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ORIGINAL INVESTIGATION

Evaluation of skin test indications for general anesthetics in real life: a prospective cohort study☆

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Abstract
Background: In daily practice, atopic patients and those who have other drug allergies are referred to allergy clinics for evaluation of possible general anesthetic allergy despite the fact that it is not recommended in recent guidelines.
Objective: The aim of this prospective study is to determine the negative predictive value of skin tests for common general anesthetic drugs prior to general anesthesia in atopic patients and in patients who had drug allergies by including the data of those who had previously tolerated or reacted to general anesthesia.
Methods: A database program was constituted to collect the preoperative skin test data of patients referred to our clinic between 2013 and 2018. Demographic and clinical history, medications implemented during perioperative period, reactions, and results of skin tests performed with anesthetic drugs and latex were evaluated.
Results: Four hundred fifty-nine out of the total 1167 patients referred fulfilled the inclusion criteria for further evaluation. Nearly 75% of the patients were female and mean age was 46.3 ± 14.3 years. History of hypersensitivity reactions (HRs) due to NSAIDs and/or antibiotics, radiocontrast agents, local anesthetics, and food were present in the 53.1%, 4.1%, 1.5%, and 2.0%, respectively. The negative predictive values of skin tests for general anesthetics were in the range of 80–100%. Only 4 patients (0,87%) experienced HRs during operation.

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Conclusion: These real-life data reveal high rates of negative predictive value of skin tests with general anesthetic drugs and a low reaction rate in atopic patients and in patients with allergy to other drugs.

Introduction

Hypersensitivity reactions (HRs) during general anesthesia are rare, however life-threatening conditions involving multiple organ systems can be seen.[1] Regardless of the mechanism, the clinical spectrum ranges from mild urticaria to severe anaphylaxis, which can lead to cardiovascular and/or pulmonary collapse and even death.[2] Possible pathomechanisms of perioperative hypersensitivity reactions can be determined in two groups: one is the allergic Immunoglobulin E (IgE)-mediated reactions, for which there is an identifiable culprit and high risk of recurrence on re-exposure, and the other group is the remainder of immediate perioperative reactions, which are either related to the pharmacological effects of anesthetic drugs or surgical management or fall in the category of nonallergic, nonspecific activation of mast cells and basophils, or other pathways.[2] One such mast cell activation can occur via the recently discovered Mas-related G protein-coupled receptor-X2 (MRGPRX2) receptor.[3] The exact mechanisms and risk of recurrence on re-exposure are poorly described for these reactions. Patients with clonal or nonclonal mast cell disorders can have an increased risk of severe reactions elicited either by specific triggers or via nonspecific activation.[4,5] Interestingly, clinical manifestations are usually more severe in IgE-mediated reactions.[6,7] The estimated incidence of HRs during general anesthesia varies widely among studies ranging from 1 in 353 to 1 in 18,600 procedures.[8–10] Prospective studies suggest incidences of 1:3180 in France[11] and 1:1480 in Spain.[12] Since a relatively high mortality rate (4–9%) of anesthetic agent-induced HRs has been reported, deciphering the predisposing risk factors for HRs, thereby the prevention of HRs in subsequent anesthesia, is of extreme importance.

Although clinical assessment is essential to understand the culprit agent and the reaction type, there are some factors complicating the true diagnosis of an HR during general anesthesia. During anesthesia, several potential culprits including drugs, such as neuromuscular blocking agents (NMBAs), antibiotics, analgesics, diagnostic dyes, and volume replacement solutions, are almost simultaneously administered and patients are concomitantly exposed to latex. The unconscious patient cannot warn the physician about unexpected symptoms, and therefore early signs and symptoms can easily be overlooked by the surgeons. Furthermore, some important findings of anaphylaxis such as hypotension can easily be confused with the pharmacologic effects of drugs used during anesthesia.[13]

Considering these circumstances, gathering clinical information related to allergy history before anesthesia is essential to decrease the risk of severe HRs. According to the recent European Academy of Allergy and Clinical Immunology (EAACI) guideline, preoperative allergological evaluation is strongly recommended for the patients who have experienced HRs or an unexplained event during previous anesthesia and who are to undergo an operation, but not for those with atopic diseases or other drug allergies.[2] Anesthesiologists are often concerned also for the patients who are atopic and especially for those having other drug allergies; consequently, they frequently request allergological consultation in these situations as a daily routine in order not to face with patients seeking for legal redress against them when there is a severe reaction afterwards. Although the recent guideline gives insight to physicians in their decision, the grade of evidence for skin testing in atopic diseases and other drug allergies is low, and mostly rely on old case-controlled descriptive studies.[2,14–18] The aim of our prospective study relying on real-life data is to determine the diagnostic value of skin tests for general anesthetic drugs in atopic patients and in patients who have drug allergies other than anesthetics, even if they have previously tolerated general anesthesia. The negative predictive value of tests for each drug is evaluated in detail.

Methods

A local database evaluating the incidence and risk factors of perioperative immediate drug hypersensitivity reactions was established in collaboration with departments of adult allergy and anesthesiology at our tertiary referral university hospital and was prospectively used by these departments between 2013 and 2018. It reflected the scope of Scandinavian, Great Britain, and Irish perioperative anaphylaxis guidelines.[15,19] Anesthesiologists added all individual patient information prior to and during surgery, including demographic data, their anesthesiology plan, medications implemented in the perioperative period, currently used drugs, detailed clinical history, atopy, drug allergies and allergic reactions developed during perioperative and postoperative periods, onto the database. In parallel, allergists prospectively included the allergic diagnostic workup information of every patient prior to surgery. We utilized the database for all patients including those who are only atopic or having any drug allergy history.

Patients in the 18 to 65 age bracket were included in the study. Patients without a full perioperative information record, individuals who underwent emergency surgery, and pregnant women were excluded. All patients prospectively underwent skin prick tests and intradermal tests with most commonly used NMBAs (i.e., mivacurium, atracurium, suxamethonium, cisatracurium, vecuronium, and rocuronium), thiopental sodium, morphine, fentanyl, remifentanil, midazolam, ketamine, propofol, tramadol, morphine as well as other agents requested to be tested by the anesthesiologist,

and latex, with the exception of volatile agents in suggested concentrations.[2,20,21] Depending on the severity of the HRs in the history, tests were started with more diluted concentrations up to the maximum nonirritant concentrations.

Suspected HRs to antibiotics and/or nonsteroidal anti-inflammatory drugs were evaluated according to recommendations of European Network on Drud Allergy (ENDA).[22] Where appropriate, penicillin skin testing was applied according to the published guidelines. For skin prick tests, 10 mg.mL^{-1} of histamine and physiologic saline solution were used as positive and negative controls, respectively. When skin prick test was negative, intradermal tests using increasing concentrations of the drugs were performed. Tests were assessed after 20 minutes according to published guidelines.[20] Atopy was defined as at least one positivity on skin prick tests with common inhalant allergens (ALK Abello, Denmark). Skin tests were defined as positive if there was a wheal of at least 3 mm greater than negative control.[23] The classification of clinical severity of perioperative immediate hypersensitivity was performed according to the modified Ring and Messmer four-step grading scale.[24,25]

The study was approved by Istanbul University, Istanbul Faculty of Medicine Ethics Committee (EK-2018/950) in June 2018, in accordance with the Declaration of Helsinki. A written informed consent for allergy skin testing was obtained from each patient as a daily routine practice in our adult outpatient clinic.

Statistical analysis

All statistical analyses were performed with SPSS version 21.0. Demographic and clinical features of the patients were evaluated with descriptive statistics including percentages and mean ± standard deviation. The *p*-values less than 0.05 were considered as statistically significant. After each operation, history of possible reactions during anesthesia was carefully assessed and all possible reactions were recorded in order to evaluate the number of patients with true or false negative skin test results. Negative predictive value was calculated as follows: Negative predictive value (NPV) = true negative / (true negative + false negative) x 100.

Results

Of the 1167 patients whose preoperative data were recorded, 708 were excluded due to missing perioperative data and/or the overlap between group 1(patients with other drug allergies) and group 2 (patients with atopy). Finally, total 459 patients were suitable for full assessment to form two groups that did not overlap with each other (Fig. 1). Of these 459 patients, nearly 75% (n = 344) were female and the mean age was 46,3 ± 14,3 years. In detailed clinical history of these patients, additional allergic conditions were found to be present in some patients, such as chronic spontaneous urticaria in 75 patients (16.33%), local anesthetic agent allergy in 7 patients (1.52%) and radiocontrast agent allergy in 19 patients (4.13%). A total of 109 patients had comorbidities including coronary artery disease (n = 4), diabetes mellitus (n = 17), hypertension (n = 20) and malignancy (n = 68). Overall, 244 patients (53.15%) had a history of DHRs due to antibiotic and/or Nonsteroidal anti-

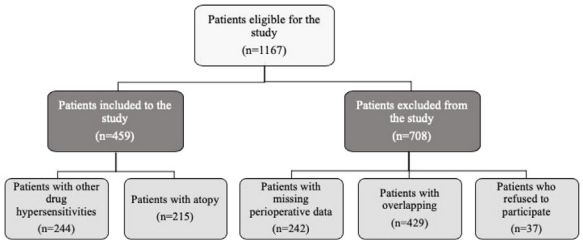

Figure 1 Flow chart of the patients included in the study.

inflammatory drugs (NSAIDs) and 215 patients (46.85%) had atopy. Of the 215 atopy patients, 123 patients had house dust mite sensitivity, 68 patients had pollen sensitivity, and 24 patients had both house dust mite and pollen sensitivity, with 9 of 24 patients having food poly-sensitivity by skin prick tests.

Nearly 65% of the patients (n = 297) were previously operated under general anesthesia and 41 of them had a history of hypersensitivity reaction during previous general anesthesia. However, which drugs induced the perioperative reactions in these patients were not known. Therefore, they were skin tested with the agents requested by anesthesiologists, starting with more diluted drug concentrations depending on the severity of their previous reactions. Five patients (12.2%) had positive skin test with latex and there was no general anesthetic drug positivity in these patients. While 4 patients had positive skin test with a single general anesthetic agent, 6 patients had positive skin test with multiple general anesthetic agents. The most common test positivity was found for propofol (14.6%). In 26 of 41 patients, no skin test positivity was found with any agent. In one of 2 patients with a history of perioperative anaphylaxis, propofol, midazolam, atracurium, thiopental, and morphine skin tests were positive. These agents were not used in the operation and no perioperative reaction was reported. The test results were shown in Fig. 2.

The skin test results were evaluated in all patients; skin test positivity with at least one agent was found in 66 of 459 patients (14.37%). The characteristics of these patients were as follows: nearly 76% (n = 66) of the patients were women, the mean age was 45.37 ± 14.1 years, 31.8% of the patients had never exposed a general anesthetic, 68.2% had a history of anesthesia in the past, and 22.7% had a previous history of hypersensitivity reaction with general anesthetics. The most common sensitizing agent was latex (9.2%). Among tested drugs, propofol was found as the most sensitizing drug (3.7%) (Fig. 3), whereas no skin test positivity was observed with cisatracurium. There was no statistically significant difference in the test positivity rate between patients with drug hypersensitivity and atopic patients or between patients who were previously exposed to general anesthetics and patients without a history of general anesthetic exposure. The test results of all patient groups and the negative predictive values of skin tests for general anesthetics in patients with atopy and other drug hypersensitivity were shown in Table 1 and Table 2, respectively.

Only four patients (female/male: 3:1, mean age: 44.75 ± 9.03 years) without a previous history of HR to general anesthesia experienced HRs during anesthesia. The demographic and clinical characteristics of these 4 patients

Table 1 Skin test results for general anesthetic drugs and negative predictive values of tests in patients with other drug hypersensitivities.

		Patients with other drug hypersensitivities[a] (n = 244)						
		Preoperative DST			Perioperative exposure to drug			NPV (%)
Agents		Total (n = 1613)	Positive (n = 43)	Negative (n = 1570)	Total (n = 1215)	Perioperative HR negative (n = 1213)	Perioperative HR positive (n = 2)	
IV anesthetics	Thiopental sodium	53	2	51	7	6	1	85.7
	Midazolam	227	1	226	221	221	0	100
	Ketamine	10	-	10	3	3	0	100
	Propofol	238	11	227	197	197	0	100
Opioids	Morphine	30	2	28	21	21	0	100
	Fentanyl	236	-	236	222	222	0	100
	Remifentanil	99	1	98	52	52	0	100
	Tramadol	188	1	187	70	70	0	100
NMBAs	Atracurium	48	3	45	5	4	1	80
	Mivacurium	41	1	40	8	8	0	100
	Vecuronium	11	1	10	2	2	0	100
	Rocuronium	236	1	235	181	181	0	100
	Cisatracurium	5	-	5	-	-	-	-
Depolarizing Muscle Relaxant	Suxamethonium	8	-	8	1	1	0	100
Latex		183	19	164	225	225	0	100

DST, drug skin test; IV, intravenous; NMBAs, Neuromuscular blocking agents; NPV, negative predictive value; HR, hypersensitivity reaction; n, number of patients.
[a] Antibiotics and/or NSAIDs.

Table 2 Skin test results for general anesthetic drugs and negative predictive values of tests in atopic patients.

	Atopic patients (n = 215)							
	Preoperative DST			Perioperative exposure to drug			NPV (%)	
Agents		Total (n = 1456)	Positive (n = 34)	Negative (n = 1422)	Total (n = 1116)	Perioperative HR negative (n = 1115)	Perioperative HR positive (n = 1)	
IV anesthetics	Thiopental sodium	**41**	-	**41**	**10**	**10**	**0**	**100**
	Midazolam	**206**	**3**	**203**	**193**	**193**	**0**	**100**
	Ketamine	**12**	**1**	**11**	**10**	**10**	**0**	**100**
	Propofol	**205**	**6**	**199**	**168**	**167**	**1**	**99.4**
Opioids	Morphine	**20**	-	**20**	**20**	**20**	**0**	**100**
	Fentanyl	**207**	**2**	**205**	**197**	**197**	**0**	**100**
	Remifentanil	**103**	-	**103**	**61**	**61**	**0**	**100**
	Tramadol	**163**	**1**	**162**	**43**	**43**	**0**	**100**
NMBAs	Atracurium	**48**	-	**48**	**2**	**2**	**0**	**100**
	Mivacurium	**29**	-	**29**	**2**	**2**	**0**	**100**
	Vecuronium	**22**	-	**22**	**1**	**1**	**0**	**100**
	Rocuronium	**205**	**1**	**204**	**182**	**182**	**0**	**100**
	Cisatracurium	**2**	-	**2**	**1**	**1**	**0**	**100**
Depolarizing Muscle Relaxant	Suxamethonium	**10**	**1**	**9**	**1**	**1**	**0**	**100**
Latex		**183**	**19**	**164**	**225**	**225**	**0**	**100**

DST, drug skin test; IV, intravenous; NMBAs, Neuromuscular blocking agents; NPV, negative predictive value; HR, hypersensitivity reaction; n, number of patients.

Table 3 Characteristics of patients who had perioperative reactions after allergological work up.

PATIENTS	SEX	AGE	ATOPY	DRUG ALLERGY HISTORY	EXPOSURE TO ANESTHESIA	PREOPERATIVE TEST RESULTS		DRUGS ADMINISTERED DURING ANESTHESIA	TYPE AND SEVERITY OF REACTIONS	POSTOPERATIVE TEST RESULTS
						Negative	Positive			
P1	M	37	Yes	No	1th time	Propofol Rocuronium Fentanyl Midazolam Tramadol Remifentanil Thiopenthal Latex		Propofol Rocuronium Fentanyl Midazolam Latex	Anaphylaxis (Grade 3)	Propofol was positive
P2	F	51	No	Yes	2nd time	Propofol Rocuronium Fentanyl Midazolam Atracurium Meperidin Remifentanil Latex		Midazolam Latex	Urticaria/ angioedema (Grade 1)	Could not be evaluated due to der-mographism
P3	F	54	Yes	No	3rd time	Rocuronium Tramadol Remifentanyl Atracurium Thiopenthal Morphine	Propofol Fentanyl Midazolam Latex	Atracurium Remifentanil Thiopenthal sodium	Urticaria (Grade 1)	Atracurium and thiopenthal were positive
P4	F	37	No	Yes	1th time	Propofol Rocuronium Fentanyl Remifentanil Midazolam Tramadol Latex		Propofol Rocuronium Fentanyl Remifentanyl Midazolam Neostigmin Atropin Latex	Urticaria/ angioedema/ hypotension (Grade 2)	Midazolam and remifentanil were positive

F, female; M, male.

Brazilian Journal of Anesthesiology 2022;72(3):350–358

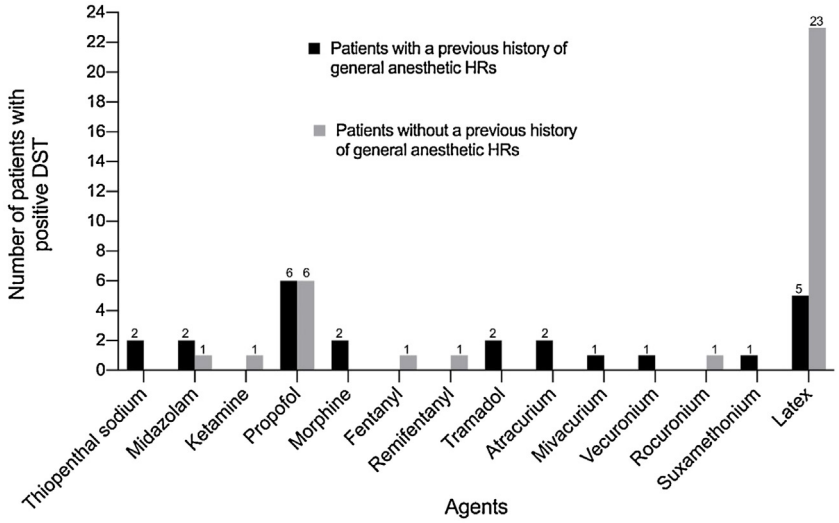

Figure 2 Number of preoperative positive skin test results of patients with or without a previous history of perioperative general anesthetic HRs. DST, drug skin test; HRs, hypersensitivity reactions.

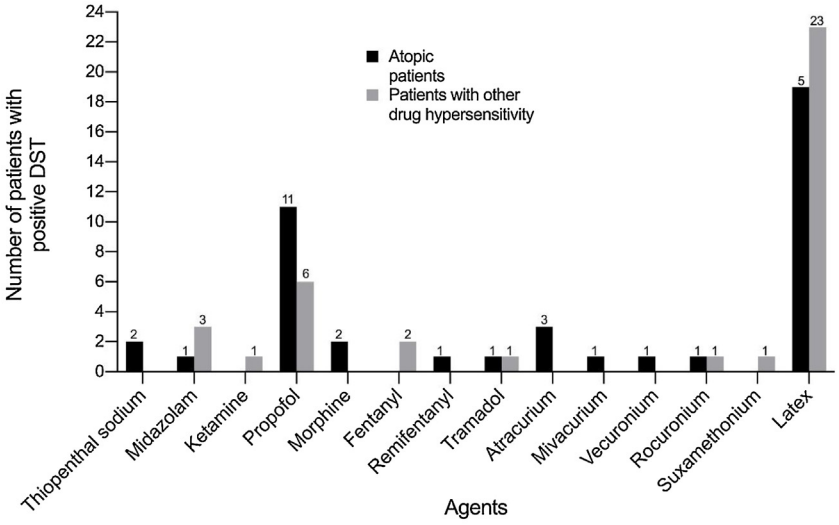

Figure 3 Results of preoperative skin tests in patients with atopy or other drug allergies. DST, drug skin test.

(P1-P4) are shown in detail in Table 3. Postoperative skin testing was performed to these patients with all the agents used during anesthesia including latex. All preoperative skin tests were negative in 3 patients (P1, P2 and P4). P3 received non-reactive anesthetics with cautions for latex-free environment during operation, because she reacted to some anesthetics and latex in skin tests (Table 3). Drug tests repeated after the operation showed new sensitizations in three patients (P1, P3, and P4) (Table 3).

Discussion

In this study, a large patient series was preoperatively evaluated with skin tests for multiple anesthetic drugs. This series was consisted of atopic patients and drug allergic patients without anesthesia related reaction history as well as those with perioperative drug allergy. Overall, skin test positivity rate was 14.37% (66 out of 459 patients), and the most frequent sensitizing agent was latex (9.2 %) followed by propofol (3.7 %). Due to ethical reasons, test positive drugs were not applied to the patients. Accordingly, we could not evaluate positive predictive value and sensitivity of these tests. However, skin test negative drugs were used without any adverse events in most of the patients with atopy or other drug allergies, indicating that negative predictive value of the skin tests was very high (above 90%). However, studies with a more homogeneous group with a greater number of patients would provide a more reliable interpretation of NPV.

Although avoidance of the agents with positive skin test results is recommended, there is not a specific suggestion for the agents with negative skin test results. The risk of false negative skin testing should be considered. In our study, we identified only 4 patients who did not have a previous HR history to general anesthetics, with negative skin testing,

displayed HRs during operation. Skin tests repeated after reactions yielded positive results in 3 of these patients. The possible explanation for this situation is either that preoperative skin test results were false negative or that these patients may be sensitized after the last exposure. So far, to our knowledge, there are no data reported about the risk of new sensitization with preoperative skin testing for general anesthetics, suggesting the necessity of more data for optimal recommendations after negative skin testing.

Among 41 patients with a previous history of HRs to general anesthetics, 2 had anaphylaxis and 15 (36.5%) reacted to different agents during preoperative skin tests, with propofol (14.6%) and latex (12.2%) as the most common sensitizing agents. None of these patients had any adverse events when re-exposed to general anesthesia, which was given according to the test results, indicating the reliability of negative skin tests with general anesthetics and latex.

In the recent EAACI guideline, it was reported that the only risk factor specifically identified for immediate perioperative anaphylactic reactions was a previous history of adverse reaction after exposure to general anesthetics.[2] In case control studies, no association between IgE-mediated reactions to general anesthetics and asthma, atopy, other drug hypersensitivities, or previous exposure to general anesthetics was reported.[9,14,15] In line with these findings, in our study, the majority of patients who did not have a previous reaction history with anesthetics and those who have atopic diseases and a drug hypersensitivity profile did not have a HR during general anesthesia. However, test positive drugs were avoided in such patients. Therefore, the positive predictive value of the positive skin test results could not be determined, nor utilized for the benefit of patients. We have to further keep in mind that although preoperative skin tests with anesthetics are recommended only for the patients who had a previous HR experience during anesthesia, a preoperative evaluation for other drugs such as antibiotics or NSAI analgesics, which are commonly used in preoperative or postoperative periods, are necessary for those who have drug allergy history.[12]

In our study, the culprit drugs were identified in 3 of the patients who had perioperative HRs. The relationship between the timing of the drug administration and the onset of the symptoms may help to determine the agents that caused the HRs. However, this is a suboptimal way, since during anesthesia, several drugs are concomitantly administered. There could be also other factors that mimic the clinical picture of anaphylaxis, such as direct mast cell mediator release and other causes of hypotension and bronchospasm, and that include the pharmacological actions of the anesthetic drugs themselves, which could complicate the detection of the culprit drugs.[26]

Nondepolarizing muscle relaxants are among the leading causes of perioperative anaphylaxis.[6,9] Sensitivity and specificity of skin testing to NMBAs are unknown. In our series, skin test positivity with muscle relaxants was very low (0.44–2%) in the patients with drug allergy history or atopy. In the patients with previous HR history with anesthetics, muscle relaxants revealed positive results in 1.08% while propofol was positive in 1.30%. As cited by the EAACI position paper, introduction of geographical environmental elements, such as pholcodine or cosmetics with quaternary substituted ammonium groups, could change incidence of NMBA hypersensitivity reactions upon first exposure.[2] Although our country also allows pholcodine use as antitussive in accordance with European Medicines Agency (EMA), we could not detect a high incidence of NMBA reactions. As mentioned above, the most common positive result in this group was observed with latex (12.2%). Similarly, latex skin test showed the highest test positivity among all the patients (9.2%). As latex allergy is among the most leading causes of perioperative anaphylaxis, to detect this sensitization before a major surgical intervention is of great importance. Of the patients, 297 had undergone general anesthesia without any problems; although this artificially reduces the likelihood of developing a perioperative hypersensitivity reaction upon re-exposure, these patients were not excluded from the study, especially since repeated encounters with latex may be a risk factor.

Perioperative hypersensitivity reactions were found significantly higher in women in previous studies.[27] HRs to anesthetic agents were reported to be more common in women, possibly related to sex hormones.[27] Furthermore, women were reported more often to be reactive to neuromuscular blocking drugs than men.[27] Although a female predominance (74.9%) was noticed in our study cohort, this was not significantly related with preoperative skin tests results.

Our study is novel, as it represents the first Turkish perioperative hypersensitivity reaction data and includes a large number of patients, but it has some limitations. Due to ethical and safety concerns, patients with positive skin test results to some general anesthetics did not further receive these drugs during operation, and therefore positive predictive value and sensitivity of these tests were not assessed. However, cooperation and data sharing between the allergists and anesthesiologists during the study resembling the real-life clinical practice and the prospective design of the study by presenting the real-life data strengthen the findings of the study. Lastly, this database only contains the information of elective surgical patients.

In conclusion, these real-life data confirm that skin testing with anesthetic agents in patients with atopy or in patients who have a drug allergy history for drugs other than general anesthetics is not necessary unless they had experienced a reaction during previous anesthesia. However, latex allergy should be evaluated carefully before any operation in high-risk groups.

Conflict of interest

The authors declare no conflict of interest.

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