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Cost analysis and safety comparison of Cisatracurium and Atracurium in patients undergoing general anesthesia

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Abstract. – BACKGROUND: Non-depolarizing neuromuscular blocking agents (NMB) differ in pharmacokinetic and pharmacodynamic parameters. An anesthesiologist according to these similarities and differences is able to choose the least costly one if the same safety profile and same clinical benefit achieved with the different alternatives.

AIM: The main objective of this study is to evaluate the economic and adverse drug reactions prevalence and differences between cisatracurium and atracurium the two non-depolarizing NMB drugs, which are widely used in adult patients undergoing surgery with general anesthesia in a teaching Hospital in Iran.

MATERIALS AND METHODS: A cost analysis and adverse drug reactions (ADR) monitoring were performed. Only direct costs were considered and data were collected through a prospective randomized study. Regardless of the type of surgery, 100 patients were randomly divided into two equal groups to receive either cisatracurium or atracurium by anesthesiologists. ADRs prevalence and cost differences between patients receiving one of the two non-depolarizing NMB agents were evaluated by independent sample t-test and Chi-square test respectively.

RESULTS: No significant difference was observed between the two groups of patients in demographic data. There was no statistical difference in the ADR prevalence in both groups. The numbers of ADR within atracurium group was higher than cisatracurium group, but this distinction was not statistically significant ($p > 0.05$). It was significant difference in cost between the two neuromuscular blocking drugs ($p < 0.05$).

CONCLUSIONS: According to our study it seems that atracurium and cisatracurium had similar safety profile and atracurium had a cost benefit relative to cisatracurium in initial loading doses. In patients with instability in hemodynamic parameters the cisatracurium was the appropriate choice.

Key Words:
Cisatracurium besilate, Atracurium besilate, Non-depolarizing neuromuscular blocking agents, General anesthesia.

Introduction

The introduction of neuromuscular blocking agents in 1942 into anesthetic practice was an important development. Non-depolarizing NMB agents differ in the onset of action, duration of action, metabolic route, potency, adverse effects and cost. An anesthesiologist is able to choose NMB drugs according to these similarities and differences[1,2]. Atracurium and Cisatracurium are two non-depolarizing NMB agents with intermediate duration of action[1]. Cisatracurium besilate is the R-cis isomer of atracurium besilate and is 3-4 fold more potent than atracurium[3]. Compared with atracurium, cisatracurium besilate was associated with a lower tendency to cause histamine release and has a longer onset time at equal doses[4]. In fact the most disadvantage of atracurium is hemodynamic instability, particularly in patients with cardiovascular problems or who have neurosurgery or staying at Intensive Care unit (ICU)[1,4,5]. Except this difference, according to literature, most of other characteristics of both drugs are similar.

The main objective of this study is to evaluate the economic and adverse drug reactions prevalence and differences between the two non-depolarizing neuromuscular blocking drugs, which are widely used in adult patients undergoing surgery with general anesthesia in a teaching Hospital.

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Materials and Methods

A prospective randomized study was designed to comparing adverse drug reactions (ADR) and cost analysis between two popular NMB agents, atracurium (Tracrium®) and cisatracurium (Nimbex®) in patients undergoing elective surgery at Shariati Hospital in Tehran. Shariati Hospital is one of the Tehran University Medical Science affiliated hospitals which provides variety procedures.

Pre-anesthetic form was used to collect patients' demographic data (gender, age, and weight, etc.). For monitoring and evaluating adverse drug reactions causing by NMB agents, major therapeutic references were checked and then the ADR form was made and used to collect information on all side effects.

Investigators, who evaluated adverse drug effects, were kept blinded of drug identity but anesthesiologists were aware of specific NMB drug. Regardless of the type of surgery, between February and August 2010, 100 patients were randomly divided into two equal groups to receive either cisatracurium (0.15 mg/kg) (Group 1) or atracurium (0.6 mg/kg) (Group 2) by anesthesiologists. General anesthesia was induced with intravenous propofol 2 nmg/kg and 3 mcg/kg sufentanil. Anesthesia during surgery was maintained with infusion of 5 mcg sufentanil every 30 minute and isoflurane 1.5 to 2%. The patients were recovered from the block with administrating neostigmine (50 mcg/kg) and atropine (15 mcg/kg).

For each patient the ADR monitoring was performed and ADR form was completed. To compare the demographic characteristics of the groups, independent sample *t*-test was performed. The chi-square test was used to compare adverse drug reactions types and frequencies. All data were expressed as means ± SD.

In order to evaluate the impact of drug costs, we compared the price differences between two groups. For as much as neuromuscular blocking drug was administered as milligrams per kilogram we evaluated the mean dosage of the used drugs and then, the cost of drugs was calculated. The results was analyzed with independent sample *t*-test and reported as mean ± SD. $p < 0.05$ was considered statistically significant.

Results

One hundred subjects were enrolled in this study. The patients within two groups had similar demographic data ($p > 0.05$).There was no significant difference in weight, age or gender in between the cisatracurium group (n=50) and the atracurium group (n=50) (Table I). Chi-square test was used for comparison of side effects of atracurium and cis atracurium. The ADR findings related to NMB drugs are summarized in Table II.

In spite of more hypotension occurrence in atracurium group, there was no statistical difference in the ADR prevalence in both groups. The numbers of ADR within atracurium group was higher than cisatracurium group, but this distinction was not statistically significant ($p > 0.05$).

For comparing the cost, mean dosage administrated and unit drug cost was calculated. Based on the estimation the mean dosage used in the atracurium group was 83.06±6.74 mg (mean±SD) and 21.01±2.43 mg (mean±SD) in the cisatracurium group. The cost calculations showed that mean costs were $8.64±1.10, and $16.63±2.71 for atracurium and cisatracurium respectively (Table III). It was significant difference in cost between the two NMB drugs ($p < 0.05$).

Discussion

There are some important points when comparing two anesthetic drugs including adverse drug reactions, drug safety profiles and cost[4].

Table I. Demographic information and two groups analogous test.

	All patients	Atracurium	Cisatracurium	*p*-value
Number of patients (n)	100	50	50	1.000
Gender (n, %)				
Male	45.45.0%	21.42.0%	24.48.0%	0.551
Female	55.55.0%	29.58.0%	26.52.0%	
Age (yr) mean ± SD	47 ± 16	43 ± 11	45 ± 14	0.153
Weight (kg) mean ± SD	69.6 ± 13.9	69.2 ± 11.2	70.0 ± 16.2	0.769

Table II. Comparison of two groups in adverse drug reaction.

Adverse drug reaction	Atracurium	Cisatracurium	*p*-value
Cardiovascular – n (%)			
Bradycardia	2 (4.0%)	0	0.159
Tachycardia	6 (12.0%)	4 (8.0%)	0.510
Hypertension	2 (4.0%)	1 (2.0%)	0.562
Hypotension	7 (14.0%)	0	0.007
Flushing	2 (4.0%)	0	0.159
Collapse	0	0	–
Respiratory – n (%)			
Hyperthermia	0	0	–
Wheezing	3 (6.0%)	1 (2.0%)	0.313
Bronchial secretion	1 (2.0%)	1 (2.0%)	1.000
Bronchospasm	2 (4.0%)	1 (2.0%)	0.562
Laryngospasm	0	0	–
Dyspnea	0	0	–
Apnea	0	0	–
Skin – n (%)			
Erythema	9 (18.0%)	4 (8.0%)	0.140
Itching	0	1 (2.0%)	0.322
Urticaria	6 (12.0%)	1 (2.0%)	0.052
Muscle – n (%)			
Acute quadriplegic myopathy syndrome	0	0	–
Myositis ossificans	0	0	–
Other – n (%)			
Seizure	0	0	–
Prolong recovery time	0	0	–
Injection reaction	5 (10.0%)	1 (2.0%)	0.098

In our Hospital ordering and the prescription of cisatracurium was dramatically more than atracurium. Most anesthesiologists at our Hospital believed that cisatracurium complications less than atracurium occurred. Hence, we designed this study for comparing ADRs and cost analysis in between these two drugs.

In this study, for both drugs, adverse drug reactions and drug safety profiles are the same. Differences between adverse reactions of these drugs, (atracurium and cisatracurium) statistically are negligible. Therefore, safety profiles of both drugs are similar in accordance with authoritative drug references. Consequently, third item (cost) is the governing factor in this comparison. In such case, it is recommended to use the more inexpensive alternative[6].

Drug usage was converted to cost by multiplying "drug usage in mg per kg" by "drug cost" in $ per unit drug dosage. The cost of neuromuscular blocking agents at the time of this study in $/unit was $4.0 for atracurium and $5.4 for cisatracurium. Initial neuromuscular blocking drug costs were substantially different meanwhile in the mentioned Hospital cisatracurium is not supported by insurance systems in contrast with atracurium. By calculating the mean drugs required for each group cisatracurium became the most expensive and atracurium the least expensive agent. As it was mentioned before, safety profiles of both drugs are similar. Therefore, indirect effecting factors such as the cost of delayed recovery and treatment of adverse effects were negligible.

Usually, 5 percent of patient's charges are related to anesthetic drugs and 30 percent of this cost is related to neuromuscular blocking agents[7,8]. Therefore, deduction of neuromuscular blocking agents' costs causes a significant de-

Table III. Comparison of two groups in cost.

Drug	Cost ($) mean ± SD	Dose (mg) mean ± SD	*p*-value
Atracurium	8.64 ± 1.10	83.06 ± 6.74	0.00
Cisatracurium	16.63 ± 2.71	21.01 ± 2.43	

crease in patient's bill. Drug prices vary between different countries and between different Hospitals in a specific country as well. Moreover, the cost of drugs is dynamic and active process, as the price of drugs and clinical practice is changing, the pharmacoeconomic analyses should be perform to access the most appropriate medication regimen. Different factors affect drug cost in a hospital. For example, drug unit price, insurance systems and some indirect factors like charge of reversing drug effects or the cost of therapy against side effects. In addition, the drug dosage form availability had a significant effect on the final cost of the treatment[8]. In our practice cisatracurium and atracurium were available on 10 mg/5 ml and 50 mg/5 ml vials respectively. Therefore, for any amount of drug used less than 10 mg or 50 mg, one vial should be used and unused drugs should be discarded.

Since the amount of usage of NMB agents varies depending on patient's needs, estimating the total cost of used drug for each patient is not simple. Nonetheless there are a few pharmacoeconomic comparison studies for anesthetic drugs and neuromuscular blocking agents. Loughlin et al[9] compared the direct costs of various NMB agents in surgical procedures with different duration. They perceived that there were no significant cost differences among the NMB agents in surgeries with duration of less than 2 hours. In a retrospective study, Ortega et al[10] analyzed the direct cost of some NMB agents which were most used in general anesthesia.They considered only the direct costs). Their analysis revealed that atracurium was cheaper than any other 3 NMB agents in that study.

Although most of physicians believed that price is an important factor in choosing a proper method of treatment, only 42 percent of anesthesiologists are aware of anesthetic drug prices and economic conditions of the hospital in which they work[11]. Therefore, the studies like this can be helpful to decrease patients' charges in hospitals. Additionally cost minimization study can be done to choose proper and more cost effective options for the hospital drug formulary.

In this study, there was no limitation for surgery types. Hence, different operations with different duration were included. As the length of anesthesia increased the need to neuromuscular blocking agents increased. For each group, the cost of initial dose of NMB drugs was calculated. But the cost of drug used for maintenance muscle relaxation was ignored. Cost of maintenance doses, affects the final cost. Splinter et al[7] concluded that mivacurium to be least expensive for brief operations less than 30 minutes.

Conclusions

We recommend to analysis drugs cost respect to duration of anesthesia in addition to other factors such as safety profile. According to our study it seems that atracurium and cisatracurium had similar safety profile and atracurium had a cost benefit relative to cisatracurium in initial loading doses. In patients with instability in hemodynamic parameters the cisatracurium was the appropriate choice.

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