Safety and side effects of suxamethonium in clinical practice – literature overview

1. Bartosz Mazur [BM]

Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland

https://orcid.org/0000-0003-0601-4350
bartoszmazur27@gmail.com

2. Anna Gregula [AG]

Independent Public Health Care Center in Łęczna Krasnystawska 52 street, 21-010 Łęczna, Poland

https://orcid.org/0009-0007-3712-7960
aniagregula19@gmail.com

3. Karol Stachyrak [KS]

Independent Public Health Care Center in Łęczna Krasnystawska 52 street, 21-010 Łęczna, Poland

https://orcid.org/0009-0008-3175-1866
karol.stachyrak@gmail.com
4. Dawid Mika [DM]

1st Military Clinical Hospital with SPZOZ Polyclinic in Lublin, Raclawickie 23 avenue, 20-049 Lublin, Poland
https://orcid.org/0009-0003-5254-5344
mikadawid@gmail.com

5. Aleksandra Kłos [AK]

Student Scientific Association at Department of Epidemiology and Clinical Research Methodology,
Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland
https://orcid.org/0009-0008-6870-2590
aleksandra.kloss@interia.pl

6. Kamila Turek [KT]

Medical University of Lublin, Raclawickie 1 avenue, 20-059 Lublin, Poland
https://orcid.org/0009-0000-6888-8913
kamila.turek26@gmail.com

7. Maciej Lambach [ML]

Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0009-0004-3348-4272
mlambach97@gmail.com

8. Mateusz Pawlicki [MP]

Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0000-0001-8318-6573
pawlak32@gmail.com
9. Aleksandra Mazurek [AM]

Student Scientific Association at Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin, ul. Radziwiłłowska 11, Lublin 20-080, Poland
https://orcid.org/0009-0007-5298-782X
amazurek2702@gmail.com

10. Wiktoria Wilanowska [WW]

Stefan Kardynał Wyszyński Province Specialist Hospital in Lublin, Kraśnicka 100 avenue, 20-718 Lublin, Poland
https://orcid.org/0009-0000-8388-8479
wiktoria.wilanowska@gmail.com

ABSTRACT

Keywords:
suxamethonium; succinylcholine; suxamethonium hyperkalemia; suxamethonium myalgia; suxamethonium anaphylaxis; suxamethonium cholinesterase deficiency; suxamethonium malignant hyperthermia.

Introduction and purpose

Muscle relaxants have been integral to medical practice for decades, benefiting both anesthesiologists for smooth patient intubation and surgeons requiring deep muscle relaxation. This article focuses on succinylcholine, a prominent muscle relaxant, exploring its historical context, efficacy, and the accumulated data on potential life-threatening side effects. The manuscript analyzes the available knowledge regarding the adverse effects of succinylcholine in clinical practice, presenting literature-identified methods aimed at risk mitigation. Summarizing the current understanding of succinylcholine's risks seeks to enhance its effective use, decrease adverse incidents in patients, and contribute to the overall safety of both patients and healthcare providers.

Material and methods
The following review of studies was based on articles obtained from the PubMed and Google Scholar databases. Key search terms included suxamethonium, succinylcholine, suxamethonium hyperkalemia, suxamethonium myalgia, suxamethonium anaphylaxis, suxamethonium cholinesterase deficiency, and suxamethonium malignant hyperthermia.

Conclusions

Suxamethonium's adverse effects range from muscle pain-related discomfort to rare, potentially lethal multi-organ complications, impacting patients' health diversely. Despite its drawbacks, succinylcholine remains crucial in anesthesiology. Ongoing research offers avenues to counteract or mitigate side effects. However, these methods necessitate further research to develop universal, widely available protocols in clinical settings.

Introduction

Muscle relaxants, have accompanied medical practitioners for decades. They are useful for both anesthesiologists, enabling optimal conditions for smooth patient intubation, and surgeons who often require deep muscle relaxation, especially during precision-demanding surgeries. Muscle relaxants can be divided into two major groups: curare derivatives and succinylcholine, the latter being the protagonist of this manuscript [1]. Succinylcholine, as the alternative name for suxamethonium, was first described in the context of its action on the neuromuscular junction by Bovet in 1949. It was introduced into everyday medical practice in Europe as early as 1951 [2,3]. The long history of this medication has allowed for the observation of its effectiveness as well as the collection of data regarding potentially life-threatening side effects. This manuscript focuses on the analysis of available knowledge concerning the adverse effects of succinylcholine in clinical practice. Additionally, it presents methods identified in the literature aimed at minimizing the risk of these effects. Summarizing the current understanding of the risks associated with the use of succinylcholine aims to promote more effective utilization of this drug, reduce the risk of adverse incidents in patients receiving this substance, and positively impact the overall safety of both patients and healthcare providers.
Metodology
The following review of studies was based on articles obtained from the PubMed and Google Scholar databases. Key search terms included suxamethonium, succinylcholine, suxamethonium hyperkalemia, suxamethonium myalgia, suxamethonium anaphylaxis, suxamethonium cholinesterase deficiency, and suxamethonium malignant hyperthermia.

State of knowledge
Suxamethonium is a short-acting skeletal muscle relaxant composed of two connected molecules of acetylcholine (Ach). It acts depolarizingly at the neuromuscular junction by binding to the acetylcholine receptors (AchR). However, the enzymes responsible for acetylcholine breakdown, serum cholinesterases, degrade succinylcholine much more slowly [4]. The substance acts quickly, initiating its effects within 60 seconds and lasting up to 360 seconds - 6 minutes. Succinylcholine ceases its action when it is broken down by pseudocholinesterase, a serum enzyme designed to prevent excessive accumulation of Ach in the postsynaptic membrane. This prevents skeletal muscle cells from undergoing further changes in potentials that govern their function [1, 5, 6]. Suxamethonium can bind not only to nicotinic receptors for Ach in the neuromuscular junction but also to all cholinergic receptors of the sympathetic and parasympathetic nervous systems. As it is often used in emergency situations and requires intensive pharmacotherapy, it can frequently create unfavorable interactions with other drugs. This observation leads to the recognition of numerous adverse effects of this preparation in daily clinical practice [6,7]. Among the most significant adverse effects of succinylcholine are hyperkalemia, malignant hyperthermia, allergic reactions, myalgia and fasciculations, and prolonged paralysis of the patient [6,8]. Below is a description of studies addressing phenomena induced by the administration of succinylcholine.

Hyperkalemia
Hyperkalemia is a common condition in clinical practice, indicating an elevated potassium concentration exceeding 5.0 mmol/L in the patient's blood serum. The prevalence among hospitalized patients ranges from 1% to 10%. It is a potentially life-threatening condition for the patient, with a mortality rate reaching 0.1% of patients [9]. Death can occur due to life-threatening cardiac arrhythmias caused by elevated potassium levels [10]. Suxamethonium, by inducing prolonged depolarization, leads to an increase in blood potassium levels by up to 1 mmol/L, depending on the administered dose of the drug. The effect can be observed as
early as 2-5 minutes, and hyperkalemia may persist for even over 15 minutes [11]. The interpretation of an ECG recording can provide initial information about an increasing potassium level. Observations may include acute QRS widening, ST elevations in leads V1 and V2, non-shockable pulseless wide-complex tachycardia, and other suspicious, abnormal ECG findings [12]. Serious burns, prolonged immobilization, muscle dystrophy, and critical multi-system diseases can lead to the appearance of alternative acetylcholine receptors. When activated, these receptors allow larger amounts of potassium to pass, causing an increase in its serum levels. Considering the mechanism of action of succinylcholine, it is easy to notice that in these cases, the use of this drug may be more risky. In situations of increased risk of hyperkalemia, if possible, an alternative medication with a different mechanism of action should be considered for the patient [13]. By keeping in mind the possibility of this complication, it can be prevented by employing appropriate patient monitoring, including continuous EKG observation, potassium level measurements, blood gas analysis, and actively seeking signs of organ failure. Early detection of an increasing potassium level allows for the initiation of early treatment and safeguards the patient from cardiac arrest [14].

Malignant hyperthermia
Malignant hyperthermia (MH) is a rarely occurring (~1:100,000) hypermetabolic response of muscles to pharmacological agents such as potent anesthetic gases and succinylcholine. This disorder manifests as hyperthermia, tachycardia, tachypnea, metabolic acidosis, rhabdomyolysis, hyperkalemia, and muscle stiffness [15,16,17]. The occurrence of this complication is associated with the presence of predisposing genetic mutations inherited in an autosomal dominant manner, which are difficult to detect without invasive specialized testing [18]. According to a multicenter study from 2019, the main non-genetic risk factors for developing malignant hyperthermia are young age, male gender, and the use of suxamethonium [19]. For a patient to survive this complication, early detection and immediate specific and symptomatic treatment of the condition are necessary. Early detection of the onset of malignant hyperthermia (MH) can be aided by continuous monitoring of the patient's body temperature during anesthesia and muscle relaxation, as well as observing end-tidal CO2 values. The first-line medication dedicated to MH is dantrolene. According to a multicenter study on the use of succinylcholine and the availability of dantrolene, researchers demonstrated that the timing of dantrolene administration, rather than its dosage, is more crucial in preventing MH complications. Hence, the conclusion that this substance should be readily available in facilities where potentially triggering agents for malignant hyperthermia
are used [20]. The dosage of dantrolene in the acute phase of MH is 2-3 mg/kg of body weight, up to a maximum of 10 mg/kg, followed by 1 mg/kg every 6 hours for the next 48 hours. Additionally, the patient should be cooled, and symptomatic management should be applied to address emerging homeostatic disturbances. Obtaining a detailed medical history, including cases of malignant hyperthermia, can prevent the occurrence of this condition in a paralyzed patient by using an alternative drug and increasing the physician's vigilance [21]. As indicated by researchers from the Czech Republic, in the largest review regarding MH in the pediatric population, the key to diagnosing the disease is awareness of its potential occurrence [22]. To reduce the risk of malignant hyperthermia, it is advisable, whenever possible, to refrain from using suxamethonium in pediatric patients, as this age group is the most vulnerable [19, 22].

**Anaphylactic Reaction**

In the operating room, doctors, especially anesthesiologists, administer a multitude of medications to the patient to facilitate a safe, painless, and effective surgery. Every medication administered intraoperatively has the potential to trigger a hypersensitivity reaction, and among those most commonly responsible for anaphylactic reactions are drugs that block neuromuscular transmission [23]. Allergic reactions can take various forms, ranging from mild skin redness to severe anaphylactic shock with life-threatening bronchial constriction [24]. According to Ciobotaru et al., Suxamethonium is associated with a higher risk of allergic reactions compared to atracurium [8]. Similar conclusions arise from an earlier study by Reedy et al., where anaphylactic reactions following the administration of rocuronium or suxamethonium were found to be ten times more frequent than those following atracurium administration [25]. Therefore, it seems that if the clinical situation allows, atracurium should be chosen over suxamethonium, as it would be safer. After the occurrence of an anaphylactic reaction, the gold standard is to perform skin tests after 6 weeks, which can confirm sensitivity to a particular drug. For more precise results, biological tests should be conducted, where data on histamine levels, tryptase, and specific IgE in the serum can help avoid false-negative tests, and identifying the sensitizing factor may protect the patient from future anaphylactic reactions [24, 26, 27]. The primary treatment involves the prompt recognition of anaphylactic shock and the administration of adrenaline along with intravenous fluids [27]. One can therefore infer that awareness of the potential occurrence of this complication will contribute to quicker recognition, leading to prompt initiation of appropriate treatment and effective patient recovery.
Myalgia and fasciculations
Muscle pain caused by suxamethonium is a common side effect of this drug. The frequency of this phenomenon varies depending on the data source, but it is most commonly reported to occur in 50% of patients [28]. In the literature, alongside myalgia, fasciculations are also mentioned—small contractions of muscle bundles that can cause minor damage and fiber ruptures. It is precisely these fasciculations, among other factors, that may be responsible for the occurrence of subsequent pain [29]. One of the ways to reduce muscle pain after the administration of succinylcholine is the preoperative administration of gabapentin or pregabalin [30]. However, this does not affect the occurrence of fasciculations. An interesting method for significantly reducing myalgia, as demonstrated by Mostafa et al. in a randomized, controlled, double-blind study, is the oral administration of 200 μg of selenium two hours before induction of anesthesia [31]. In another clinical study, Amornyotin et al. demonstrated a significant reduction in suxamethonium-induced myalgia when a lidocaine infusion at a dose of 1.5 mg/kg of body weight was administered before succinylcholine administration [32]. Similar results were found in the study by Bayable et al., where lidocaine proved to be more effective than vecuronium bromide in reducing myalgia, while vecuronium was better at reducing fasciculations [29]. The study by Mostafa et al. indicates another medication that reduced postoperative myalgia—duloxetine at a dose of 30 mg. Patient satisfaction was higher, and the demand for analgesic medications was lower [31].

Prolonged paralysis
Succinylcholine is broken down by serum cholinesterase produced in the liver. It happens that patients suffer from a deficiency of this enzyme, and the causes can be congenital or acquired [33]. Enzyme deficiency can be caused by systemic diseases, pregnancy, rare genetic mutations, and malnutrition [34]. A deficiency in cholinesterase may not manifest itself earlier in any noticeable way; suspicion arises during patient observation when prolonged paralysis occurs after the administration of succinylcholine or mivacurium. In such cases, we may observe respiratory muscle failure persisting longer than expected based on the doses of neuromuscular blocking drugs. Patients with such deficiencies may require mechanical ventilation in the intensive care unit until normal respiratory muscle function is restored [33]. Andersson et al. demonstrated in their review that a deficiency in cholinesterase leads to an extension of the duration of action of succinylcholine and mivacurium from several minutes to even several hours [35]. In the case study by Cornelius and Jacobs, it is indicated that individuals with any deficiency in serum cholinesterase should not receive neuromuscular
blocking drugs [36]. Al-Emam proposes a specific algorithm for managing a detected deficiency in cholinesterase in his work. The author recommends continuing mechanical ventilation until the patient fully recovers, measuring enzyme levels in the patient's family, avoiding paralyzing agents, and educating the patient to inform doctors about the enzyme deficiency in the future [37].

**Conclusions**

Suxamethonium and its adverse effects have a diverse impact on patients' health – from discomfort associated with muscle pain to rarely occurring potentially lethal multi-organ complications. Despite its drawbacks, succinylcholine still holds a significant place in anesthesiology. Thanks to new research, we can explore various possibilities to counteract the occurrence of side effects or reduce their intensity. Numerous methods fulfill this task. For instance, educating about potential consequences of succinylcholine administration can increase the awareness of medical staff, maintaining a thorough patient history, administering additional drugs to secure the patient, or simply considering a switch from succinylcholine to an alternative drug that is more tailored to the patient and reduces the risk of complications. These methods require further research and the development of appropriate, universal, and widely available protocols for clinical situations.

**Author’s contribution**

Conceptualization, Bartosz Mazur, Anna Greguła and Karol Stachyrak; methodology, Mateusz Pawlicki; software, Dawid Mika; check, Dawid Mika, Aleksandra Klos and Maciej Lambach; formal analysis, Aleksandra Mazurek and Wiktoria Wilanowska; investigation, Kamiala Turek and Wiktoria Wilanowska; resources, Aleksandra Mazurek; data curation, Anna Gregula; writing - rough preparation, Bartosz Mazur; writing - review and editing, Maciej Lambach, Kamila Turek; visualization, Bartosz Mazur; supervision, Mateusz Pawlicki; project administration, Dawid Mika; receiving funding, Karol Stachyrak

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References:


