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Assessment of comparison of effect of oral aspirin and intravenous diazepam on succinylcholine induced postoperative myalgia

Dr. Deepak Kumar Maurya
Senior Resident, Department of Anesthesia and Critical Care, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India

Abstract
A hypothesis suggests a possible role for prostaglandins and cyclooxygenases in Succinlycholine induced myalgia. Pre-treatment with a prostaglandin inhibitor is effective in reducing the incidence of myalgia. Succinylcholine induced myalgia increases length of stay in hospital thereby increasing the cost of treatment. Therefore prevention of myalgia is very important. Various agents have been attempted to decrease the postoperative muscle pain namely, Non-depolarising neuromuscular blockers, NSAIDS, benzodiazepines, phenytoin, ketorolac, vitamin E derivatives, local anaesthetics. Hence based on above findings the present study was planned for Assessment of Comparison of Effect of Oral Aspirin and Intravenous Diazepam on Succinylcholine Induced Postoperative Myalgia.

Total 30 patients undergoing the elective surgery under general anaesthesia were enrolled in the present study. The patients divided in two study groups as 15 patients in each group. The patients were administered with the oral aspirin and intravenous diazepam on succinylcholine induced postoperative myalgia. The present study was planned in Department of Anesthesia and Critical Care, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. The study was conducted from the duration of February 2018 to Nov 2018. Postoperatively all the patients were assessed for myalgia. Myalgia was defined as "muscle pain not related to surgical intervention".

The data generated from the present study concludes that oral aspirin prevents succinylcholine induced myalgia more effectively than intravenous diazepam. Prevention of succinylcholine induced myalgia is most important and various methods have been used to prevent the same.

Keywords: aspirin, diazepam, myalgia, succinyl choline, etc

Introduction

Myalgia, or muscle pain, is a symptom that presents with a large array of diseases. While the most common cause is the overuse of a muscle or group of muscles, acute myalgia may also be due to viral infections, especially in the absence of a traumatic history. Longer-term myalgias may be indicative of a metabolic myopathy, some nutritional deficiencies, or chronic fatigue syndrome.

Suxamethonium chloride, also known as suxamethonium or succinylcholine, is a medication used to cause short-term paralysis as part of general anesthesia. This is done to help with tracheal intubation or electroconvulsive therapy. It is given either by injection into a vein or muscle. When used in a vein onset of action is generally within one minute and effects last for up to 10 minutes. Common side effects include low blood pressure, increased saliva production, muscle pain, and rash. Serious side effects include malignant hyperthermia and allergic reactions. It is not recommended in people who are at risk of high blood potassium or a history of myopathy. Use during pregnancy appears to be safe for the baby. Suxamethonium is in the neuromuscular blocker family of medications and is of the depolarizing type. It works by blocking the action of acetylcholine on skeletal muscles [1].

Its medical uses are limited to short-term muscle relaxation in anesthesia and intensive care, usually for facilitation of endotracheal intubation. It is popular in emergency medicine due to its rapid onset and brief duration of action. The former is a major point of consideration in the context of trauma care, where endotracheal intubation may need to be completed very quickly. The latter means that, should attempts at endotracheal intubation fail and the person cannot be ventilated, there is a prospect for neuromuscular recovery and the onset of spontaneous breathing before low blood oxygen levels occurs. It may be better than rocuronium in people without contraindications due to its faster onset of action and shorter duration of action [2].

Suxamethonium is also commonly used as the sole muscle relaxant during electroconvulsive therapy, favoured for its short duration of action. [Medical citation needed]

Suxamethonium is quickly degraded by plasma butyrylcholinesterase and the duration of effect is usually in the range of a few minutes. When plasma levels of butyrylcholinesterase are greatly diminished or an atypical form is present (an otherwise harmless inherited disorder), paralysis may last much longer, as is the case in liver failure or in neonates [3].

It is recommended that the vials be stored at a temperature between 2°-8 °C for optimal effect, a key consideration in temperate and tropical countries where room temperatures can reach 30 °C. Side effects include malignant hyperthermia, muscle pains, acute rhabdomyolysis with high blood levels of potassium [3], transient ocular hypertension, constipation [3] and changes in cardiac rhythm, including slow heart rate, and cardiac arrest. In people with neuromuscular disease or burns, an injection of

suxamethonium can lead to a large release of potassium from skeletal muscles, potentially resulting in cardiac arrest. Conditions having susceptibility to suxamethonium-induced high blood potassium are burns, closed head injury, acidosis, Guillain–Barré syndrome, cerebral stroke, drowning, severe intra-abdominal sepsis, massive trauma, myopathy, and tetanus.

Suxamethonium does not produce unconsciousness or anesthesia, and its effects may cause considerable psychological distress while simultaneously making it impossible for a patient to communicate. Therefore, administration of the drug to a conscious patient is contraindicated.

The side effect of high blood potassium may occur because the acetylcholine receptor is propped open, allowing continued flow of potassium ions into the extracellular fluid. A typical increase of potassium ion serum concentration on administration of suxamethonium is 0.5 mmol per liter. The increase is transient in otherwise healthy patients. The normal range of potassium is 3.5 to 5 mEq per liter. High blood potassium does not generally result in adverse effects below a concentration of 6.5 to 7 mEq per liter. Therefore, the increase in serum potassium level is usually not catastrophic in otherwise healthy patients. Severely high blood levels of potassium will cause changes in cardiac electrophysiology, which, if severe, can result in asystole.

Malignant hyperthermia (MH) from suxamethonium administration can result in a drastic and uncontrolled increase in skeletal muscle oxidative metabolism. This overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated quickly.

Susceptibility to malignant hyperthermia is often inherited as an autosomal dominant disorder, for which there are at least six genetic loci of interest, the most prominent being the ryanodine receptor gene (RYR1). MH susceptibility is phenotype and genetically related to central core disease (CCD), an autosomal dominant disorder characterized both by MH symptoms and by myopathy. MH is usually unmasked by anesthesia, or when a family member develops the symptoms. There is no simple, straightforward test to diagnose the condition. When MH develops during a procedure, treatment with dantrolene sodium is usually initiated; dantrolene and the avoidance of suxamethonium administration in susceptible people have markedly reduced the mortality from this condition.

The normal short duration of action of suxamethonium is due to the rapid metabolism of the drug by non-specific plasma cholinesterases. However plasma cholinesterase activity is reduced in some people due to either genetic variation or acquired conditions, which results in a prolonged duration of neuromuscular block. Genetically, ninety six percent of the population have a normal (Eu:Eu) genotype and block duration; however, some people have atypical genes (Ea, Es, Ef) which can be found in varying combinations with the Eu gene, or other atypical genes (see Pseudocholinesterase deficiency). Such genes will result in a longer duration of action of the drug, ranging from 20 minutes up to several hours. Acquired factors that affect plasma cholinesterase activity include pregnancy, liver disease, kidney failure, heart failure, thyrotoxicosis, and cancer, as well as a number of other drugs [5].

If unrecognized by a clinician it could lead to awareness if anesthesia is discontinued whilst still paralyzed or hypoxemia (and potentially fatal consequences) if artificial ventilation is not maintained. Normal treatment is to maintain sedation and ventilate the patient on an intensive care unit until muscle function has returned. Blood testing for cholinesterase function can be performed.

Mivacurium, a non-depolarizing neuromuscular blocking drug, is also metabolized via the same route with a similar clinical effect in patients deficient in plasma cholinesterase activity.

Deliberate induction of conscious apnea using this drug led to its use as a form of aversion therapy in the 1960s and 1970s in some prison and institutional settings [6]. This use was discontinued after negative publicity concerning the terrifying effects on subjects of this treatment and ethical questions about the punitive use of painful aversion.

Phase 1 blocking has the principal paralytic effect. Binding of suxamethonium to the nicotinic acetylcholine receptor results in opening of the receptor's monovalent cation channel; a disorganized depolarization of the motor end-plate occurs and calcium is released from the sarcoplasmic reticulum. In normal skeletal muscle, acetylcholine dissociates from the receptor following depolarization and is rapidly hydrolyzed by the enzyme acetylcholinesterase. The muscle cell is then ready for the next signal.

Suxamethonium has a longer duration of effect than acetylcholine, and is not hydrolyzed by acetylcholinesterase. By maintaining the membrane potential above threshold, it does not allow the muscle cell to repolarize. When acetylcholine binds to an already depolarized receptor, it cannot cause further depolarization. Calcium is removed from the muscle cell cytoplasm independent of repolarization (depolarization signaling and muscle contraction are independent processes). As the calcium is taken up by the sarcoplasmic reticulum, the muscle relaxes. This explains muscle flaccidity rather than tetany following fasciculations. The results are membrane depolarization and transient fasciculations, followed by paralysis.

While this phase is not abnormal and is a part of its mechanism of action, it is undesirable during surgery, due to the inability to depolarize the cell again. Often, patients must be on a ventilator for hours if Phase 2 block occurs. It is caused by the blood concentration of suxamethonium exceeding the therapeutic window. Desensitization occurs at the nerve terminal, and the myocyte becomes less sensitive to acetylcholine; the membrane repolarizes and cannot be depolarized again.

Suxamethonium is an odorless, white crystalline substance. Aqueous solutions have a pH of about 4. The dihydrate melts at 160 °C, whereas the anhydrous melts at 190 °C. It is highly soluble in water (1 gram in about 1 mL), soluble in ethyl alcohol (1 gram in about 350 mL), slightly soluble in chloroform, and practically insoluble in ether. Suxamethonium is a hygroscopic compound [7]. The compound consists of two acetylcholine molecules that are linked by their acetyl groups. It can also be viewed as a central moiety of succinic acid with two choline moieties, one on each end.

Suxamethonium was first discovered in 1906 by Reid Hunt and René de M. Taveau. When studying the drug, animals were given curare and thus they missed the neuromuscular blocking properties of suxamethonium. Instead in 1949 an Italian group led by Daniel Bovet was first to describe succinylcholine induced paralysis. The clinical introduction

of suxamethonium was described in 1951 by several groups. Papers published by Stephen Thesleff and Otto von Dardel in Sweden are important but also to be mentioned is work by Bruck, Mayrhofer and Hassfurther in Austria, Scurr and Bourne in UK, and Foldes in America [8].

A hypothesis suggests a possible role for prostaglandins and cyclooxygenases in Succinlycholine induced myalgia. Pre-treatment with a prostaglandin inhibitor is effective in reducing the incidence of myalgia. Succinylcholine induced myalgia increases length of stay in hospital thereby increasing the cost of treatment. Therefore prevention of myalgia is very important. Various agents have been attempted to decrease the postoperative muscle pain namely, Non-depolarising neuromuscular blockers, NSAIDS, benzodiazepines, phenytoin, ketorolac, vitamin E derivatives, local anaesthetics. Hence based on above findings the present study was planned for Assessment of Comparison of Effect of Oral Aspirin and Intravenous Diazepam on Succinylcholine Induced Postoperative Myalgia.

Methodology

Total 30 patients undergoing the elective surgery under general anaesthesia were enrolled in the present study. The patients divided in two study groups as 15 patients in each group. The patients were administered with the oral aspirin and intravenous diazepam on succinylcholine induced postoperative myalgia. The present study was planned in Department of Anesthesia and Critical Care, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India. The study was conducted from the duration of February 2018 to Nov 2018. Postoperatively all the patients were assessed for myalgia. Myalgia was defined as “muscle pain not related to surgical intervention”.

Aspirin 600mg was given orally one hour prior to surgery and diazepam 0.05mg/kg intravenously was given 15 minutes before induction. Timing of the drugs given was based on the pharmacokinetic principles of the drug. Premedication Inj. Ranitidine 50 mg and Inj. Ondansetron 4 mg IV was given. In the operating room, monitors connected and preoperative vital parameters were recorded. Anaesthesiologist unaware of the study drug given to patients administered general anaesthesia and monitored the patient subsequently. All patients were preoxygenated with 100% oxygen. Induction with thiopentone 3-5mg/kg IV and paralysed with succinylcholine 1.5mg/kg IV.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Patients aged 18-55 yrs, Patients with ASA (American society of anaesthesiologists) grade I &II, Patients posted for elective surgery under general anaesthesia.

Exclusion criteria: Patient refusal, Patients undergoing major surgeries, Pregnancy, burns, infection, emergency surgical procedures, H/O allergy to drugs, Coagulation disorders, Previous history of pain, trauma, neuromuscular disorders, musculoskeletal and endocrine disorders.

Results & Discussion

Succinylcholine is a depolarizing muscle relaxant and is the only one of its kind in use today. It is favored for its rapid onset of action and fast emergence. Succinylcholine is used as muscle relaxant for ambulatory anaesthesia, short surgical procedures and rapid sequence induction as it provides almost ideal intubating conditions. Postoperative myalgia is a minor and a frequent adverse effect of succinylcholine administration. Bourne and Collier first described the phenomenon of post-operative myalgia in 1952. They attributed post-operative myalgia to occur due to the vigour of uncoordinated muscle contractions after succinylcholine injection [9]. The reported incidence of succinylcholine-induced myalgia ranges from 1.5 to 89%. The duration of myalgia can last from 2-3 days to a week. The first postoperative day finds the patient with neck, abdomen and shoulder pain. It is self-limiting but can cause distress to the patient. The first attempt to reduce the incidence and severity of muscle pains was made by Churchill Davidson when he used gallamine for pretreatment in 1954. 4 Since then, many methods have been tried, the most common of which, was the prior administration of a suboptimal dose of a non-depolarising neuromuscular blocker. This was done with the intention of reducing both postoperative myalgia as well as visible fasciculations. With respect to prevention of myalgia, controversy still exists about the agent of choice for premedication, the time of administration of the drug and the accurate dose.

Succinylcholine is a short acting depolarizing muscle relaxant with rapid onset and short duration of action. Its use is associated with a number of side effects like fasciculation, postoperative myalgia, increased serum levels of creatine kinase and potassium, malignant hyperthermia, myoglobinuria, raised intraocular pressure and intracranial pressure precluding its routine use. Fasciculations are relatively benign side effects of its use; most anesthesiologists prefer to prevent them due to a possible association between fasciculations and postoperative myalgia [10].

Different pre-treatment modalities have been attempted to reduce the incidence and severity of fasciculations and myalgia. This includes precurarization with a small dose of non-depolarizing muscle relaxant, pre succinylcholine use of lidocaine, calcium gluconate, magnesium sulphate, nonsteroidal anti-inflammatory drugs (NSAIDs), dexmedetomidine, benzodiazepines, remifentanil, phenytoin or ketorolac. The efficacy of each is variable.

Table 1: Demographic Details

Groups	Group A	Group B
Administration of	Diazepam	Aspirin
No. of Cases	15	15
Age	31 – 45 years	29 – 44 years
Weight	48 – 62 kg	50 – 61 kg

Table 2: Surgery Details

Groups	Group A	Group B
Administration of	Diazepam	Aspirin
Duration of Surgery	55 – 74 mins	56 – 75 mins
ASA Grade		
Grade 1	12	13
Grade 2	3	2
Fasciculations		
Grade 1	4	5
Grade 2	11	10
Grade 3	0	0

Table 3: Myalgia & Potassium Levels

Groups	Group A	Group B
Administration of	Diazepam	Aspirin
Myalgia		
1 hr	1.5 – 2.5	1.1 – 2.4
6 hr	1.3 – 2.4	0.8 – 1.6
12 hr	1.3 – 2.3	0.7 – 1.5
21 hr	0.9 – 1.8	0.3 – 1.1
Potassium Levels		
Pre-Operative	3.5 – 4.5	3.6 – 5.1
1 hr	3.8 – 4.9	4.1 – 5.2
24 hr	3.7 – 5.1	3.8 – 4.8

Oxorn and coworkers in 1992 compared the efficacy of pretreatment with atracurium and placebo before administration of succinylcholine, in the prevention of postoperative myalgia in patients having ambulatory surgery. On the second postoperative day the patients in the atracurium group suffered less postoperative myalgia than those receiving placebo [11]. Sosis and associates in 1987 compared the incidence of postoperative myalgia and fasciculations when atracurium or d-tubocurarine was given prior to succinylcholine. The conclusion reached was that d-tubocurarine is better at reducing the incidence of fasciculations than atracurium. However, d-tubocurarine was not significantly better than saline in preventing postoperative myalgia [12]. Drolet and coworkers in 1997 concluded that rocuronium prevents succinylcholine-induced fasciculations and postoperative myalgia. Rocuronium also delays the onset of succinylcholine and shortens its duration of action [13].

Several mechanisms have been proposed to explain the phenomenon of postoperative myalgia. Postoperative myalgia is often described as being similar to myalgia after unaccustomed exercise. Fasciculations involve vigorous contraction by muscle bundles with no possibility of shortening and without synchronous activity in adjacent bundles. This might produce fibre rupture or damage, thus causing pain [14]. This is in contrast to muscle contractions in the voluntary movement of physical exercise, when the whole muscle contracts synchronously. Postoperative myalgia has been attributed to muscle damage produced by the shearing forces associated with the fasciculations at the onset of phase one block [15]. Muscle pain parallels electromyographic discharge frequencies at the onset of depolarising block, with frequencies > 50 Hz being associated with pain [16]. It has been suggested that the occurrence of symptoms is an 'all or none' response above a certain threshold frequency. [17]. Electromyographic spike trains of succinylcholine-induced fasciculations in patients with myalgia have been studied, and raise the possibility of the development of microdamage at the extrafusal muscles. [18].

Release of potassium from the muscle cells is known to occur after succinylcholine administration. Potassium release is prevented by the prior administration of tubocurarine, and increased serum potassium levels have been suggested to be an aetiological factor [19]. The plasma potassium increases to a higher level in patients who develop succinylcholine pains than in those who do not [25]. During the fasciculations produced by succinylcholine, muscle fibre damage gives rise to both the hyperkalaemia and the subsequent muscle pains [20]. However, no simple correlation exists between the severity of muscle fasciculations, serum potassium changes and the development of postoperative myalgia.

Conclusion

The data generated from the present study concludes that oral aspirin prevents succinylcholine induced myalgia more effectively than intravenous diazepam. Prevention of succinylcholine induced myalgia is most important and various methods have been used to prevent the same.

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