alone without muscle relaxants [3]. The mechanisms of the neuromuscular blockage occurred by these antibiotics are by postjunctional effect or by causing a prejunctional effect [2,4-6]. Many scientists tried to do a classification of those antibiotics regarding their mechanism of neuromuscular blockage whether it is prejunctional or postjunctional. However it was difficult to understand the actual mechanism that antibiotics follow to exert their neuromuscular blocking activity. Hence, it was hard to choose certain antibiotics to be used in the same time with the muscle relaxants and this made a conclusion that the continuous mechanical ventilation may be the convenient treatment for the complication of this prolongation of the muscle relaxants [6]. Atracurium is one of the non-depolarizing muscle relaxants that have many advantages as rapid onset, high potency and no cardiovascular side effect. In the same time atracurium does not release histamine and it has no cumulative properties. atracurium metabolism produces nontoxic metabolites and pharmacologically inactive substances and it can be used safely in hepatic and renal patients [7]. Aminoglycoside antibiotics such as gentamicin is specially used to treat infections caused by gram negative bacteria and also for many other types of bacterial infections [1]. A neuromuscular blockage can be increased by all aminoglycoside antibiotics. It was previously reports that there is a real difficulty to antagonize the action of rocuronium after using oral neomycin [8]. There is an animal study

[9] showed that gentamicin has prolonged the neuromuscular blocking action of atracurium. gentamicin is involved in this study as it is known to have a neuromuscular blocking activity [10]. It is also believed that the action of atracurium is prolonged by gentamicin [11]. Hence, the aim of this study was to investigate the clinical effect of gentamicin on the muscle relaxant activity of atracurium to detect if there was a serious interaction that can cause risks for patients who may have them in the same time.

Patients and Methods

The study was carried out at Beni Suef University Hospital in the period from January 2012 to October 2012 after approval of the local research and ethics committee and included forty patients who underwent different operations under general anesthesia with muscle relaxation by atracurium. Patients were divided into two groups: Group I (20 patients) received (atracurium and gentamicin). Group II (20 patients) received (atracurium) only.

Inclusion criteria

Patients aged 20 - 60 years, The American Society of anesthesiologists (ASA) physical status I-II and undergoing elective surgery in the supine position e.g. upper and lower limb surgeries.

Exclusion criteria

Patients with conditions that affect the action of muscle relaxants e.g. patients with neuromuscular diseases and patients with renal or hepatic impairment

Patients receiving drugs that may interact with muscle relaxant e.g. MgSO_4

Patients that does not require muscle relaxation to perform the operation

Patients with ASA physical status more than II

Methods:

All patients were subjected to:

-Full examination to be preceded by history, for proper selection of patients.

-Pre-medication with I.V. midazolam at dose of 2 mg 10 minutes before induction.

*Patients were assigned randomly to either:

- **Group 1:** atracurium-gentamicin i.e. study group (n = 20).
- **Group 2:** atracurium alone i.e. control group (n = 20).

Study group patients received Intravenous (IV) gentamicin at a dose of 2 mg/kg 5 minutes before induction of General Anesthesia (G.A).

Anesthesia was induced by I.V. propofol 2mg/kg, fentanyl 1 microgram/kg, Atracurium 0.5 mg/kg used for achieving muscle relaxation. Followed by mask ventilation and intubation, then patients were ventilated with 1 Minimum Alveolar concentration (MAC), Isoflurane and 1 Fraction of Inspired Oxygen (FiO₂).

Degree of muscle relaxation was monitored with peripheral nerve stimulator with recording of Train of Four (TOF) ratio every 10 minutes. Additional doses of Atracurium were given if needed only if Train of Four (TOF) ratio is 0.7 or more.

The following items were assessed:

1. Onset time: defined as the time between the administration of muscle relaxant and 90 percent twitch depression.
2. Clinical duration: defined as the time between administration of muscle relaxant and 25 percent twitch recovery.
3. Time to spontaneous recovery of T4/T 1 ratio: it is time since injection of muscle relaxant till recording TOF ratio of 0.70.
4. of recurrence of neuromuscular blockade: After using neostigmine with one hour the neuromuscular function of the patients will be checked by one of two methods:
 - Asking the awake patients if they could raise their head for five seconds
 - the tactile method was used to detect any residual of the muscle block for sleeping patients through receiving 50 HZ supramaximal tetanus at the ulnar nerve for 5 seconds.

At the end of the operation muscle relaxation was discontinued in an appropriate time before the end of the operation. Inhalational anesthesia was discontinued at the end of the operation and the patient was allowed to breathe 100% oxygen. Reversal of muscle relaxant was given at Train of Four (TOF) ratio of 0.7 at dose of 0.05 mg/kg neostigmine and 0.02 mg/kg atropine. Before extubation the cuff was deflated. After extubation, suction of any secretions in the upper airway and face mask with 100% oxygen was applied till the patient became fully awake.

One hour after antagonism with neostigmine, the neuromuscular function of the patients was checked as mentioned before.

Statistical analysis:

A comparison was made between Group I and Group II according to age, sex, onset time, clinical duration and time to spontaneous recovery using:

*Description of qualitative variables by frequency and percentage.

*Description of quantitative variables in the form of mean and standard deviation (mean $\pm$ SD).

*Comparison between quantitative variables was carried by using:

-Student t-test of two independent samples.

Significance level (p) was set as $P < 0.05$.

Results

Mean $\pm$ SDs age, onset time, clinical duration and time to spontaneous recovery of T4/T1 ratio of 0.70 of the two groups are shown in Table 1. There were no significance differences among the groups regarding gender, age, duration of surgery (130 $\pm$ 40 min for Group I and 120 $\pm$ 25 min for Group II), the ASA risk score, skin temperatures at the neuromuscular blockage monitoring site, onset time, clinical duration and time to spontaneous recovery (T4/T1 ratio). None of the patients had recurrence of neuromuscular blocker. None of the patients had a core temperature less than 35°C. Among the groups, the difference in core temperature at the end of operation was insignificant.

Table 1: Mean±SD age, onset time, clinical duration and time to spontaneous recovery of T4/T1 ratio of 0.70 of the two groups.

		Group I (gentamicin and atracurium)	Group II (atracurium)	p-value
Age (years)		44.9± 7.79	45.0± 7.82	0.984
Onset time (min.)		4.32± 0.78	4.40± 0.80	0.767
Clinical duration (min)		39.8± 3.33	39.6± 3.79	0.893
Time to spontaneous recovery of T4/T1 ratio of 0.70 (min.)		64.4± 3.95	64.1± 3.85	0.840
Gender	Males	20	20	NS
	Females	20	20	
ASA Risk factor		I-II	I-II	NS
Core temperature		Below 35	Below 35	NS

Discussion

The aim of the study was to investigate the effect of gentamicin treatment (Group I) as compared with no gentamicin (Group II) given before surgery on the degree of neuromuscular blockade produced by atracurium. Antibiotics are used before surgery to prevent postoperative infections. Anesthesiologists can administer antibiotics before or during surgery even if these antibiotics were already prescribed by physician [1]. Many reports talked about the neuromuscular blocking effect of antibiotics either used with muscle relaxants or alone [2, 12-15]. gentamicin neuromuscular effect was mentioned in some previous reports on some muscle relaxants as d-tubocurarine [16], pancronium [17] and vecuronium [18]. The mechanism of gentamicin neuromuscular blocking action is supposed to be the same as magnesium. The muscle paralysis caused by Magnesium is due to reduction of Acetylcholine release and that action can be reversed by calcium. In the same way, gentamicin decreases the release of Acetylcholine and also blocks the calcium channels at the motor nerve terminal [6, 17, 19]. However, Gentamicin produces tetanic fade but not a tetanic ascent as it happens with Magnesium [20]. Drugs as Isoflurane and halothane can Interact with atracurium [21, 22]. atracurium can also interact with other drugs [23-26]. This study focused on the interaction between gentamicin and atracurium there are some studies discussed that effect of

aminoglycosides on the actions of the neuromuscular blockers. M Lippman et al studied the effect of using gentamicin and tobramycin on the action of d. tubocurarine and their results showed that there was no interaction between the group who took gentamicin and the control group who took only d-tubocurarine. According to reversal of the block by using neostigmine there was no problem observed though the degree of neuromuscular transmission was variable[27]. Another study made by Dupuis et al reported the action of gentamicin and tobramycin on the neuromuscular action of atracurium and vecuronium. They found no change in onset time but a prolongation of clinical duration and time to recovery of vecuronium group than control, while there was no change in onset time, clinical duration or time to recovery of atracurium group. They mentioned that though there were many case reports showed the effect of aminoglycosides on the action of muscle relaxants but there was no clinical trials to investigate that effect [28]. The short half life of atracurium and its pharmacokinetics may be the reason for its rapid metabolism and that does not allow high concentrations of atracurium in blood to interact with gentamicin. This study does not illustrate the effect of higher doses of gentamicin if used in combination with atracurium. So the effect of using higher doses of gentamicin on atracurium may need further investigations. All patients had no recurrence of neuromuscular blocker. All of them could sustain a head lift for five seconds and that was an indication of no recurrence of the neuromuscular block according to our protocol.

Conclusion

Gentamicin given preoperatively in dose 2 mg/kg did not prolong the onset time, the clinical duration or the time to spontaneous recovery of atracurium. Atracurium is a good choice as a muscle relaxant to be used with gentamicin, when gentamicin is used in its normal therapeutic dose. This study focused on investigating the effect of gentamicin in its regular clinical dose when used in the same time with atracurium as a muscle relaxant. Sometimes patients take gentamicin in higher doses than the one used in this study. Toxicity with gentamicin may happen with some patients for a reason. So to have a general opinion about the effect of gentamicin in any dose on the action of atracurium further studies need to be done.

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