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REVIEW ARTICLE

Succinylcholine-associated postoperative myalgia

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Summary

The subject of postoperative myalgia associated with the use of succinylcholine is reviewed. We discuss the mechanisms of succinylcholine-induced myalgia and the techniques available to prevent and treat the myalgia. In situations where patients are at risk of developing myalgia and succinylcholine is the neuromuscular blocker of choice, the use of a combination of techniques may prove to be a useful strategy.

Keywords Succinylcholine, myalgia, fasciculations, neuromuscular blocker.

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Succinylcholine is considered by many to be the best drug for providing ideal intubating conditions for short surgical procedures and rapid sequence induction. However, in addition to a number of infrequent, but well-known, untoward effects, its usefulness is limited by the frequent occurrence of postoperative myalgia. This is often listed as a minor adverse effect but it may be a very distressing experience for the patient. The phenomenon of postoperative myalgia was first noted in 1952: 'The first visible effects of injections of succinylcholine were diffuse uncoordinated contractions of muscle bundles and groups ... The occasional vigour of these contractions ... may give rise to a feeling of muscular stiffness after consciousness has been regained' [1]. Churchill-Davidson [2] was the first to describe the syndrome of postoperative myalgia: 'Succinylcholine is unsuitable for use as a muscle relaxant for out-patient procedures, because it may be followed by severe muscle stiffness.'

The first attempt to reduce the incidence and severity of muscle pains was pretreatment with gallamine in 1954 [2]. Since then, a wide variety of regimens has been tried. The most common practice is to administer a subparalysing dose of a nondepolarising neuromuscular blocker a few minutes before succinylcholine, with the aim of abolishing both the visible fasciculations and the postoperative myalgia. Although much has been written about this technique, controversy exists about the agent of choice for pretreatment, the optimal dose of the agent and the ideal timing interval between pretreatment and succinylcholine administration. The purpose of this article is to review the mechanisms of succinylcholine-induced myalgia, the various techniques that may alleviate the myalgia, the rationale for using them and their effectiveness.

The reported incidence of succinylcholine-induced myalgia ranges from 1.5 to 89% [3, 4]. The most commonly quoted figure is around 50%. The duration of the discomfort is highly variable. It usually lasts for 2 or 3 days but occasionally persists for as long as a week. It usually appears on the first day after surgery, is most commonly described as the pain one might suffer after an unaccustomed degree of physical exercise, and is usually located in the neck, shoulder and upper abdominal muscles. Although self-limiting, it is generally agreed that iatrogenic postoperative myalgia is unacceptable in modern anaesthetic practice [5].

Several factors have been described as having an influence on this phenomenon. Females are more likely to suffer than males [6]. The incidence of postoperative myalgia is lower in pregnant than in nonpregnant women of childbearing age, possibly due to the influence of progesterone or oestrogens [3, 7]. There does not seem to be a difference between different ethnic groups [8]. Myalgia is less frequent in children [9] and in patients aged over 50–60 years [10]. There is an association between the state of training of the muscle and the occurrence of

muscle pains. Usually, there is a lower incidence and a lesser severity in patients with greater muscular fitness [11]. The extent of surgery is also important. Patients who undergo minor operations are more likely to complain of postoperative myalgia [12]. Early ambulation increases both the likelihood of the development of pain and its severity [2, 13, 14].

Mechanisms of postoperative myalgia

The neuromuscular junction comprises prejunctional and postjunctional components. In the prejunctional component, acetylcholine is synthesised, stored and released in quanta via a complicated vesicular system. Acetylcholine diffuses across the junctional cleft and binds to acetylcholine receptors in the postjunctional component, and is thereafter metabolised by acetylcholinesterase in the junctional cleft. Binding of acetylcholine to its postjunctional receptor evokes muscle contraction [15].

Mechanisms of fasciculation

Fasciculations have been attributed to a prejunctional depolarising action of succinylcholine, resulting in repetitive firing of the motor nerve terminals and antidromic discharges that manifest as uncoordinated muscle contractions [16, 17]. Studies have been undertaken to evaluate the prejunctional mechanism of succinylcholine-induced fasciculation using neurotoxins and drugs that act predominantly at the prejunctional site. It has been shown that they almost completely suppress fasciculations in animals [17]. The classical view of the physiology of neuromuscular transmission holds that the actions of d-tubocurarine and related drugs are postjunctional. They act to block the recognition sites of the acetylcholine receptors and thereby interrupt neuromuscular transmission. It is now widely believed that they may act at sites other than the postjunctional membrane. The effectiveness of d-tubocurarine in reducing fasciculations may actually be related to its presynaptic effects [18]. Fasciculations are caused by antidromically conducted axonal depolarisations initiated by the agonist action of succinylcholine on prejunctional nicotinic receptors at the neuromuscular junction. d-Tubocurarine and phenytoin pretreatment acts prejunctionally to prevent the action of succinylcholine on motor nerve terminals that would otherwise lead to the asynchronous repetitive firing responsible for generalised fasciculations [19]. This view is supported by the ability of d-tubocurarine to induce a strong train-of-four fade, an indicator of prejunctional effect, correlated with its ability to prevent fasciculations [20]. In fact, the degree of train-of-four fade indicates the relative prejunctional effect of nondepolarising neuromuscular blockers [18, 21].

Pathogenesis of postoperative myalgia

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 [22]. 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 [23]. Muscle pain parallels electromyographic discharge frequencies at the onset of depolarising block, with frequencies > 50 Hz being associated with pain [24]. It has been suggested that the occurrence of symptoms is an 'all or none' response above a certain threshold frequency [25]. 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 [26].

In an attempt to correlate succinylcholine-induced fasciculation with muscle injury and the ensuing muscular pain and stiffness, changes in serum creatine phosphokinase after succinylcholine administration were studied. However, there was no correlation between muscle pain and creatine phosphokinase elevation [27]. Further studies showed no obvious relationship between pain and biochemical changes [28, 29]. Another theory is that postoperative myalgia is due to the release of large amounts of lactic acid in the muscle [30]. There is insufficient evidence to substantiate this view.

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 [31]. 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 [32]. However, no simple correlation exists between the severity of muscle fasciculations, serum potassium changes and the development of postoperative myalgia.

Relationship between fasciculations and postoperative myalgia

The relationship between fasciculations and postoperative myalgia has not been well defined. Attempts to relate pain severity to the strength or even the presence of visible

fasciculations have failed. There have been suggestions that fasciculations and muscle pains are related [1, 33, 34]. Although pretreatment decreases the incidence of fasciculations significantly, most investigators agree that the severity of fasciculations has no direct correlation with the frequency of postoperative myalgia [12, 22, 35–39]. However, most of these studies did not have sufficiently large subject groups to be able to provide definitive answers.

Methods used to reduce myalgia

Many studies have been performed in order to identify the ideal method of decreasing the incidence of postoperative myalgia. The different methods and their proposed mechanisms of action are discussed below. Of all the methods mentioned, the one that is most commonly used is pretreatment with a nondepolarising neuromuscular blocker. Other less common methods are also reviewed. The majority of these have undergone only limited evaluation and there is insufficient evidence to prove their efficacy.

Stretching exercises

If it is assumed that postoperative myalgia is caused by damage to muscles after fasciculations, stretching exercises may reduce postoperative myalgia. Stretching exercises have been shown to reduce significantly the incidence of both fasciculations and postoperative muscle pains [40]. The muscle stretch receptors are progressively desensitised as the receptor potential adapts under conditions of prolonged slow stretch. Muscles manifest decreased tone after slow stretching. With a reduction in the rate of gamma efferent discharge from the muscle spindles, the excitability of alpha motor neurones is modified. It has been suggested that this may increase the threshold for motor units, thus altering the action of succinylcholine [40, 41]. It is unfortunate that no further studies are available to substantiate the results of the original work, since stretching exercises cost nothing and are safe.

Vitamin C

High doses of vitamin C are beneficial in alleviating the pain and stiffness experienced after unaccustomed exercise. The benefit of vitamin C may be a result of its action in maintaining the endothelial linings of capillaries, thus preventing damage or rupture of muscle fibres, and in promoting the detoxification of metabolites [42]. A reduction in the incidence of postoperative myalgia was shown when vitamin C was given peri-operatively [43]. However, no studies have been performed that compare this relatively safe method with other techniques aimed at reducing the incidence of succinylcholine myalgia.

Dantrolene

The primary event of postoperative myalgia may be the disruption of delicate muscle spindles, since the pain is most severe in those muscles with the greatest spindle density. The transient reduction in serum calcium levels after succinylcholine is closely associated with the subsequent development of muscle pain. It has been postulated that an influx of calcium into the muscle cells enhances the intensity of fasciculations and muscle fibre contractions, thus causing spindle damage and subsequent pain [25]. Thus, drugs that interfere with intracellular calcium release, such as dantrolene, should decrease the incidence of postoperative myalgia. Oral dantrolene has been shown to reduce succinylcholine-induced myalgia. Its specific action in depressing intracellular calcium transfer mechanisms might explain its beneficial actions after succinylcholine, despite the lack of changes in plasma calcium [44]. It has been shown that oral dantrolene as a pretreatment prevented the increase in serum myoglobin produced by succinylcholine administration, and it has been suggested that it might be a useful agent for the reduction of postoperative myalgia [45]. However, a subsequent study [46] failed to demonstrate this with small doses of intravenous dantrolene. This use of dantrolene is also associated with a 10% incidence of postoperative side-effects, comprising weakness, fatigue and dizziness [44].

Calcium gluconate

It has been demonstrated that calcium gluconate pretreatment reduces the incidence of postoperative myalgia. The hypothesis is that it prevents the movement of electrolytes across the cell membrane and its membrane stabilisation action is protective against postoperative myalgia [47]. In contrast, another study showed that calcium was only partly successful in reducing the incidence of myalgia [29]. However, a smaller dose of calcium was used in this study. Giving a small dose of calcium gluconate is usually quite safe, unless it is given in the presence of hypercalcaemia, digitalis toxicity or certain cardiac conditions.

Lidocaine

There is good evidence to support the view that lidocaine is useful in reducing postoperative myalgia. There are minimal side-effects when lidocaine is given in the doses studied ($1.5\ mg.kg^{-1}$). It was first shown in 1967 that it is an effective pretreatment agent [48]. Later studies [49–53], except one [54], supported this finding. In one study, it was shown that lignocaine pretreatment restricted the increase in serum potassium and the decrease in serum calcium. This effect of lignocaine was attributed to its cell membrane stabilising properties, which probably prevented ionic exchange across the cell membrane [50].

Phenytoin

There is limited evidence that phenytoin is effective in decreasing postoperative myalgia. Its suppression of succinylcholine fasciculations at the prejunctional site has been shown *in vitro* [19]. Phenytoin pretreatment significantly reduces postoperative myalgia but no significant correlation has been found between muscle fasciculations and postoperative myalgia. The hypothesis is that phenytoin, by causing a decrease in the influx of calcium ions during depolarisation, either independently or as a consequence of reduced intracellular concentration of sodium ions, may prevent muscle damage [55]. It is not used as a pretreatment agent at present.

Magnesium

Magnesium has been shown to abolish fasciculations [56, 57] and to reduce the increase in potassium [58] following the use of succinylcholine. A bolus dose of magnesium reduces fasciculations after succinylcholine. However, a reduction in fasciculations does not necessarily reduce myalgia. Magnesium sulfate has no place in the prevention of succinylcholine-induced muscle pain at present [59, 60].

Aspirin and nonsteroidal anti-inflammatory drugs

There is some evidence that prostaglandin inhibitors reduce the incidence and severity of succinylcholine-induced myalgia [61]. There may be parallels between the calcium influx seen after succinylcholine and that observed in experimentally induced muscle damage. Lipo-oxygenase products are mediators of calcium-induced intracellular enzyme efflux from skeletal muscle, whereas cyclo-oxygenase products may mediate myalgia. Prostaglandins produce further tissue damage, resulting in more pain and damage. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may interrupt this prostaglandin-mediated destructive cycle and this may provide a rationale for their use in preventing postoperative myalgia [62–64]. A significant reduction in postoperative myalgia was noted with aspirin 600 mg given 1 h before operation [65]. However, results from studies designed to evaluate the effectiveness of NSAIDs in reducing postoperative myalgia have been inconclusive [37, 66].

Chlorpromazine

Chlorpromazine has the ability to inhibit cellular phospholipases, specifically phospholipase A_2, which is activated by increased myoplasmic calcium concentrations [64]. There is some evidence that it is effective in preventing postoperative myalgia [29]. Its effectiveness suggests the involvement of phospholipases in the pathogenesis of succinylcholine-induced muscle damage. The side-effects of chlorpromazine make its use in the prevention of a self-limited phenomenon, such as myalgia, inadvisable.

Diazepam and midazolam

The evidence that benzodiazepines decrease postoperative myalgia is inconclusive. Diazepam has been shown to decrease the incidence and severity of succinylcholine-induced postoperative muscle pains [67–70]. Pretreatment with diazepam inhibits the action of succinylcholine [71]. It is also postulated that the effects of diazepam on pain threshold and its amnesic effect on the timing of the perception of pain might contribute to its ability to decrease the severity of postoperative myalgia [72]. Neither diazepam nor midazolam influenced the incidence or severity of fasciculations seen with succinylcholine or the duration of the neuromuscular block [73]. It has been hypothesised that diazepam may act centrally at the level of the spinal cord to exert its neuromuscular blocking effects [74].

Choice and timing of induction agent

The influence of induction agent and the time between the administration of the induction agent and of succinylcholine on postoperative myalgia has been investigated. The incidence of postoperative myalgia has been shown to be less after methohexitone than after thiopental or thialbarbitone when equipotent doses were used for the induction and maintenance of anaesthesia [75]. In one study, injection of succinylcholine immediately after thiopentone was associated with a lower incidence of myalgia than injection 5 min later [76]. With the knowledge that propofol has antioxidant properties, an ability to form stable radicals and to inhibit propagation of reactions involving free radicals [77, 78], studies to evaluate the incidence and severity of postoperative myalgia after the use of propofol as an induction agent in comparison with thiopental were performed. Induction of anaesthesia with propofol is associated with less myalgia after succinylcholine $1.5\ mg.kg^{-1}$ than when thiopental is used [79, 80]. However, one study showed that neither the induction agent nor the time between the induction agent and succinylcholine administration had any significant influence on the incidence of muscle pain following succinylcholine [81]. In summary, the effect on myalgia of the induction agent and the timing of its administration is still questionable.

Self-taming

Self-taming of succinylcholine-induced muscle fasciculations can be achieved by the administration of a small dose of succinylcholine used as a pretreatment before the subsequent full dose used for neuromuscular blockade for intubation. The taming effect of the pretreatment dose may be attributed to the induction of neuromuscular desensitisation or accommodation. The depolarisation achieved by the subsequent dose of succinylcholine may therefore be enough to produce neuromuscular block

without reaching the threshold necessary for electrical excitation of the nerve terminals and the muscle membrane [82]. Although the incidence and extent of fasciculation after succinylcholine can be decreased by pretreatment with a 10-mg dose of the drug, the self-taming technique seems to offer no advantage in decreasing the occurrence or severity of postoperative myalgia [83].

Dose of succinylcholine

The evidence that there is a relationship between the dose of succinylcholine and postoperative myalgia is limited. It has been shown that there is a tendency for succinylcholine-induced muscle pain to decrease when larger single doses are used and that multiple doses, each given after full recovery from the preceding dose, were likely to increase the probability of the occurrence of pain [23]. Muscle pain is more severe when succinylcholine is administered at a dose of 1.5 $mg.kg^{-1}$ compared with 0.5 $mg.kg^{-1}$ [84]. The severity of postoperative myalgia after succinylcholine did not increase progressively with dose but reached a peak in patients receiving 1.5 $mg.kg^{-1}$. The absence of a progressive dose response for severity of fasciculations associated with succinylcholine suggests that increasing the dose above 1.5 $mg.kg^{-1}$ might reduce the severity of myalgia by producing more synchronous muscle contractions, thereby reducing the shearing forces on muscle spindles. It has been shown that a dose of 3 $mg.kg^{-1}$ provided a better combination of intubating conditions and minimal postoperative myalgia than the two lower doses (0.5 and 1.5 $mg.kg^{-1}$) [85]. However, uncertainty about the effects of the large dose on other side-effects, such as potassium concentrations and intragastric and intraocular pressures, make this an inadvisable method.

Nondepolarising neuromuscular blocking agents

Nondepolarising neuromuscular blockers presumably block prejunctional nicotinic receptors and thus prevent fasciculations, producing a decrease in postoperative myalgia [18–20, 86, 87]. Administration of a small dose of nondepolarising neuromuscular blocker before succinylcholine is commonly practised to lessen the incidence and severity of postoperative myalgia. The timing of the pretreatment agent is important. In order to gain benefit, an optimal pretreatment interval of 3 min has been recommended for many commonly used nondepolarising agents [88–90]. A rapid precurarisation technique using rocuronium, with a pretreatment dose of 0.1 $mg.kg^{-1}$ given 60 s before propofol, was effective in decreasing postoperative myalgia [34].

Nondepolarising neuromuscular blockers can affect the desirable neuromuscular effects of succinylcholine. The mechanism whereby nondepolarising neuromuscular blockers cause resistance to subsequently administered succinylcholine is not entirely clear but the common theory is that the defasciculating dose binds to a number of the cholinergic receptors, thereby preventing succinylcholine from gaining access to them. Thus, this method is not free from problems, such as inadequate conditions for tracheal intubation, which may be hazardous during a rapid induction sequence. This is why a higher dose of succinylcholine (1.5 $mg.kg^{-1}$) is commonly recommended after pretreatment [38, 52, 91–94]. Clinical opinion regarding pretreatment with nondepolarising drugs before succinylcholine has been substantiated by numerous studies. An extensive literature on this subject has been developed, including studies of all the available nondepolarising neuromuscular blockers in a variety of doses (Table 1). These include gallamine, d-tubocurarine, vecuronium, pancuronium, atracurium and rocuronium [29, 35, 36, 38, 52, 74, 92, 95]. In these studies, different doses and pretreatment administration times were studied. Pretreatment time ranged from < 1 min to 4 min. Thus, results are inconsistent and inconclusive.

To summarise the studies in the literature about the efficacy of nondepolarising neuromuscular blockers, as well as other pretreatment regimens, in reducing postoperative myalgia, a meta-analysis of agents that prevent postoperative myalgia was published [51]. All drugs for which four or more studies testing pretreatment efficacy had been published were combined for statistical analysis. Of the 102 papers identified, only 45 fulfilled the criteria for inclusion in the meta-analysis. Four classes of preventive drugs with typical doses were quoted: nondepolarising neuromuscular blockers, i.e. atracurium (3 mg), d-tubocurarine (3 mg), gallamine (10 mg) and pancuronium (1 mg); succinylcholine (10 mg) in self-taming doses; benzodiazepines – diazepam (10 mg); and local anaesthetics – lidocaine (150 mg) were reported in sufficient detail to allow inclusion in the analysis. Succinylcholine in self-taming doses was not effective, all the others significantly decreased the frequency of myalgias by about 30%. An extension of this meta-analysis was performed with Bayesian meta-analysis software [96]. The results of 41

Table 1 Nondepolarising neuromuscular blockers used for pretreatment

Nondepolarising neuromuscular blocker	Dose ($mg.kg^{-1}$)
Atracurium	0.05
Gallamine	0.2
Pancuronium	0.01
Rocuronium	0.05
Tubocurarine	0.05
Vecuronium	0.01

studies used in the first meta-analysis and four studies published since 1989 were pooled. All pretreatments that were shown to be effective in the first meta-analysis were shown to have statistically significant effects in lowering the incidence of myalgia and that, with the available indirect evidence, lidocaine was the best pretreatment to prevent postoperative myalgia.

Rocuronium is a very popular nondepolarising neuromuscular blocker but was not included in Pace's meta-analysis. It seems to be quite effective in reducing postoperative myalgia [94, 97, 98], except in two studies [39, 99] which showed that rocuronium was effective in preventing muscular fasciculations but did not prevent postoperative myalgia. However, in both studies, none of the nondepolarising pretreatment agents used prevented postoperative myalgia, which is contrary to the findings of the majority of myalgia studies.

A few recent studies demonstrate an additive effect in the reduction of succinylcholine-induced myalgia when two pretreatment agents are used together [52, 53, 86]. It has been shown that a combination of d-tubocurarine and lignocaine was more effective in decreasing myalgia than either agent given alone [53]. Similar results were found with a combination of atracurium and lidocaine [52]. More studies need to be carried out to evaluate further the effectiveness of combining pretreatment agents and the possibility of a consequent combination of adverse effects.

Although the use of nondepolarising neuromuscular blocking drugs as pretreatment agents has been shown to be effective and is commonly practised, the fact that some patients may be sensitive to the dose used for defasciculating needs to be taken into account. Although the effects that this these patients experience may not be dangerous, the symptoms of partial neuromuscular blockade can be distressing.

Conclusions

The mechanism by which succinylcholine produces postoperative muscle pain is still not understood fully, although the drug has been in routine clinical use for nearly 40 years. The mechanism of postoperative myalgia may be complex, involving many steps that can be used as clinical targets for different pretreatment agents (Table 2). However, the most effective way to prevent succinylcholine-induced myalgia is to avoid the use of succinylcholine itself. The use of nondepolarising neuromuscular blockers with a rapid onset of action and a short duration of clinical effect for intubation or the use of the laryngeal mask airway to avoid neuromuscular blockade altogether may be reasonable alternatives in the prevention of myalgia in the rapidly growing out-patient population [100–102]. In situations where succinylcholine is used because of its superiority in providing fast and good intubating conditions, clinicians can treat those who are at greatest risk of developing myalgia. Combining two agents may prove to be the most useful method for reducing the incidence of fasciculations and myalgia. The different pretreatment drugs represent different lines of attack on cellular mechanisms, and thus a combination may be a sensible rationale for further decreasing postoperative myalgia.

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Table 2 Postulated mechanisms of action of pretreatment agents

Component in mechanism of postoperative myalgia	Pretreatment agent	Postulated mechanism of action
Neuromuscular junction	Nondepolarising neuromuscular blockers	Prejunctional
	Phenytoin	Prejunctional
	Self-taming	Neuromuscular desensitisation
Muscle fibres, stretch receptors	Stretching exercises	Desensitisation of stretch receptors
	Vitamin C	Prevents damage to muscle fibres
Cell membrane, intracellular calcium mechanisms	Lidocaine	Cell membrane stabilisation
	Calcium gluconate	Cell membrane stabilisation
	Dantrolene	Interferes with intracellular calcium transfer
Fasciculations	Dose of suxamethonium	Synchronicity of muscle contractions
	Magnesium	Abolishes fasciculations
Muscle damage	Aspirin/nonsteroidal anti-inflammatory drugs	Interrupt prostaglandin-mediated destructive cycle
	Chlorpromazine	Inhibits cellular phospholipases

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