Postanesthetic skin erythema due to succinylcholine versus atracurium

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Abstract. Intraoperative anaphylactic reactions may range from mild, erythema-like to anaphylactic shock, with tension crash and bronchospasm. The substances considered to be most responsible for the occurrence of intraoperative allergic reactions are neuromuscular blocking agents, antibiotics and latex. Recent studies have identified a new receptor, Mas-Related G-Protein-coupled Receptor X2 (MRGPRX2), considered as a target for some neuromuscular blockers such as atracurium, rocuronium or fluoroquinolone, resulting in pseudoallergic or anaphylactoid reactions. Induction of anesthesia can use both depolarizing myorelaxants, useful especially in emergency situations, in the patient with gastric plenitude or at high risk of intubation, and non-depolarizing myorelaxants such as atracurium, cisatracurium and rocuronium. Succinylcholine has a short time of action and it is rapidly metabolized. Atracurium, although having a slightly longer time to action, has the benefit of a low risk of increased levels of potassium in blood, which is extremely important in patients with cardiac pathology or associated kidney diseases. The present study compared the side effects of systemic anesthesia with succinylcholine vs. atracurium.

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Introduction

Intraoperative anaphylactic reactions may range from mild, erythema-like to anaphylactic shock, with tension crash and bronchospasm (1). Usually, severe allergic reactions which results in vertigo or loss of consciousness is preceded by intense itching, redness and swelling over some body areas, new skin eruption or hives, runny nose, itchy eyes and later on, a feeling of light-headedness, as if the world is turning, then followed by vertigo. Anaphylaxis during anesthesia is an unpredictable, severe, and rare reaction. The substances considered to be most responsible for the occurrence of intraoperative allergic reactions are neuromuscular blocking agents, antibiotics and latex (2). Allergic reactions to latex occur intraoperatively as time is needed to absorb the allergen through the mucosa or peritoneum.

Patients and methods

A retrospective study was conducted in two hospitals on a total of 905 patients divided into two groups, depending on the muscle relaxant used in induction: Succinylcholine or atracurium.

Because the purpose of the study was to follow the allergic reactions of succinylcholine versus atracurium, all other medications used in induction were identical, both as an order of administration, and as a dose in relation to the patient's weight.

In order to maintain anesthesia, atracurium was always used as a muscle relaxant.

Immediate allergic reaction consisting of erythema on the face, neck and/or upper back, post-induced anesthesia with succinylcholine or atracurium, within the first 10 min after administration of myorelaxant, was observed, noted and described.

Table I. Descriptive statistics of the two groups: Succinylcholine and atracurium.

	Succinylcholine		Atracurium	
Variables	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)
Sex				
Female	376	82.6	136	30.2
Male	79	17.4	314	69.8
BMI, kg/m^2				
<18.5	71	15.6	25	5.6
18.5-24.9	172	37.8	215	47.8
25-29.9	127	27.9	139	30.9
30-34.9	65	14.3	46	10.2
35-39.9	20	4.4	25	5.6
Age, years				
<40	65	14.3	35	7.8
40-60	259	56.9	190	42.2
>60	131	28.8	225	50.0
Provenance				
Urban	172	37.8	225	50
Rural	283	62.2	225	50

The doses administered were 1 mg/kg succinylcholine (Lysthenon = Suxamethonium chloride, 0.1 g/5 ml; Takeda) and 0.4-0.5 mg/kg over 60 sec, atracurium (Tracrium = atracurium besylate, 50 mg/5 ml; Aspen) according to 'Morgan and Mikhail's Clinical Anesthesiology' (3).

Inclusion criteria: Patients undergoing surgery under general anesthesia, scheduled surgical operations, signed informed consent from the patients involved in the study, according to ethical requirements (4).

Exclusion criteria: patients in whom surgery was performed in an emergency, patients whose surgery started with locoregional anesthesia then converted into general anesthesia, patients whose anesthesia was performed or continued by other anesthesiologists, patients with a history of allergic reactions to drugs or food, patients with asthma.

The present study is a retrospective study based on the side effects to drugs that were already included in the treatment protocol, according to 'Morgan and Mikhail's Clinical Anesthesiology', and are commonly used for anesthesia in the clinic. Signed informed consent was obtained from each patient.

Statistical analysis. The analyzed database stores the information in the form of nominal/categorical variables (sex, place of origin, if the patient had erythema, type of anesthetics, age groups or BMI groups). The relationships between variables were determined by calculating the values of the correlation coefficients at nominal level ϕ, C and V, as well as the probabilities associated with them. If the associated probability, $P < \alpha = 0.05$ (the significance threshold), it results in variables that are correlated (there is a dependency relationship between them) (5,6). The values of the coefficients show how strong the correlation is. The choice of correlation tests depends on the type of data and the number of possible variants for each of the variables analyzed.

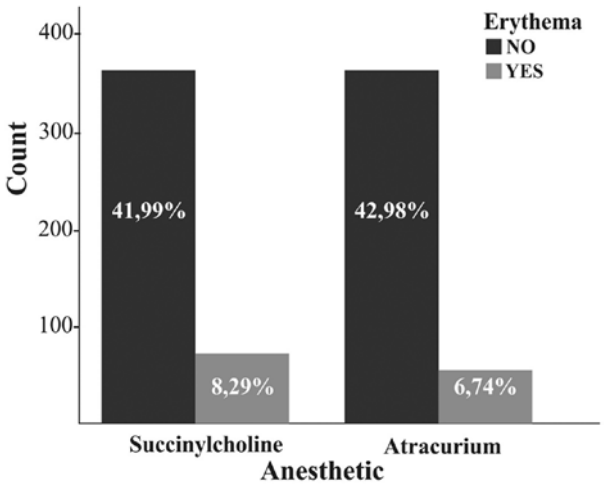

Figure 1. The presence of erythema after injecting myorelaxant.

Another method for determining the degree of association between two categorical variables is the Pearson Chi-square test.

The software package used for statistical analysis was IBM SPSS Statistics version 23.

Results

The 905 patients under study were divided into two groups. In the first group, consisting of 455 subjects, anesthesia was induced by succinylcholine, and the second group, consisting of 450 subjects, by atracurium (Table I).

Looking at the entire study group, analyzing the occurrence of erythema within the first 10 min after injection of myorelaxant in induction phase of anesthesia, a higher frequency was found in patients who received succinylcholine (Fig. 1).

The statistical analysis revealed a poor correlation between the type of subjects and the occurrence of erythema after the muscle relaxant in the case of succinylcholine ($P<0.001 < \alpha=0.05$; $\phi=-0.204$) and in the case of atracurium ($P=0.023 < \alpha=0.05$; $\phi=-0.107$), women being the most affected. Post-induction allergic reaction was found in 19.94% of patients who received Lysthenon and none was male in this group, and in the second group of atracurium, in 19.11% of the women and 11.11% of the men.

Regarding the home environment, a weak correlation ($P<0.001 < \alpha=0.05$, $\phi=0.224$) was observed in the succinylcholine group, most of the patients experiencing allergic reaction being urban (22.96% of urban area vs. 5.81% in rural areas). In the second lot, between these two nominal parameters there was no statistical correlation ($P=0.890 > \alpha=0.05$).

In the age groups, each of the two groups was divided into 3 subgroups: Patients up to 40 years of age, patients aged 40 to 60, and patients over 60 years of age. Finding an average correlation between the age and the occurrence of erythema in the first group ($P<0.001 < \alpha=0.05$, $V=0.414$; $C=0.382$), the most affected being young patients under the age of 40, 7% of those who experienced post-injection allergy). No relationship

between these two parameters was observed when using atracurium (P=0.310 >α=0.05.

In both groups there was a weak correlation between the body mass index and the allergic reactions occurring after induction, posterior injection of the Lysthenon (P<0.001 <α=0.05, V=0.218, C=0.213) and Tracrium (P=0.002 <0.05, V=0.197 and C=0.193), with the highest percentage of erythema being present in overweight patients with BMI between 25-29.9 kg/m^2 (40% in the first group and 50.8%, in the second).

Allergic reactions, in the studied group, were only of erythematous type, which spontaneously resolved within 15 min of the occurrence.

Discussion

Lysthenon is a commonly used depolarizing agent. It is a drug that acts as an agonist at neuromuscular junction acetylcholine receptors which results in nerve cell depolarization that leads to sustained cell excitation. Succinylcholine results in nerve endplate resistance to further activation by acetylcholine, which paralyses the muscle. Tracrium is a highly selective, competitive or non-depolarising neuromuscular blocking agent. A neuromuscular non-depolarizing agent is a form of neuromuscular blocker that does not depolarize the motor end plate.

Isolated cutaneous reactions appear to be primarily due to non-IgE mediated anaphylaxis, and severe side effects such as arterial hypotension, bronchospasm, are due to type IgE mediated allergy mechanisms (1,7,8). Other side effects may be induced by first cellular mechanisms interleukin-modulated because of topical medication or may occur on common medication and may be locally complicated (9-13).

As an intraanesthetic sensitivity response, the incidence was reported to be between 1/1,250 and 1/13,000 anesthetic interventions (8-10). Other studies have reported the incidence of anaphylactic reactions as being between 1/4,000 to 1/25,000 (4) and 1/5,000 of these are caused by neuro-muscular blockers (14).

The 6th National Audit Project (NAP6) that looked at perioperative anaphylactic reactions based on 266 cases reported in the United Kingdom with 3-5 grade anaphylactic reactions over a 1 year period found that 24.4% of these were due to neuromuscular blocking. Succinylcholine (depolarizing myorelaxant) is the cause of twice as frequent occurrence of anaphylactic reactions. There was no difference between non-depolarizing muscle relaxants (15).

The mechanism by which muscle relaxants cause anaphylactic reactions is either IgE-dependent, such as succinylcholine, or by direct activation of mast cells or basophils, a mechanism encountered in the case of atracurium (16).

IgE-recognized immunodominant determinant is represented by the ammonium group at the level of muscle relaxants, and cross-reactions between muscle relaxants and other perioperative substances such as neostigmine or morphine may occur (17,18). IgG-mediated perioperative anaphylactic reactions are those that most commonly occur after muscle relaxants, followed by latex and antibiotics (2,19).

Atracurium, being a benzyl-isoquinolinium-type muscle relaxant, produces a non-IgE-mediated anaphylactoid reaction (20-29), releases more histamine than the aminosteroid neuro-muscular blockers. This could be prevented by slow injection, possibly using antihistamines before induction (30).

From a clinical point of view, allergic immune and non-immune recurrences cannot be differentiated.

As a result of clinical phenomena, immediate reactions of hyper reactivity are classified into several degrees (31): Grade I: Cutaneous signs, generalized erythema, angioedema, urticaria; grade II: Not life-threatening, cutaneous signs, tachycardia, hypotension, respiratory dysfunction (cough, difficulty in breathing); grade III: Life threatening, arrhythmias, tachycardia or bradycardia, bronchospasm, collapse; grade IV: Cardiac/respiratory arrest (32-34). In this study, all patients were ranked grade I in severity.

Referring to patient-responsiveness, in a study published in 2018 that followed the 'skin test' response to muscle relaxants, it was found that 87% of the subjects who tested positive for this test were female, the most allergenic one being succinylcholine (35,36). This study is in agreement with the results of our research, according to which a greater predisposition of the female to develop allergic reactions post-administration of muscle relaxants (37-39).

A nationwide analysis in France over the period 2000-2012 and published in 2018 that followed the occurrence of post-administration anaphylactic reactions of suxamethonium and rocuronium versus atracurium or cisatracurium found the involvement of suxamethonium in 64% of the adverse reactions (40).

Finally, we wondered if it would justify skin testing of all patients preoperatively. The Petipain study considers that skin tests should be performed more frequently in order to prevent allergic post-muscle relaxant reactions (40). Sánchez Palacios considered that testing for all patients was not justified due to the small number of patients who had allergic reactions (41).

An article published in 2019 draws attention to the risk of mortality secondary to the administration of atracurium, independent of previous anesthesia with this neuromuscular drug. The mechanism can be by producing IgE upon previous contact with the drug or with quaternary ammonium moiety that can be found in some foods, as well as secondary to direct activation of cellular mast cells (42).

In patients whose risk of anaphylactic reactions is increased and the skin test is inconclusive, complementary tests such as basophil activation test (BAT) may be used (43).

In conclusion, succinylcholine is more allergenic than atracurium, the most affected being female patients. The subjects in the urban area and those under the age of 40 were statistically more affected only in the succinylcholine group. Overweight patients were the most susceptible to adverse reactions in both groups. Regarding the use of pre-operative skin test in all patients, we leave this topic open considering further studies are required in order to determine their efficacy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ORC and MNL contributed to the study design, participated in the entire review process and prepared the manuscript. DCV, MNM, RGC and NM contributed to the collection of the relevant literature, as well as the analysis and critical interpretation of the data. GS, OCC and AG conceived the study and drafted the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This is a retrospective study based on the side effects to drugs that were already included in the treatment protocol, according to 'Morgan and Mikhail's Clinical Anesthesiology', and are commonly used for anesthesia in the clinic. Signed informed consent was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

All the authors declare that they have no competing interests.

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