PERIOPERATIVNA ANAFILAKSA IZAZVANA MIŠIĆNIM RELAKSANTIMA: DA LI ZNAMO DOVOLJNO?

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REVIEW ARTICLE

PERIOPERATIVE ANAPHYLAXIS CAUSED BY MUSCLE RELAXANTS: DO WE KNOW ENOUGH?

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SAŽETAK

Perioperativna anafilaksa izazvana mišićnim relaksantima predstavlja relativno retku ali ozbiljnu komplikaciju tokom anestezije, koja za rezultat može imati ozbiljne zdravstvene posledice ili čak smrtni ishod. Ova reakcija se uglavnom događa neposredno pre ili nakon intubacije, odnosno, par minuta nakon ordiniranja mišićnog relaksanta. Nastanak reakcije može, u zavisnosti od intenziteta simptoma, promaći i najiskusnijem anesteziologu, te je od izuzetne važnosti podići svest o postojanju mogućnosti njene pojave u svakodnevnoj praksi. U literaturi ne postoje zvanične smernice o terapiji, te se ista bazira na smernicama koje se tiču anafilakse uopšte. Takođe, u mnogim zemljama ne postoje zvanični podaci o učestalosti nastanka perioperativne anafilakse. Ova tema je samim tim jedna od onih kojima će anesteziološka praksa morati da se intenzivnije bavi u budućnosti.

Ključne reči: anestezija, anafilaktička reakcija, mišićni relaksanti

ABSTRACT

Perioperative anaphylaxis caused by muscle relaxants represents a relatively rare, albeit a serious complication during anesthesia. It can result in serious morbidity or even mortality. This reaction usually happens before or after intubation of a patient, that is, a few minutes after muscle relaxant administration. The beginning of the reaction can be missed, even by the most experienced anesthesiologist, since its recognition depends on the severity of the symptoms. There are no guidelines specific to the therapy of muscle relaxant anaphylaxis and therefore therapy is based simply on the general guidelines. Also, in many countries, there are no registries of the incidence of anaphylaxis caused by muscle relaxants. Therefore, this is an extremely important subject for anesthesiology practice, and it requires more attention.

Keywords: anesthesia, anaphylactic reaction, muscle relaxants

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UVOD

Perioperativna anafilaksa predstavlja ozbiljnu komplikaciju koja se javlja tokom anestezije i koja zahteva pravovremeno prepoznavanje i reakciju od strane anesteziologa [1]. Anafilaktička reakcija tokom anestezije se može dogoditi u bilo kom trenutku, međutim, anafilaktička reakcija izazvana mišićnim relaksantima najčešće nastaje tokom indukcije. Period uvođenja u anesteziju se karakteriše ordiniranjem velikog broja lekova, te je anesteziologu jako komplikovano da odredi šta je takvu reakciju uzrokovalo [2].

Antibiotici i mišićni relaksanti su među najčešćim uzročnicima alergijskih reakcija nastalih u perioperativnom periodu. Od mišićnih relaksanata, najčešći izazivači alergijskih reakcija su: suksametonijum, rokuronijum, vekuronijum, pankuronijum i atrakurijum [3,4]. Incidencija perioperativne anafilakse je nepoznata, međutim, studije ukazuju na to da se učestalost kreće između jedan na 3.000 i jedan na 20.000 slučajeva [5]. Podaci se posebno teško dobijaju u manje razvijenim zemljama, u kojima se retko vodi evidencija, a mogućnost postoperativnog testiranja nije široko dostupna. Interesantno je da se u literaturi nailazi na podatke da su anafilaktičke reakcije u perioperativnom periodu izuzetno česte u Francuskoj, Britaniji, Belgiji, Australiji, Novom Zelandu i Španiji [4,6]. Ovakvi podaci ne moraju da znače da je anafilaktička reakcija na mišićne relaksante zaista karakteristična za pomenuta područja, već je najverovatnije da u ovim zemljama postoji registar i evidencija o nastanku anafilakse u perioperativnom periodu.

Prepoznavanje anafilakse tokom perioperativnog perioda nije uvek lako, te je i to jedan od uzroka izostanka tačnijih podataka o incidenciji anafilaktičke reakcije na mišićne relaksante. Najčešće se prepoznaje po prisustvu kožnih manifestacija, kao i po nastanku abnormalnih vitalnih znakova, koji su očigledni zbog prisustva monitoringa u operacionoj sali. Činjenica je da je koža pacijenta tokom hirurške intervencije mahom pokrivena hirurškim čaršafima, pa se u literaturi anesteziologu savetuje da na anafilaktičku reakciju tokom anestezije posumnja uvek kada je kod pacijenta prisutna neobjašnjiva hipotenzija, koja može biti refraktorna na inotrope i vazopresore [1]. Čak i kada dođe do nastanka ozbiljnijih reakcija, lekari nisu sigurni koji je konkretni lek uzročnik reakcije, te u nedostatku adekvatnih testova, ovakvi događaji ostanu nezabeleženi. Takođe, otežavajuća okolnost je neinformisanost lekara da anafilaktička reakcija na mišićne relaksante može da nastane i bez ikakve prethodne senzitizacije pacijenta na konkretni agens [7].

INTRODUCTION

Perioperative anaphylaxis represents a serious complication which occurs during anesthesia, and which requires timely recognition by the anesthesiologist and their timely reaction [1]. Anaphylactic reaction during anesthesia may occur at any moment, however, anaphylactic reaction caused by muscle relaxants most commonly occurs during the induction of anesthesia. The induction period of anesthesia is characterized by the administration of a number of medicaments, which is why it is very complicated for the anesthesiologist to determine what caused the reaction [2].

Antibiotics and muscle relaxants are amongst the most common causes of allergic reactions occurring in the perioperative period. Among the muscle relaxants, the most common triggers of allergic reactions are the following: suxamethonium, rocuronium, vecuronium, pancuronium, and atracurium [3,4]. The incidence of perioperative anaphylaxis is unknown; however, studies indicate that frequency of occurrence ranges between one per 3,000 cases and one per 20,000 cases [5]. It particularly difficult to obtain data in less developed countries where records of these occurrences are rarely kept and the availability of postoperative testing is limited. It is interesting that data can be found in literature indicating that anaphylactic reactions in the perioperative period are exceptionally frequent in France, Great Britain, Belgium, Australia, New Zeeland, and Spain [4,6]. Such data do not necessarily have to indicate that anaphylactic reaction to muscle relaxants is indeed characteristic of the above listed regions, rather it is more probable that in these countries there is a registry in place recording the occurrence of anaphylaxis in the perioperative period.

Recognizing anaphylaxis in the perioperative period is not always easy, and this is yet another reason for the lack of more precise data on the incidence of anaphylactic reaction to muscle relaxants. It is most commonly recognized by manifestations on the skin and upon the development of abnormal vital signs, which are immediately apparent as they are monitored in the operating theatre. The fact is, however, that the skin of the patient is mostly covered with surgical drapes during a procedure, which is why literature advises anesthesiologists to suspect anaphylactic reaction during anesthesia whenever the patient displays unexplained hypotension, which may be refractory to inotropes and vasopressors [1]. Even when severe reactions occur, doctors are not sure which particular drug is the cause of the reaction, and, when appropriate tests are not available, these events remain unrecorded. Another aggravating factor is lack of knowledge on behalf of the doctor that anaphylactic reaction to muscle relaxants may occur even without any pervious sensitization of the patient to the particular agent [7].

ETIOLOGIJA

Još uvek nije poznat tačan mehanizam senzitizacije, zbog činjenice da se anafilaksa javlja čak i kod pacijenata koji prethodno nisu imali kontakt sa mišićnim relaksantima. Ovakvi događaji ukazuju na to da postoji mogućnost da senzitizaciju uzrokuju neki spoljašnji faktori [6]. U literaturi se nailazi na podatke da je jako česta pojava klinički relevantne alergijske reakcije na ukrštene reaktivne alergene. Naime, ukrštena reaktivnost je jako česta kada su mišićni relaksanti u pitanju, a uzrok tome leži upravo u kvaternarnoj amonijumskoj strukturi epitopa koji su prisutni na površini molekula mišićnih relaksanata, kao i u sklopu molekula drugih lekova ili dezinfekcionih sredstava [3]. Veoma je česta ukrštena reaktivnost u okviru grupe mišićnih relaksanata (predominantno između rokuronijuma, pankuronijuma i vekuronijuma) kao i između mišićnih relaksanata i drugih klasa lekova, kao što su: acetilholin, morfin, holin, neostigmin, folkodin, i drugi [3,6]. U literaturi se nailazi i na podatke o aktivaciji specifičnih IgE antitela, nakon kontakta pacijenta sa određenom hranom, kozmetičkim proizvodima i industrijskim materijalima [3,8,9]. Agens za koji se smatra da najčešće dovodi do 'tihe' senzitizacije jeste folkodin, opioidni antitusivni agens [6].

Kada je u pitanju preosetljivost na rokuronijum, veoma je česta pojava ukrštene reaktivnosti sa drugim mišićnim relaksantima. U istraživanju Breretona i saradnika, ukrštene reakcije su zabeležene u čak 65% slučajeva, a od tih reakcija je 29% bilo izazvano sukcinilholinom [10].

Većina alergijskih reakcija na mišićne relaksante je posredovana imunoglobulinom E (IgE) i u svoj mehanizam uključuje bazofile i mastocite. Za ovaj mehanizam nastanka reakcije je odgovorna prethodno pomenuta kvaternarna amonijum struktura [10]. Primećeni su i drugi mehanizmi nastanka anafilaktičke reakcije – imunski mehanizmi (posredovani imunoglobulinom G – IgG) i neimunski (direktna aktivacija mastocita *MRGPRX2* receptorima) [6].

SIMPTOMI

Prvo upozorenje anesteziologu na mogućnost postojanja anafilaktičke reakcije tokom perioperativnog perioda predstavlja podatak dobijen tokom preoperativne vizite ili ambulantnog pregleda o postojanju alergije na druge agense, takozvana atopijska konstitucija. Retko kada se od pacijenta dobije podatak o prethodnom pojavljivanju alergijske reakcije tokom anestezije [6]. Iz svih ovih razloga, od izuzetnog je značaja da se tokom preoperativne pripreme postavi pitanje pacijentu da opiše kako se alergijska reakcija manifestovala.

Brzo prepoznavanje anafilaktičkih znakova i simptoma je od najveće važnosti za uspešan tretman i pozitivan

ETIOLOGY

The precise mechanism of sensitization remains unknown, due to the fact that anaphylaxis occurs even in patients who had previously had no contact with muscle relaxants. Such events indicate the possibility of sensitization being caused by some external factors [6]. Data can be found in literature confirming that the occurrence of a clinically relevant allergic reaction to cross-reactive allergens is a very common occurrence. Namely, cross-reactivity is very common when muscle relaxants are concerned, and the cause of this lies in the very quaternary ammonium structure of epitopes present on the surface of the molecules of muscle relaxants and also within the structure of the molecules of other drugs and disinfection agents [3]. Cross-reactivity within a group of muscle relaxants is very common (predominantly among rocuronium, pancuronium, and vecuronium) as well as between muscle relaxants and other classes of drugs, such as: acetylcholine, morphine, choline, neostigmine, pholcodine, and others [3,6]. Data on the activation of specific IgE antibodies, after the patient has had contact with certain foods, cosmetic products, and industrial products, can be found in literature [3,8,9]. Pholcodine, an opioid cough suppressant, is considered to be the most common 'silent' sensitizing agent [6].

When hypersensitivity to rocuronium is concerned, cross-reactivity with other muscle relaxants is very common. In a study by Brereton et al., cross-reactions were recorded in as many as 65% of the cases, of which 29% were caused by succinylcholine [10].

Most allergic reactions to muscle relaxants are IgE mediated and include basophiles and mastocytes in their mechanisms. The above-mentioned quaternary ammonium structure is responsible for this mechanism of the reaction development [10]. Other mechanisms of anaphylaxis reaction development have been observed – immunological mechanisms (IgG mediated) and non-immunological (direct activation of mastocytes by MRGPRX2 receptors) [6].

SYMPTOMS

For the anesthesiologist, the first potential warning sign for the possibility of anaphylaxis reaction in the perioperative period is data obtained during an examination/consultation with the patient or during preoperative rounds, indicating an allergy to other agents, the so-called atopic disposition. It is rarely that data on previous allergic reactions during anesthesia are obtained from the patient [6]. For all of the above-stated reasons, it is particularly important to ask the patient, during preoperative preparation, to describe how the allergic reaction had previously manifested.

ishod. Prednost koju anesteziolog ima je prisustvo monitoringa koji je u svakoj operacionoj sali obavezan, kao i postojanje venske linije koja je plasirana pre ulaska u salu [1].

U zavisnosti od ozbiljnosti hipersenzitivne reakcije, opisano je četiri vrste kliničkih manifestacija [1]: gradus 1 (kožne manifestacije), gradus 2 (kožne manifestacije uz evidentne ali ne i životno ugrožavajuće simptome, kao što su hipotenzija, tahikardija, kašalj, i drugo), gradus 3 (životno ugrožavajući simptomi: kolaps, tahikardija ili bradikardija, aritmije, bronhospazam), gradus 4 (srčani ili respiratorni zastoj). U slučaju intraoperativne anafilakse izazvane mišićnim relaksantima, simptomi se uglavnom javljaju odmah nakon uvođenja u anesteziju, i oni uključuju kožne, respiratorne i kardiovaskularne simptome [6].

Kožne manifestacije se obično javljaju prve, u vidu eritema, urtikarije i angioedema, uz najveću učestalost (80 – 90%). Činjenica je, međutim, da se, ukoliko ovi simptomi izostanu u početku intervencije, često kasni sa dijagnozom anafilakse. Kožne manifestacije mogu da izostanu kod pacijenata koji su tokom pripreme za intervenciju primili kortikosteroide. Veoma često, kožne manifestacije nastaju kasnije, te se otkriju tek nakon uklanjanja hirurških čaršafa [1]. Kardiovaskularni simptomi, u vidu tahikardije, bradikardije, aritmije, hipotenzije, kardiovaskularnog kolapsa i, u krajnjem slučaju, srčanog zastoja, obično su prvi simptomi koji se uočavaju nakon kožnih manifestacija. Činjenica je da su oni i najlakše uočljivi u uslovima koje obezbeđuje operacioni blok, odnosno u prisustvu mahom neinvazivnog monitoringa pacijenta tokom svake procedure. Mogu se takođe uočiti hladna i vlažna periferija uz filiforman puls. Respiratorni simptomi u vidu bronhospazma obično postaju evidentni nakon trahealne intubacije i manifestuju se u vidu 'tvrdog balona', a ukoliko respiratorni simptomi nastanu ranije, manifestuju se otežanom ventilacijom na masku, i tada treba što brže pristupiti intubaciji i adekvatnoj terapiji [1]. Nekada je intubacija ovakvih pacijenata zaista zahtevna i može predstavljati ozbiljan izazov [11]. Respiratorni simptomi su prisutni u 70% slučaja. Simptomi centralnog nervnog sistema veoma često nisu evidentni u perioperativnom periodu jer je pacijent sediran ili u anesteziji [1].

Počev od 1991. godine, kliničari su u okviru prikaza slučaja predstavili akutni koronarni sindrom uzrokovan koronarnim vazospazmom i uglavnom je opisivan kao alergijska angina ili Kunisov sindrom [12,13]. Većinom se javljao kod muškaraca starosti između 40 i 80 godina i primećen je oko sat vremena nakon administracije agensa izazivača. Klinički znaci koji su uočeni tokom ovakvih epizoda su bili: ST elevacija (mahom u II odvodu EKG zapisa), duboka hipotenzija, pad nivoa *ET*CO2, tahikardija sa ventrikularnim ekstrasistolama [12].

Recognizing the signs and symptoms of anaphylaxis is of the utmost importance for successful treatment and a positive outcome. The advantage that the anesthesiologist has is intraoperative monitoring, which is mandatory in each operating theatre, as well as availability of the venous catheter, which is placed before the patient is taken into the operating room [1].

Depending on the severity of the hypersensitivity reaction, four types of clinical manifestations have been described [1]: grade 1 severity (skin reactions), grade 2 severity (skin reactions together with evident, but non-life-threatening symptoms, such as hypotension, tachycardia, coughing, and other), grade 3 severity (life-threatening symptoms: collapse, tachycardia, bradycardia, arrythmia, bronchospasm), grade 4 severity (cardiac or respiratory arrest). In case of intraoperative anaphylaxis caused by muscle relaxants, symptoms usually occur immediately after anesthesia is induced in a patient, and they include skin, respiratory and cardiovascular symptoms [6].

Skin reactions usually occur first, in the form of erythema, urticaria, and angioedema, and they have the highest incidence (80 – 90%). However, the fact remains that, if these symptoms are absent at the beginning of the procedure, there is often a delay in diagnosing anaphylaxis. Skin manifestations may be absent in patients who were given corticosteroids during their preoperative preparation. Often, skin manifestations occur later and are discovered only after the surgical drapes are removed [1]. Cardiovascular symptoms, in the form of tachycardia, bradycardia, arrythmia, hypotension, cardiovascular collapse, and, in the most severe cases, cardiac arrest, are usually the first symptoms to be observed after skin manifestations are noted. These symptoms are the ones most easily spotted in the environment of the surgical suite, i.e., in the presence of predominantly non-invasive patient monitoring, during every procedure. Also, cold and wet hands and feet and a thready pulse can be noted. Respiratory symptoms, in the form of bronchospasm, usually become evident after tracheal intubation and manifest as failure of the balloon to deflate, while if the respiratory symptoms occur earlier, they manifest as labored breathing through the mask, which is when intubation should be performed, and appropriate therapy should be administered as soon as possible [1]. Sometimes, intubation of such patients is really difficult and challenging [11]. Respiratory symptoms are present in 70% of the cases. Symptoms of the central nervous system are very often not evident in the perioperative period, since the patient is sedated or anesthetized [1].

As of 1991, in their case reports, clinicians started reporting acute coronary syndrome caused by coronary vasospasm and mainly described it as allergic angina or Kounis syndrome [12,13]. It occurred mostly in

Činjenica je da smrtni ishod, kao posledica perioperativne anafilaktičke reakcije, nije tako redak. Kada je u pitanju anafilaksa izazvana mišićnim relaksantima, smrtnost je procenjena na čak 4%, uprkos pravovremeno preduzetim merama reanimacije [6]. Takođe, statistički podaci su ukazali na to da je anafilaktička reakcija za posledicu imala signifikantni morbiditet, a 2% pacijenata je razvilo dugoročne neurološke sekvele [5].

Ne postoji nikakvo pravilo koje će anesteziologa pripremiti na adekvatnu reakciju, jer iskustva ukazuju na to da inicijalni simptomi mogu biti blagi, u vidu hipotenzije, dok se kod nekog drugog pacijenta kardiovaskularni simptom može inicijalno pokazati kao teži oblik bradikardije koji progredira do srčanog zastoja [14]. Iako su simptomi anafilakse lako prepoznatljivi kod budnog pacijenta, oni mogu biti zamaskirani tokom anestezije i promaći čak i iskusnom anesteziologu. Simptomi koji se najčešće javljaju se lako mogu pripisati predoziranju lekova koji su korišćeni pri uvođenju u anesteziju, kao i oslobađanju histamina. Tahikardija i respiratorni simptomi, u rukama neiskusnijih anesteziologa, mogu biti interpretirani kao posledica plitke anestezije ili maligne hipertermije. Važno je zapamtiti da odsustvo kožnih manifestacija ne isključuje dijagnozu anafilakse [14].

TERAPIJA

Prema preporukama za terapiju perioperativne anafilakse, najpre je potrebno prekinuti sa ordiniranjem leka izazivača, ukoliko postoji osnovana sumnja o tome koji je lek odgovoran za konkretnu reakciju. Od izuzetne je važnosti obezbediti disajni put i krenuti sa ordiniranjem kiseonika. Lek prvog izbora je adrenalin 1%, 0,15 – 0,6 mg intramuskularno, a u težim slučajevima bolusno, u dozi od 1 mcg/kg telesne težine, intravenski. Doza se može ponavljati na svakih 10 do 15 minuta ili na svakih pet minuta, ukoliko je u pitanju teži oblik reakcije. Adrenalin deluje na alfa i beta receptore, i samim tim za posledicu ima vazokonstrikciju, redukciju vaskularnog permeabiliteta, bronhodilataciju, smanjenje edema i inotropno dejstvo na srčani mišić. Bez obzira da li se ordinira intramuskularno ili intravenski, adrenalin ima najbrže dejstvo od svih lekova koji se mogu koristiti u anafilaksi. Postoji takođe mogućnost ordiniranja adrenalina inhalacijom, u slučaju postojanja edema larinksa i u slučaju nastanka bronhospazma. Kod bronhospazma se predlaže da se inhalaciji adrenalina doda beta agonista, na primer salbutamol. Lekovi koji se takođe mogu koristiti u tretmanu anafilakse su: dopamin, noradrenalin, vazopresin. Ukoliko ne postoji već obezbeđeni venski put, neophodno ga je obezbediti pre eventualnog nastanka vaskularnog kolapsa. Venski put je neophodno održavati stalnom aplikacijom tečnosti.

men aged between 40 and 80 years and was observed around an hour after the administration of the causative agent. Clinical signs observed during these episodes were as follows: ST elevation (predominantly on lead II of the ECG printout), severe hypotension, drop in the level of ETCO2, tachycardia with ventricular extrasystoles [12].

It is a fact that the lethal outcome, as the consequence of perioperative anaphylactic reaction, is not that rare. With respect to anaphylaxis caused by muscle relaxants, mortality is estimated to be as high as 4%, despite the timely execution of resuscitation measures [6]. Also, statistical data indicated that anaphylactic reaction resulted in significant morbidity, while 2% of the patients developed long-term neurological sequelae [5].

There is no established rule that would prepare an anesthesiologist for the appropriate reaction, since experience has shown that initial symptoms may be mild, in the form of hypotension, while in a different patient a cardiovascular symptom may initially present as a severe form of bradycardia progressing to cardiac arrest [14]. Although the symptoms of anaphylaxis are easily recognizable in a patient who is awake, they may be disguised during anesthesia and may remain unnoticed even by an experienced anesthesiologist. The most commonly occurring symptoms may easily be attributed to the overdosing of drugs used in the induction of anesthesia, as well as to histamine release. Tachycardia and respiratory symptoms may be interpreted by inexperienced anesthesiologists as the consequence of shallow anesthesia or malignant hyperthermia. It is important to remember that the absence of skin reactions does not necessarily exclude the diagnosis of anaphylaxis [14].

TREATMENT

According to the recommendations for the treatment of perioperative anaphylaxis, it is necessary to first discontinue the administering of the drug causing the anaphylaxis, if there is reasonable suspicion as to which drug is the cause of the particular reaction. It is of the utmost importance to secure the airway and to begin with the administration of oxygen. The drug of choice is adrenalin 1%, 0.15 – 0.6 mg, administered intramuscularly, and in more severe cases, administered in a bolus, at the dose of 1 mcg/kg of body weight, intravenously. The dose may be readministered every 10 to 15 minutes, or even every five minutes, if the reaction is of a greater severity. Adrenalin acts on alpha and beta receptors, and therefore, as a consequence, its action results in vasoconstriction, vascular permeability reduction, bronchodilatation, edema reduction, and inotropic action on the myocardium. Regardless of whether it is administered intramuscularly or intravenously, adrenalin is the fastest acting of all drugs

Tokom ordiniranja tečnosti, važno je znati da su dekstrani i hidroksietil skrob (HES) apsolutno kontraindikovani u tretmanu anafilakse. Nakon primene adrenalina, može se primeniti aminofilin, u dozi od 6 mg/kg telesne težine, intravenskim putem. Takođe, indikovano je primeniti anithistaminik. Glukokortikoidi nisu od koristi u akutnoj fazi anafilaktičke reakcije [15–17].

Važno je zapamtiti da je adrenalin terapija prvog izbora kod anafilakse uz dosta tečnosti, takozvano 'punjenje vaskularnog korita', kao i da se sa terapijom kreće odmah nakon sumnje na nastanak anafilakse [6]. Korišćenje adrenalina je ograničeno individualnom procenom kliničara o postojanju rizika za nastanak ozbiljnih aritmija kod konkretnog pacijenta. Aritmije uglavnom nastaju kao komplikacija ordiniranja adrenalina u višoj dozi od potrebne u datoj situaciji, jer je činjenica da se preporuke koje postoje ne slažu u određivanju inicijalne doze i puta aplikacije. Takođe, dokazano je da se rizik nastanka štetnih efekata po kardiovaskularni sistem smanjuje ordiniranjem adrenalina intramuskularno. Važno je napomenuti da se tretman anafilaktičke reakcije mora prilagoditi kliničkoj slici, pacijentovoj istoriji bolesti i adekvatnosti odgovora na primenjenu terapiju [1].

Hašimoto i saradnici su opisali dva prikaza slučaja u kojima su svi simptomi koji su nastali nakon ordiniranja mišićnog relaksanta nestali posle davanja sugamadeksa. Ovakav događaj su opisali i Kim i saradnici [2,14]. Svakako, sugamadeks ne predstavlja lek prvog izbora, jer je tokom tretiranja anafilakse od primarnog značaja održati hemodinamiku [2]. Ono što se mora izdvojiti kao činjenica jeste da su mišljenja o terapijskoj moći sugamadeksa u tretmanu anafilakse oprečna. Naime, neki radovi opisuju da je sugamadeks zapravo jedan od izazivača anafilaktičke reakcije, koja se najčešće ispoljava postoperativno, tokom oporavka pacijenta od anestezije. Reakcije mogu biti takve da neretko zahtevaju ponovnu intubaciju pacijenta van operacione sale [1,8,19]. Teorija o korišćenju sugamadeksa kao terapijskog sredstva tokom anafilaktičke reakcije na određene mišićne relaksante se bazira na činjenici da sugamadeks enkapsulira molekul mišićnog relaksanta, međutim smatra se da to nije dovoljno da bi sprečilo dalju interakciju amonijumskih grupa sa IgE antitelima. Takođe, enkapsulacija mišićnog relaksanta nije dovoljna da bi se sprečilo dalje oslobađanje medijatora od strane već aktiviranih mastocita i bazofila [1]. Ukoliko anesteziolog nije siguran u uzrok reakcije, bolje je reagovati simptomatski.

Odluka koja se stavlja pred anesteziologa je izuzetno teška – da li nastaviti sa intervencijom uprkos evidentnoj kliničkoj slici koja odgovara anafilaktičkoj reakciji? Odgovor na ovo pitanje jeste: ukoliko je reakcija blaža i reaguje na datu terapiju bilo bi razumno nasta-

that can be used in anaphylaxis. Adrenalin can also be administered through inhalation, in case of laryngeal edema and in case of bronchospasm. In bronchospasm it is recommended that a beta agonist, for example salbutamol, is added to the adrenalin inhalation. Other drugs that may also be used in the treatment of anaphylaxis are the following: dopamine, noradrenalin, vasopressin. If a venous catheter is not already in place, it is necessary to provide for one, before the possible occurrence of vascular collapse. The venous catheter needs to be preserved through constant fluid application. During fluid administration, it is important to understand that dextrans and hydroxyethyl starch (HES) are absolutely contraindicated in the treatment of anaphylaxis. After the administration of adrenalin, aminophylline may be applied, at a dose of 6 mg/kg of body mass, intravenously. Also, it is advised to administer an antihistamine. Glucocorticoids are not useful in the acute phase of anaphylactic reaction [15–17].

It is important to remember that adrenalin is the therapy of choice in anaphylaxis, combined with plenty of fluids – the so called "filling of the circulatory system". It is also important to bear in mind that therapy must be introduced immediately after anaphylaxis is suspected [6]. The use of adrenalin is limited by the individual assessment of the clinician regarding the risk of the development of severe arrythmia in the individual patient. Arrythmia mainly occurs as a complication of adrenalin administration, when it is applied in a dose exceeding the one necessary for the situation at hand, which stems from the fact that existing recommendations are not in agreement regarding the initial dose and the route of administration. Also, it has been proven that the risk of the development of harmful effects to the cardiovascular system is reduced when adrenalin is administered intramuscularly. It is of note that the treatment of anaphylactic reaction must be adjusted to the clinical presentation, the patient's medical history, and the level of response to the applied therapy [1].

Hashimoto et al. described two case reports wherein all the symptoms developing upon the administration of the muscle relaxant disappeared after the administration of sugammadex. Such an event was described by Kim et al., as well [2,14]. Definitely, sugammadex is not the drug of first choice, as it is of the utmost importance to preserve hemodynamics whilst treating anaphylaxis [2]. What must be pointed out is the fact that there are conflicting opinions on the therapeutic potential of sugammadex in treating anaphylaxis. Namely, some studies describe that sugammadex is, in fact, one of the triggers of anaphylactic reaction, which most commonly presents postopera-

viti sa intervencijom, posebno ukoliko je intervencija od izuzetne važnosti za pacijenta i njegovo zdravlje ili ukoliko je u pitanju hitna hirurška intervencija [20].

POSTOPERATIVNO POSTUPANJE

Postoperativni postupak koji sledi nakon postojanja osnovane sumnje na alergijsku reakciju izazvanu mišićnim relaksantima je obaveštavanje pacijenta o tome i pisanje izveštaja koji će pacijent nositi sa sobom dok god se hipersenzitivnost ne potvrdi ili opovrgne. Drugi korak je upućivanje pacijenta na ispitivanje tokom kojeg se meri koncentracija histamina/triptaze. Merenja se, u idealnom slučaju, vrše odmah nakon događaja (u roku od 15 do 60 minuta) i nakon izvesnog vremena [1]. U našoj zemlji, u manjim centrima, ispitivanje odmah nakon nastanka anafilakse nije moguće. Takođe, preporučuje se da se uradi kožni test, koji predstavlja i treći oblik potvrde postojanja alergijske reakcije na mišićne relaksante. U slučaju nejasnih rezultata, specifični IgE test i test aktivacije bazofila protočnom citometrijom (engl. *flow cytometry-assisted basophil activation test – BAT*) mogu tačnije da odrede dijagnozu [6]. Prednost ovih testova se sastoji u tome što ne mogu da izazovu anafilaktičku reakciju, jer pacijenta ne dovode u kontakt sa alergenom [1]. Još jedna prednost ovih testova jeste njihova preciznost, jer je *BAT* test pokazao senzitivnost i specifičnost za anafilaksu izazvanu rokuronijumom od 91,7% i 100% [21]. Kada su u pitanju drugi mišićni relaksanti, *BAT* test je pokazao visoku specifičnost uz nižu senzitivnost. Ovakav nedostatak se prevazilazi kombinacijom više testova [1].

Izuzetno je važno odlučiti o budućim vrstama anestezije kod pacijenata sa poznatom istorijom anafilaktičke reakcije na mišićne relaksante, u saradnji sa hirurgom i samim pacijentom. Ukoliko hirurška intervencija dozvoljava, najbolje je pribeći regionalnoj anesteziji. Međutim, ukoliko izostane saglasnost pacijenta za regionalnu anesteziju, najbolje je uraditi testiranje na senzitivnost prema ostalim mišićnim relaksantima i nakon toga pacijenta uvesti bezbedno u opštu anesteziju [22,23].

Ukoliko je evidentirana anafilaktička reakcija izazvana sukcinilholinom, razumno je pribeći korišćenju rokuronijuma, kao adekvatne zamene za rapid sekvens indukciju, ukoliko je ista neophodna. Ovakva praksa se podrazumeva, posebno u zemljama gde je dostupan sugamadeks, kao efikasna reverzija mišićne relaksacije izazvane rokuronijumom [7,24,25]. Opsežne epidemiološke studije su pokazale da je incidencija anafilaktičke reakcije na vekuronijum niža od one za rokuronijum. Reakcija na atrakurijum je deset puta ređa nego na rokuronijum i sukcinilholin, dok se najniža incidencija anafilaktičkih reakcija povezuje sa cisatrakurijumom,

tively, during the patient's recovery from anesthesia. The reactions may be such as to require the patient to be intubated again, after he/she has left the operating theatre [1,8,19]. The theory of using sugammadex as a therapeutic agent during an anaphylactic reaction to certain muscle relaxants is based on the fact that sugammadex encapsulates the muscle relaxant molecule, however, it is believed that this is not enough to prevent further interaction of ammonium groups with IgE antibodies. Also, the encapsulation of the muscle relaxant is not enough to prevent further mediator release by the already activated mastocytes and basophils [1]. If the anesthesiologist is not certain as to the cause of the reaction, it is better to treat the symptoms.

The decision placed before the anesthesiologist is particularly difficult – should the surgical procedure be continued despite the evident clinical presentation that matches anaphylactic reaction? The answer to this question would be the following: if the reaction is mild and responds to the administered therapy, it is only reasonable to continue with the surgery, especially if the surgical procedure is of great importance to the patient and their health or if the surgery in question is an emergency procedure [20].

POSTOPERATIVE PROCEDURE

The postoperative procedure which follows a reasonable suspicion of allergic reaction caused by muscle relaxants begins with informing the patient of this event and writing a report which the patient will be carrying with them until the suspected hypersensitivity is either confirmed or disproved. The second step is referring the patient for testing, wherein the concentration of histamine/tryptase is measured. Ideally, the measurements are performed immediately after the event (within 15 to 60 minutes), and again after a certain amount of time has elapsed [1]. In Serbia, in smaller centers, testing immediately after anaphylaxis is not possible. Also, it is recommended that a skin test is performed as well, and it represents the third method of confirming the existence of an allergic reaction to muscle relaxants. In case the results are inconclusive, the specific IgE test and the flow cytometry-assisted basophil activation test (BAT) can determine the diagnosis more precisely [6]. The advantage of these tests is that they cannot cause an anaphylactic reaction, as they do not put the patient in contact with the allergen [1]. Another advantage of these tests is their precision, since the BAT test has shown a sensitivity and specificity for anaphylaxis caused by rocuronium of 91.7% and 100%, respectively [21]. With respect to other muscle relaxants, BAT has shown a high specificity with a lower sensitivity. Such a flaw is overcome by combining several tests [1].

te on može predstavljati lek prvog izbora tokom budućih intervencija [7,8]. Ovi podaci mogu biti vodilja pri izboru lekova za uvođenje u anesteziju, kod pacijenata sa osnovanom ili potvrđenom sumnjom na alergiju na mišićne relaksante.

ZAKLJUČAK

Anafilaktičke reakcije tokom anestezije predstavljaju relativno redak događaj, te se, do današnjeg dana, literatura bazira mahom na revijalnim radovima, prikazima slučaja i preporukama pojedinačnih radnih grupa. Svakako, ovakvi događaji mogu biti fatalni i potrebno je u skorijoj budućnosti sprovesti ozbiljnija ispitivanja, a neophodno je i donošenje zvaničnih preporuka o postupku nakon nastanka anafilaktičke reakcije tokom anestezije.

Sukob interesa: Nije prijavljen.

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It is of the utmost importance to decide on the future types of anesthesia in patients with a known history of anaphylactic reaction to muscle relaxants, in cooperation with the surgeon and the patient themselves. If the surgical procedure permits it, the best option is to revert to regional anesthesia. However, if the patient does not consent to this type of anesthesia, it is best to test the sensitivity of the patient to other muscle relaxants and then safely anesthetize the patient [22,23].

If the recorded anaphylactic reaction was caused by succinylcholine, it is reasonable to revert to the use of rocuronium, as an appropriate substitute for rapid sequence induction, if it is necessary. Such a practice is in place, especially in countries where sugammadex is available, as an efficient reversal of muscle relaxation caused by rocuronium [7,24,25]. Extensive epidemiological studies have shown that the incidence of anaphylactic reaction to vecuronium is lower than it is for rocuronium. The reaction to atracurium is ten times less frequent than the reaction to rocuronium and succinylcholine, while the lowest incidence of anaphylactic reaction is for cisatracurium, which is why it can be considered as the drug of choice for future procedures [7,8]. These data can be a guide in choosing drugs for the induction of anesthesia, in patients with suspected or confirmed allergy to muscle relaxants.

CONCLUSION

Anaphylactic reactions during anesthesia are a relatively rare occurrence, which is why literature is still mainly based on review papers, case reports, and recommendations of individual work groups. These events can definitely be fatal, and it is necessary to carry out more comprehensive research in the near future, as well as to introduce official recommendations on the procedure following the occurrence of an anaphylactic reaction during anesthesia.

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