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Anaphylactic reaction cases induced by neuromuscular blocking agents (NMBAs) used in surgery

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Abstract
Anaphylactic reactions to neuromuscular blocking agents (NMBAs) can be severe and fatal. Two thousand and twenty-two cases of NMBAs hypersensitivity were retrieved, of which 84 were fatal (4.1%). Among the 1247 cases of severe NMBAs anaphylaxis (grades 3 and 4), independent risk factors associated with a fatal outcome in a multivariate analysis were male gender, an emergency setting, a history of hypertension or other cardiovascular diseases, obesity, and ongoing beta-blocker treatment. According to international guidelines, all 31 patients with a fatal outcome received epinephrine in a titrated manner. Obese males with a history of cardiovascular disease receiving ongoing beta-blocker treatment and undergoing surgery in an emergency setting were at high risk of a fatal outcome after NMBA-induced anaphylaxis. Some epinephrine-resistant cases may play a role in our high mortality rate. New therapeutic approaches need to be developed to treat these cases. Anaphylactic shock is an issue of great concern to anesthesiologists. It is defined as a severe, life-threatening, generalized, or systemic immediate hypersensitivity reaction. Hypersensitivity reactions that occur at anaesthesia induction tend to be immune allergic reactions, and in France, they are most commonly caused by neuromuscular blocking agents (NMBAs). Epinephrine is the recommended first-line treatment, although epinephrine-resistant shock does also occur. Despite several surveys of perioperative allergic reactions, mortality from NMBAs anaphylaxis remains poorly evaluated, and its risk factors have yet to be established.

Keywords: anaphylactic shock, neuromuscular blocking agents (NMBAs)

Introduction

Hypersensitivity reactions in about 60-70% of anaesthetic cases occur due to immunoglobulin (Ig) E (immediate hypersensitivity allergic reactions) [1]. More than 7000 cases of IgE-dependent allergic reactions to anaesthetic drugs ranged worldwide in the last 25 years. Most cases are from France, Australia, New Zealand, and recently in Scandinavia. Mortality ranges from 3% to 9%, depending on which country. The most violent deaths are usually in patients with anoxic cerebral injury when the brain is severely hypoxic [2].

The incidence of anaphylaxis associated with muscle relaxants in surgery is infrequent. Incidence rates vary from country to country: 1/5,500 in France and 1/5,200 in Norway. Substances responsible for causing anaphylaxis include [3]: muscle relaxants (63%), latex (14%), sleeping pills/hypnotics (7%), antibiotics (6%), plasma substitutes (3%), and morphine-like substances (2%). Other substances that can cause anaphylactic shock under anaesthesia include aprotinin, chlorhexidine, papain, heparin, and NSAIDs. All muscle relaxants can cause allergic reactions, even on first exposure, and most often do is *suxamethonium*. The substance causing anaphylaxis in infants is similar to that used in adults.

The allergic reaction is produced by activating basophils and mast cells stimulated by IgE that attaches itself to the surface of these cells. Mediators such as histamine, tryptase, and other granular mediators, lipid arachidonic acid metabolites, and cytokines such as tumour necrosis factor. These all cause changes in capillary permeability (urticaria, oedema), vasodilation, bronchoconstriction, hypotension with tachycardia, as well as other symptoms of anaphylaxis. While non-allergic reactions usually produce milder clinical manifestations. They are produced by activating basophils and mast cells that specific IgE does not stimulate [4].

The first phase of anaphylactic shock is usually followed by hyperkinetic shock with tachycardia, systemic vascular resistance failure, and peripheral arterial vasodilation leading to decreased venous return and cardiac output [5]. Delay in handling or improper management can cause tissue anoxia, leading to organ failure syndrome and irreversible shock. In cases of anaphylaxis, usually, epinephrine is given as first-line aid. If given too late, it will cause death. Based on the above background, the researcher's questions can be formulated: a) What is the pathophysiology of muscle relaxants causing anaphylactic shock? b) How to treat anaphylactic shock caused by muscle relaxants?, and c) How to reduce risk factors for anaphylactic shock under anaesthesia? This research aims to find out: a) how the pathophysiology of muscle relaxants causes anaphylactic shock; b) how to treat anaphylactic shock caused by muscle relaxants; and c) how to reduce risk factors for anaphylactic shock under anaesthesia.

Literature Review

Muscle relaxants are drugs that can be used during intubation and surgery to facilitate anaesthesia and facilitate intubation. Muscle relaxants are drugs used to relax skeletal muscles or paralyze muscles and are usually used before surgery to facilitate an operation or insert a device into the body [6]. The mechanism of neuromuscular blocking drugs is to inhibit the transmission of nerve impulses at the muscle-nerve junction. These drugs can be classified into nondepolarizing and depolarizing neuromuscular relaxants (similar to the action of acetylcholine). Nondepolarizing neuromuscular blocking agents consist of the *benzylisoquinoline* and *aminosteroid* groups [7].

Nondepolarizing muscle relaxants can be classified based on their duration of action: a) Short-acting muscle relaxants, b) Intermediate-acting muscle relaxants, and c) Long-acting muscle relaxants. Nondepolarizing neuromuscular blocking agents bind to nicotinic acetylcholine receptors without causing activation of ion receptor channels. This drug will compete with acetylcholine in the alpha subunit of the nicotinic acetylcholine receptor post-muscle-nerve junction without causing a configuration change at these receptors [8]. It can block ion receptor channels at high doses and act on pre-muscle-neuro-muscular junctional nicotinic acetylcholine receptors, but the post-nerve junction mechanism of action is predominant.

The transmission of the musculoskeletal junction will fail if 80-90% of the receptors are successfully blocked, whereas if the inhibition is only 70%, it does not show inhibition of the musculoskeletal junction. Nondepolarizing muscle-nerve inhibition has characteristics of skeletal muscle responses evoked by electrical stimulation using a peripheral nerve stimulator, including a) decreased twitch response to a single stimulus; b) loss of response during continuous stimulus; c) TOF (Train of Four) ratio < 0.7; d) post-tetanic potentiation; e) potentiation of other nondepolarizing paralytic drugs; and f) can be antagonized with anticholinesterase [9].

Drug potency is generally expressed as a relationship between dose and response. The dose of muscle relaxant required to produce a 50%, 90%, and 95% depressed effect of twitch height is generally expressed as ED 50, ED 90, ED 95 (Effective Dose) and is a measure of drug potency. Each muscle-nerve relaxant drug has a different potency, *Atracurium* has an ED of 50 (0.12 mg/kg), an ED of 90 (0.18 mg/kg), and an ED of 95 (0.21 mg/kg) [10]. The rapid onset of action of muscle relaxants is necessary to rapidly secure the airway in emergency patients and those at high risk of aspiration. It is influenced by several factors, including the rate of drug delivery to the muscle-nerve junction, receptor affinity, plasma clearance, and the mechanism of muscle-nerve inhibition (depolarizing or nondepolarizing). The onset of action is inversely proportional to the potency of the neuromuscular blocking agent. A high ED 95 has a low potency but can provide fast onset of action and vice versa. *Atracurium* differs slightly from other nondepolarizing muscle relaxants [11]. ED 50 and 95 are expressed as molar potentials (microM/kg). The more potent a drug (*cisatracurium*), the slower the onset of action and the less potent a drug rocuronium, the faster the onset of action.

The onset of action of neuromuscular blocking agents is faster on the muscles associated with intubation, such as the laryngeal adductor, diaphragm, and masseter, than on the muscles that are generally monitored (adductor policies). Therefore, the neuromuscular-relaxing effect will be faster, faster recovery in these muscles. The blood flow to the muscles is more important than the intrinsic potency of the drug in determining the start and end of the action of a muscle-nerve relaxant [12]. The greater the blood flow (per gram of muscle) in the diaphragm and larynx, the greater the plasma drug concentration in the muscle will be. The onset of action of muscle relaxants occurs 1-2 minutes earlier in the larynx than in the adductor policies after administration of nondepolarizing neuromuscular blocking agents. The pattern of inhibition in terms of onset, depth, and recovery speed in the orbicularis oculi muscle is similar to the larynx. By monitoring the onset of action of muscle relaxants on the orbicularis oculi muscle, we can predict intubation conditions. The onset of maximal inhibition in the larynx corresponds to when the adductor pollicis shows evidence of attenuation.

Furthermore, the return of the thumb response indicates that the efferent muscles to maintain the protective airway reflex have returned to their normal state. Succinylcholine remains the preferred choice for rapid tracheal intubation because it consistently provides muscle relaxation within 60–90 seconds. The onset of action of a nondepolarizing musculoskeletal relaxant can be accelerated by administering a priming dose before the total dose of intubation or by using high doses of any neuromuscular blocking agent or by using a combination of neuromuscular blocking agents [13].

The priming technique is administering an initial dose of nondepolarizing muscle-nerve paralysis that aims to occupy the acetylcholine receptor, which will shorten the time required for the next dose to occupy the remaining acetylcholine receptors and provide a better relaxing effect. Since the discovery of rocuronium, the use of priming doses has decreased. Some investigators recommend administering a small dose of *subparalysis* of about 20% of ED 95 or 10% of the intubation dose, given 2-4 minutes before the second larger dose [14]. This procedure will accelerate the onset of nondepolarizing muscle relaxants by 30-60 seconds, whereas intubation can be performed 90 seconds after the second dose. The conditions of intubation that occurred after priming did not match the administration of succinylcholine. Priming also carries the risk of aspiration, difficulty swallowing, and visual disturbances with a degree of inhibition that can interfere with patient comfort. If this patient complains of induction, drugs or sedation should be given immediately. However, this side effect only occurs in critically ill and geriatric patients. Priming doses usually do not cause significant paralysis, whereas paralysis occurs when 75% to 80% of acetylcholine receptors are blocked. Large doses of muscle relaxants are recommended when intubation must be performed in less than 90 seconds. These larger doses are associated with duration of action and an increased risk of cardiovascular side effects. Increasing the dose of rocuronium

0.6 mg/kg (2 x ED 95) to 1.2 mg/kg (4 x ED 95) shortens the onset of action from 89 seconds to 55 seconds but significantly extends the duration of action from 37 minutes to 73 minutes [15].

Pharmacology *Atracurium* - *Atracurium* is a nondepolarizing neuromuscular spasm drug from the bis quaternary *benzylisoquinoline* class. At ED 95, 0.2 mg/kg BW *atracurium* has an onset of action of 3-5 minutes and a duration of action of 20-35 minutes. The site of action of *atracurium*, as with other nondepolarizing neuromuscular blocking agents in the presynaptic and postsynaptic cholinergic receptors. *Atracurium* also causes direct neuromuscular inhibition by affecting ion flow through nicotinic cholinergic receptor channels. It is estimated that 82% of *atracurium* is bound to plasma proteins, primarily albumin. *Atracurium* is designed for spontaneous degradation *in vivo* (Hoffman elimination) at average body temperature and pH. Besylate iodide salt is added to make *atracurium* more water-soluble and adjust the pH of the solution between 3.25–3.65 to minimize spontaneous in vitro degradation. Because commercial preparations have a low pH, *atracurium* should not be mixed with alkaline drugs. Exposure of *atracurium* to alkaline solutions before it enters the circulation would theoretically result in premature deterioration of the drug. The potency of *atracurium* stored at room temperature will decrease about 5% every 30 days [16]. *Atracurium* undergoes spontaneous nonenzymatic degradation at average body temperature and pH, known as Hoffman elimination. Furthermore, *atracurium* will be simultaneously hydrolyzed by nonspecific plasma esterase. *Laudanosine* is a significant metabolite of both metabolic pathways. This metabolite is inactive at the muscle-nerve junction, but it causes central nervous system stimulation in experimental animals at high concentrations.

On the other hand, ester hydrolysis is a biological mechanism. Both of these metabolic routes are independent of liver and kidney function and plasma cholinesterase activity. The *atracurium*'s action duration did not differ between regular patients, patients with decreased renal and hepatic function, and patients with atypical plasma cholinesterase. The absence of prolongation of the action of *atracurium* in patients with atypical cholinesterase suggests a nonspecific dependence of plasma esterase hydrolysis on plasma esterase unrelated to plasma cholinesterase. Hoffman elimination and ester hydrolysis also answer the minimal cumulative effect of drugs by repeated dosing or continuous infusion [17]. Peak plasma concentrations of *laudanosine* in humans occur 2 minutes after rapid IV administration of *atracurium* and persist at approximately 75% of peak levels for about 15 minutes. *Laudanosine* depends on liver clearance; about 70% is excreted in the bile and the remainder in the urine. Liver cirrhosis in humans does not affect *laudanosine* clearance, whereas excretion of this metabolite is impaired in patients with biliary obstruction. Plasma concentrations of *laudanosine* after a single dose of 0.5 mg/kg iv *atracurium* are increased in patients with renal failure compared with regular patients. *Laudanosine* will not cause seizure activity in anaesthetized patients because *atracurium* causes muscle paralysis; on the other hand, hypnotic sedation will depress the central nervous system. Although Hoffman elimination is pH-dependent (accelerated in alkalosis and slowed in acidosis), it is necessary to have a significant enough change in pH to affect Hoffman elimination. Changes in pH will affect the rate of ester hydrolysis in the opposite direction to the Hoffman elimination rate. Therefore, the slow Hoffman elimination is counteracted by increasing the rate of ester hydrolysis.

Rocuronium bromide is a nondepolarizing muscle relaxant of *aminosteroid* derivatives, with its main post-junctional effect and high selectivity of the neuromuscular junction receptors. Muscle paralysis results from competitive antagonism of the nicotinic cholinergic receptors of skeletal muscle, the potency of which is approximately 15-20% of vecuronium. Rocuronium does not block autonomic ganglia, has a rapid onset of action, moderate duration of action, rapid recovery and minimal accumulation, and a low tendency to release histamine [19]. Depolarizing Muscle Relaxing Drugs - Depolarizing muscle relaxants are very similar to acetylcholine and bind to acetylcholine receptors, generating a potential muscle action prolonged depolarization of the muscle cells (muscle endplate). Continuous endplate depolarization causes muscle relaxation because the lower gate opening of the prejunctional sodium channels is time-limited. After initial excitation and opening (figure 3b), these sodium channels close (figure 3c) and cannot reopen until endplate repolarization [20]. The endplate cannot repolarize as long as the depolarizing muscle relaxant binds to the acetylcholine receptor; this is called a phase I block. After some time, prolonged endplate depolarization can cause ion changes at the acetylcholine receptor to give rise to phase II block, which clinically represents a nondepolarizing muscle relaxant.

Sodium channels are transmembrane proteins that have two available gates. Sodium ions only pass when both gates are open. The opening of the lower gate inactivation is time-dependent, whereas the upper gate opening is voltage-dependent. This channel has three functional parts. At rest, the lower gate is open, but the upper gate is closed: a) when the muscle membrane reaches the threshold of depolarization, the upper gate opens, and sodium can pass; b) as soon as the upper gate opens, the lower gate which is dependent on time is closed; c) when the membrane repolarizes to the resting voltage the upper gate closes, and the lower gate opens. Succinylcholine is a depolarizing muscle relaxant used for intubation and treatment of laryngospasm. Although it has a very rapid onset (<1 minute) and a short duration of action (7-8 minutes), its use is limited because other drugs cannot counteract its action. Significant side effects include hypertension, tachycardia, bradycardia, ventricular arrhythmias, *hyperkalemia* and, less commonly, increased intracranial pressure and malignant hyperthermia [21].

Muscle relaxants are helpful in OK for various clinical conditions, including emergency intubation, acute respiratory distress syndrome, status asthmaticus, increased intracranial pressure, increased intra-abdominal pressure, and therapeutic hypothermia following cardiac arrest associated with ventricular fibrillation. The use of muscle relaxants in OK includes, among other things, the aims of [22] a) improving patient-ventilator synchrony

to increase gas exchange and to reduce the risk of barotrauma; b) facilitating mechanical ventilation and assist oxygenation, e.g. in adult patients with respiratory failure syndrome, by improving chest wall adjustment, lowering maximal airway pressure, and preventing uncoordinated respiratory movements; c) facilitate tracheal intubation; d) control of increased intracranial pressure, e.g. after the head injury, neurosurgery; e) preventing unwanted movement in patients with increased intracranial pressure; and f) decreased muscle tone in tetanus, malignant neuroleptic syndrome, status epilepticus.

The ideal muscle relaxant drug for use in OK is a drug that causes muscle relaxation with rapid onset, can be titrated, and the duration of action is not long so that repeated neurological assessments can be carried out, does not cause adverse hemodynamic effects or does not cause cardiovascular. Other physiological side effects, elimination is independent of liver and kidney function, does not produce active metabolites (metabolites with neuromuscular blocking activity), does not interact with other drugs or has no tendency to accumulate, and is stable for 24 hours for continuous infusion. OK, staff should be trained in administering and monitoring muscle relaxants. Adequate airway control, mechanical respiratory support, and adequate sedation and analgesia are essential before initiating muscle relaxant drug therapy. Equipment for monitoring cardiorespiratory function and assessing the degree of muscle relaxation should be available. The selection of muscle relaxants should be based on the individual characteristics of each patient: a) patients with normal liver and kidney function who require muscle relaxation for more than 1 hour: *pancuronium*; and b) patients with hepatic and renal impairment: *atracurium* and *cisatracurium* because they are relatively independent of hepatic and renal elimination [23].

Muscle relaxants are given by continuous infusion or intermittent intravenous injection. Long-acting muscle relaxants are suitable for intermittent injection, while short-acting muscle relaxants are suitable for continuous infusion. The total neuromuscular block is not required for all patients, depending on the clinical situation. It is more appropriate to think about the patient's control than the extent of the patient's muscle relaxation. Clinical monitoring and train-of-four (ToF) are recommended. Repeated clinical assessment, both qualitative and quantitative, of the depth of neuromuscular block can reduce the dose of muscle relaxants and reduce the risk of residual neuromuscular block complications. Clinicians should evaluate the reason (at least daily) and the depth of neuromuscular blockade (on an ongoing basis) so that mobility can be achieved more rapidly, decreasing the prevalence of delirium, increasing functional independence, and increasing ventilator-free days. It is recommended to use tetanic stimulation or train-of-four (ToF) for peripheral nerve stimulation in monitoring the degree of neuromuscular blockade. The depth of inhibition is assessed by peripheral nerve stimulation every 2-3 hours until the muscle relaxant dose stabilizes, then every 8-12 hours. When no muscle twitching, the dose is decreased by 10%; if 3 or 4 muscle twitches are seen, the dose is increased by 10%. In patients who can tolerate interrupted neuromuscular blockade, the infusion of muscle relaxants should be interrupted daily to assess motor function and level of sedation. The action of nondepolarizing muscle relaxants can be countered by administering anticholinesterase drugs such as neostigmine 0.035-0.07 mg/kg BW. Anticholinesterase side effects can be prevented by giving atropine 15 mcg/kg BW [24].

Side effects of anaphylaxis due to muscle relaxants are infrequent. Cardiovascular side effects are associated with stimulation or inhibition of the autonomic nervous system and vasodilatory effects due to histamine release. Drugs with the lowest risk of cardiovascular complications were *cisatracurium*, *doxaccurium*, *pipecuronium*, *rocuronium*, and *vecuronium*. Drugs that depend on renal clearance (*doxaccurium*, *methocurin*, *pancuronium*, *pipecuronium*) may accumulate in patients with renal failure if dose adjustment is not made in response to peripheral nerve stimulation and may cause continued neuromuscular blockage for one week after discontinuation of the drug. The prolonged prolongation of the effect of muscle relaxants after discontinuation of the drug is due to accumulation of the drug and active metabolites, or acute myopathy. Prolonged prolongation of the effect of muscle relaxants can lead to an acute myopathic syndrome with selective loss of myosin filaments. Muscle relaxant drugs that produce active metabolites are *pancuronium*, vecuronium, and *atracurium*. Most cases of myopathy occur after administration of combination corticosteroid therapy with muscle relaxants.

Muscle relaxants are helpful in OK for various clinical conditions, including emergency intubation, acute respiratory distress syndrome, status asthmaticus, increased intracranial pressure, increased intra-abdominal pressure, and therapeutic hypothermia following cardiac arrest associated with ventricular fibrillation. Muscle relaxant drugs that are ideal for use in OK are drugs with rapid onset, titration, and short duration of action and do not cause cardiovascular disease. Other physiological side effects, elimination is independent of liver and kidney function, do not produce active metabolites, do not interact with other drugs or has no tendency to accumulate, and is stable for 24 hours for continuous infusion. The selection of muscle relaxants should be based on the pharmacology of the muscle relaxants and the individual characteristics of each patient. Repeated clinical assessment, both qualitative and quantitative, of the depth of neuromuscular block can reduce the risk of complications from residual neuromuscular block.

Shock is a hemodynamic and metabolic disorder due to inadequate blood flow and oxygen delivery to capillaries and body tissues, and this condition is manifested by hypotension, tachycardia, oliguria, moist skin, restlessness and altered level of consciousness. Shock is usually the result of heart failure and neurological damage. Shock can be classified into cardiogenic, hypovolemic, distributive and obstructive shock.

Anaphylaxis is a type I hypersensitivity reaction that can be fatal and occurs within minutes. Anaphylaxis is a Gell and Coombs type I hypersensitivity reaction or a rapid, life-threatening allergic reaction caused by IgE. Anaphylaxis is generally the result of releasing vasoactive mediators such as histamine, which results in vasodilation, increased capillary permeability and smooth muscle contraction. Reactions can be triggered by

various allergens such as food, drugs or insect stings, latex, exercise, and other diagnostic materials. In 2/3 of patients with anaphylaxis, the specific trigger cannot be identified.

The manifestations of anaphylaxis are difficulty breathing, laryngeal oedema, and bronchospasm, often followed by a drop in blood pressure or shock. Skin manifestations of itching and urticaria with or without swelling are systemic anaphylactic reactions. Gastrointestinal manifestations include nausea, vomiting, abdominal cramps and diarrhoea. Aetiology and Predisposing Factors - There is no strong enough evidence that age, gender, occupation or living environment are predisposing factors for anaphylactic reactions except through exposure to immunogens. The causes of anaphylaxis are very diverse, including antibiotics, allergen extracts, horse serum, diagnostic substances, venom, blood products, local anaesthetics, food, enzymes, hormones, etc [24]. Antibiotics can be in the form of penicillin and its derivatives, bacitracin, neomycin, tetracycline, streptomycin, *sulfonamides*, and others. Some materials that are often used for diagnostic procedures and can cause anaphylaxis are *radioopaque* substances, *bromsulphalein*, *benzylpenicillin-polylysine*, likewise, with local anaesthetics such as procaine or lidocaine. Clinically, anaphylaxis progresses rapidly and is characterized by sudden symptoms: itching, facial flushing, cyanosis, urticaria, followed by a rapid fall in blood pressure. Then there may also be oedema with increased vascular permeability, progressing to tracheal obstruction causing respiratory distress followed by loss of consciousness until death. Pathophysiology - Anaphylactic reactions occur when specific IgE has been formed against certain allergens. Allergens that enter the body through the skin, mucosa, respiratory system and food, are exposed to plasma cells and cause the formation of specific IgE against certain allergens. This specific IgE then binds to the surface receptors of mastocytes and basophils [25]. On subsequent exposure, the allergen will bind to specific IgE and trigger an antigen-antibody reaction that causes the release of mediators, including histamine from granules contained in cells. Antigen-antibody binding releases histamine, a component of complement, cytokines and other vasoactive substances that cause vasodilation, increased capillary permeability and bronchoconstriction and this binding also triggers the synthesis of SRS-A (Slow Reacting Substance of Anaphylaxis) and the degradation of arachidonic acid in cell membranes, which leads to producing leukotrienes and prostaglandins. This reaction immediately reaches its peak after 15 minutes. Management - The initial action taken is to position the patient in a supine state, and the level of consciousness of the patient experiencing anaphylactic shock must be considered. If the patient's consciousness decreases and cardiac arrest is found, CPR must be done (Cardiopulmonary and Brain Resuscitation). The stages of CPR carried out on a dental chair are: a) get rid of all dangerous and disturbing items or objects such as dental instruments; b) position the chair horizontally from the floor; c) the position of the operator is next to the dental chair, and the operator's knee is parallel to the patient's body; and d) carry out the CPR stage [26]. Early recognition of an anaphylactic reaction is mandatory, as death occurs within minutes to hours after the first symptoms. Mild symptoms such as pruritus and urticaria can be controlled by administering 0.3-0.5 ml of epinephrine subcutaneously or intramuscularly, repeating doses as needed at 20-minute intervals for severe reactions. Intravenous injection is started at a dose of 2-10 ml of epinephrine diluted 1:100,000 at 5-10 minutes intervals. To increase the solution's volume, normal saline and dopamine can be added in case of severe hypotension. The antihistamine diphenhydramine is also necessary, which works for urticaria, angioedema, and bronchospasm. The dose given is 50-100 mg intravenously or intramuscularly [27]. The best way to treat anaphylaxis is prevention. The incidence of anaphylaxis can be prevented by taking a proper and good history on the patient before the procedure is performed. The history consists of asking for a medical history and carefully avoiding drugs suspected of causing a reaction. Prior to anaesthetic action, there is testing for allergy to local anaesthetics, including *in vivo* tests such as puncture, scratch and patch test, intradermal injection and even dose escalation. Intradermal injection, commonly known as a skin test, is often done when the patient does not know whether he or she has an allergy to anaesthetics or drugs. A skin test is performed on the skin to identify allergic substances (allergens) that trigger allergic reactions.

Research Method

The research approach used in this study is a qualitative research approach, namely a systematic research method used to examine or examine an object in a natural setting, qualitative research is descriptive research and tends to use inductive binding analysis. The research design used in this study is library research design, which is research that utilizes library resources to obtain research data. The data collection method used in this research is the documentation method. After the author has collected data, then read, studied, understood, selected, and collected and analyzed, then the next stage is to conclude based on the data that has been collected and analyzed. At this stage of data analysis, the author uses the method of content analysis and semiotic analysis. The content analysis technique is a research technique that aims to draw conclusions by identifying certain characteristics in messages from a text systematically and objectively. In this content analysis view statements and signs as raw material that must be summarized in order to produce: The main purpose of the content analysis is to make inferences. The content analysis method is basically a systematic technique for analyzing message content and processing messages or a tool for observing and analyzing the open communication behavior of the selected communicator.

Discussion

An anaphylactic reaction or anaphylaxis is an exaggerated immunological response to a substance, substance, or protein, which an individual has previously been sensitized. When the patient comes into contact with these

substances, histamine, serotonin, tryptase and other vasoactive substances are released from basophils and mast cells. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but these reactions are mediated directly by certain drugs or substances and not through IgE antibody sensitization. Immediate release of small amounts of histamine is familiar with drugs such as morphine and nondepolarizing muscle relaxants (*tubokurare, alcuronium*, *atracurium*) [28]. Clinical manifestations are usually mild, consisting of urticaria (redness and swelling of the skin), usually along the veins, redness of the body and sometimes mild hypotension. Various kinds of drugs can cause allergic reactions, including those used in anaesthetic practice. Anaesthetic drugs that can cause anaphylactic reactions include thiopentone, *suxamethonium*, nondepolarizing muscle relaxants, local ester anaesthetics, antibiotics, plasma expanders (dextran, starch and gelatin) and latex.

Heart as organ shock in anaphylaxis - Chemical mediators in anaphylaxis directly affect the myocardium. H1 receptors mediate coronary artery vasoconstriction and increase capillary permeability, while H2 receptors increase atrial and ventricular contractility, atrial frequency, and coronary artery vasodilation. The interaction of H1 and H2 receptors stimulation results in a decrease in diastolic pressure and a decrease in pulse pressure. Animal studies suggest a possible modulating role for H3 receptors. Platelet-activating factor also reduces coronary blood flow, delays atrioventricular conduction and has a depressant effect on the heart [29]. Clinically, anaphylaxis is associated with myocardial ischemia, atrial and ventricular conduction defects, and arrhythmias and T wave abnormalities. These changes are associated with a direct effect of mediators on the myocardium or an exacerbation of pre-existing myocardial insufficiency due to the hemodynamic stress of anaphylaxis is unclear. Raper and Fisher described two previously healthy subjects who developed myocardial depression during anaphylaxis. Echocardiography, nuclear imaging, and hemodynamic measurements confirmed the presence of myocardial dysfunction. Anaphylactic therapy is given with an intra-aortic balloon pump to support *hemodynamics*. A balloon pump is required for more than 72 hours because of persistent myocardial depression, even though other clinical signs of anaphylaxis have diminished. Both subjects recovered without any myocardial dysfunction [30].

During anaphylaxis, the increase in vascular permeability can result in a displacement of 50% of the intravascular to extravascular fluid within 10 minutes. This shift in practical blood volume activates the renin-angiotensin-aldosterone system and causes a compensatory release of catecholamines, both of which can have varying clinical effects. Some subjects had an abnormally elevated peripheral vascular resistance (maximal vasoconstriction), while others had a decreased systemic vascular resistance, despite elevated catecholamine levels. Mast cells accumulate plaque and cause coronary artery thrombosis because antibodies that bind to mast cell receptors can cause degranulation. Histamine release by mast cells causes plaque disruption by increasing hemodynamic arterial stress, inducing vasospasm, or both [31].

The causative agent of anaphylaxis - In fact, any agent that can activate mast cells or basophils can cause anaphylaxis. However, as previously stated, more than one mechanism may be activated in some cases of anaphylaxis. The most common identified causes of anaphylaxis are food, drugs, insect stings, allergen injection, immunotherapy. Anaphylaxis in nuts is of particular interest because it is potentially life-threatening, particularly in subjects with asthma and a propensity to be sensitive to these foods throughout life. The investigators reported that most children (52%) with peanut allergy developed life-threatening symptoms with a gradual reaction, although previously, atopic dermatitis was the only clinical manifestation. Idiopathic anaphylaxis is one of the most common causes, accounting for approximately 1/3 of cases in retrospective studies. A detailed history and diagnostic examination of foods, spices, and vegetables can sometimes identify the cause in a subject before being classified as idiopathic anaphylaxis [32].

Clinical features of anaphylaxis - Cardiovascular effects are the most frequently seen features. Not all symptoms occur in every patient – one symptom may be more prominent than another. Reactions range from mild to life-threatening. A conscious patient will present with a range of symptoms, but diagnosis is more difficult in anaesthetized patients. Anaphylaxis is suspected in anaesthetized patients if hypotension or bronchospasm develops suddenly, primarily if this occurs after the administration of a drug or fluid. Latex allergy may have a slow onset, sometimes taking up to 60 minutes to manifest [33]: a) Cardiovascular: Hypotension and cardiovascular collapse, tachycardia, arrhythmias. The ECG may show ischemic changes. Cardiac arrest; b) Respiratory System: Edema of the glottis, tongue, and airways can cause stridor or airway obstruction. Bronchospasm – in severe; c) Gastrointestinal: There is abdominal pain, diarrhoea or vomiting; d) Haematology: *Coagulopathy*; and e) Skin: Redness, *erythema*, *urticaria*.

Muscle relaxants - Muscle relaxants are high-alert agents (drugs that carry a high risk when misused) used to treat critically ill patients with impaired gas exchange and ventilation, control life-threatening intracranial hypertension, and reduce brain metabolism due to shivering. When there is therapeutic hypothermia or also called targeted temperature management. To promote patient safety and inform clinical decision making when applying these agents to practice, emergency department team members should be familiar with efficacy data, pharmacology, pharmacokinetics, dosage, drug interactions, monitoring required, and adverse events. Essential considerations for optimizing treatment with muscle relaxants include patient-based drug selection, systematic identification and assessment for treatment purposes, titration of agents for parameter purposes (using clinical assessment and TOF monitoring), use of intermittent therapy whenever possible, and daily assessment of the continuous need for therapy [34].

Muscle relaxants have been used in critical medical conditions for decades. Because of the risk of frequently reported side effects, the continued use of this drug is controversial. Muscle relaxants may be used for short-term

procedures, such as for immobilization (e.g., rapid sequence intubation [RSI], tracheostomy), or for more lengthy procedures of hours to days to reduce oxygen consumption in severe hypoxaemia, facilitating ventilation, mechanics, reducing intracranial pressure, prevents shivering, and manages tetanus. Muscle relaxants are most commonly used in surgery to facilitate mechanical ventilation for patients with Acute Lung Injury (ALI) and acute respiratory distress syndrome (ARDS). Recent observational studies estimate that 25-50% of patients with ARDS receive muscle relaxants, and this percentage increases when the supine position or high-frequency oscillations are used. Treatment of hypothermia after cardiac arrest is a new indication for muscle relaxants in OK because these agents are often included in protocols to prevent or treat shivering.

Conclusion

Anaphylactic shock caused by muscle relaxants is responsible for a mortality rate of more than 4%, even after immediate administration of epinephrine. Death did not depend on the type of muscle relaxant. It is more common in men, in patients with a history of cardiovascular disease, in patients taking beta-blockers, and in emergencies. Of the two thousand and twenty-two cases of hypersensitivity muscle relaxants found in France, 84 were fatal (4.1%), 1,247 cases of anaphylactic shock. Therefore, it is still necessary to do further research on the use of muscle relaxants and prevent the occurrence of anaphylactic shock because this writing has not been widely carried out in Indonesia. With further investigation, it is hoped that more precise information and a better understanding of the use of muscle relaxants can be obtained to improve the quality of life for patients who have undergone surgery and use muscle relaxants and reduce the mortality that results from it.

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