The quest for the origin and prevention of postoperative myalgia following succinylcholine : new insights in an old problem

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The quest for the origin and prevention of
postoperative myalgia following succinylcholine.

New insights in an old problem

The quest for the origin and prevention of postoperative myalgia following succinylcholine.

New insights in an old problem

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Universiteit Maastricht op gezag van de
Rector Magnificus,
Prof. mr. G.P.M.F. Mols
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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door

JAN-UWE SCHREIBER

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Promotores

Prof. dr. M. van Kleef

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Chapter 1

Introduction

Since the introduction of curare into clinical practice by Griffith and Johnson [1] the use of neuromuscular blockers has become an essential part in clinical anaesthesia. Originally, these agents were used to improve surgical conditions in different settings due to muscle relaxation with less requirements for (mostly) inhalative anaesthetics. In anaesthesia, neuromuscular blocking agents might be useful because they may improve the conditions for endotracheal intubation and, thus, may reduce the incidence of intubation related morbidity [2].

In 1952, a few years after the introduction of curare, which was the first non-depolarizing neuromuscular agent in anaesthesia, succinylcholine was introduced [3].

Due to its unique pharmacological properties succinylcholine has become a widely used agent in the field of anaesthesia. Succinylcholine is a quaternary, depolarizing muscle relaxant that affects skeletal muscles. The substance has been first described in 1906 by Hunt and Taveau. However, the neuromuscular effects of the compound have been demonstrated for the first time by Bovet in 1949 [4].

Pharmacologically, the compound activates the nicotinic acetylcholine receptors at the neuromuscular junction and, thus, initiates a muscular response. The paralyzing effect occurs due to over stimulation of the receptor and has been described in detail elsewhere. The agent has an rapid on- and offset of action.[5] Over the years succinylcholine has become the drug of choice in clinical situations, where a rapid and complete relaxation of the patient following induction of anaesthesia is wanted; especially to facilitate optimal conditions for endotracheal intubation. Such situations may occur in emergency patients, who have an increased risk for the aspiration of gastric content. A dedicated technique to prevent patients from aspiration following an emergency induction is widely known as ‘rapid sequence induction’ (RSI) that can be described as follows: after applying pure oxygen to the patient over several minutes via face mask and optional administration of an analgesic an adequate dose of an hypnotic agent is injected followed by succinylcholine immediately after loss of eye lash reflex. No manual ventilation by mask should be performed between loss of consciousness and endotracheal intubation. Due to the rapid onset of succinylcholine the performing anaesthesiologist can expect optimal intubation conditions within 60 to 75 seconds after injecting the agent [6]. Furthermore, it is still a popular drug in ambulatory anaesthesia and day case procedures when a short duration of action is wanted [7].

Due to its depolarizing effect, succinylcholine has several undesirable effects. Some of them are possibly life threatening or may cause serious complications such as malignant hyperthermia, bradycardia, cardiac arrest, increase of intra-gastric or intraocular pressure [8]. Others may cause discomfort to the patient (and also to the treating anaesthesiologist). Two of the most frequent side effects associated with succinylcholine are fasciculations and postoperative myalgia. Clinically, fasciculations appear immediately after injection of the drug and might be best described as uncoordinated generalized muscular contractions of various intensity. Postoperative myalgia can be described as muscular stiffness and pain that is comparable to muscular soreness following unaccustomed muscular stress. Succinylcholine-associated pain and stiffness can last for up to one week. The incidence varies from 1.5 to 90% with different grades in pain perception [9]. In specific patient populations such as morbidly obese patients succinylcholine-associated myalgia has been associated to increase the postoperative morbidity [10].

Postoperative myalgia as a succinylcholine-related adverse effect has been described by Churchill-Davidson for the first time in 1952 even shortly after the clinical introduction of succinylcholine. Furthermore, he was the first who investigated the effects of a pretreatment with the non-depolarizing neuromuscular blocker gallamine prior to succinylcholine to avoid succinylcholine-associated myalgia and fasciculations [11].

In the following 50 years a huge number of studies on the effect of various compounds and strategies in the prevention of succinylcholine-associated myalgia were done. These studies investigated pharmacological strategies as well as physical methods such as stretch exercises. Pharmacological interventions included compounds with direct effects on the neuromuscular junction or central nervous effects such as small doses of different non-depolarizing neuromuscular blocking agents, magnesium, diazepam, lidocaine, dantrolene, and succinylcholine itself in a small precursor dose. Further trials tested calciumgluconate, vitamin C, chlorpromazine, and NSAID [9]. However, none of the tested interventions was found to be completely reliable in the prophylaxis of succinylcholine-associated myalgia and some trials ended with inconclusive results. One of the main problems in finding an optimal pretreatment in the prevention of succinylcholine-associated myalgia is the fact that the pathogenesis of this adverse effect is still unknown and it was suggested very early that this might be multifactorial. Firstly, Myalgia has been attributed to muscle damage produced by shearing forces with upcoming fasciculations during depolarization. Sec-

ondly, fibre rupture may occur as well as microdamage of muscle cells. Succinylcholine-induced fasciculations may induce an increase of chemical markers such as serum creatine kinase, potassium and myoglobin [12,13] and it has been hypothesized that the activation of prejunctional nicotinic acetylcholine receptors due to succinylcholine and the following repetitive firing and antidromic discharge might be the reason for fasciculations. Therefore, several investigators tried to find a correlation between succinylcholine-induced fasciculations, increase in biochemical markers, and postoperative myalgia but none of the performed studies could find a clear relationship between these three issues [14-17].

Methods used for the prevention of succinylcholine-associated myalgia

Non-depolarizing neuromuscular blockers are supposed to inhibit the activation of prejunctional nicotinic acetylcholine receptors. Most of the currently available non-depolarizing neuromuscular blockers have been tested on their effect in preventing succinylcholine-associated myalgia. A very popular technique called ‘precurarization’ has been used by several investigators. With this technique a small dose of a non-depolarizing neuromuscular blocker will be administered prior to succinylcholine at the beginning of induction. Most of the trials found that this technique may reduce the incidence of fasciculation and myalgia to some extent. However, these drugs may have side effects due to their paralyzing effect that may cause serious adverse events [18].

Lidocaine and phenytoine are sodium channel blockers with cell membrane stabilising properties that might reduce both, fasciculations and myalgia. Lidocaine has been firstly described as a pretreatment agent in 1967 by Usubiaga and co-workers [19]. It also inhibits the increase of serum potassium and the decrease of serum calcium which may occur following the administration of succinylcholine. Unfortunately, the preventive effect of sodium channel blockers was not observed by all investigators [13].

Benzodiazepines are sedatives that also may have muscle relaxing effects due to their central nervous mechanism of action. It has been hypothesized that these are located on the level of the spinal chord [20]. Furthermore, amnesic effects of benzodiazepines may have an influence on pain perception and, thus, can also decrease the perception of myalgia. However, data about the effect of benzodiazepines on myalgia have remained inconclusive.

In 1987 Naguib and colleagues published one of the first studies on the preventive effect of aspirin on succinylcholine-associated myalgia with promising results [21]. Aspirin as well as other non-steroidal antiinflammatory drugs inhibit the prostaglandin synthesis. Prostaglandins are playing an important role in pain mediation and inflammation-related tissue damage. Therefore, the use of these compounds to prevent succinylcholine-associated myalgia was supposed to be a rationale. But these findings could not be confirmed in further studies by all investigators. Furthermore, aspirin and non-steroidal antiinflammatory drugs do have inhibiting effects onto haemostasis and, thus, may increase the risk of perioperative blood loss.

Dantrolene inhibits the intracellular calcium release in muscle cells and has become the agent of choice in the treatment of malignant hyperthermia. It has been suggested that a lack of serum calcium may play an important role in the development of myalgia. Thus, dantrolene should avoid an additional influx of calcium into the muscle cells. While oral dantrolene was tested successfully on the prevention of postoperative myalgia intravenous dantrolene failed in decreasing the incidence. Furthermore, dantrolene may cause postoperative side effects such as weakness, fatigue, and dizziness.

Succinylcholine itself has also been tested to prevent myalgia in various trials. A technique known as 'self-taming' uses a small dose of succinylcholine prior to the main dose. Other studies have tested the effect of high-dose succinylcholine during induction of anaesthesia.

A first approach to bundle the knowledge on the prevention of succinylcholine-associated fasciculations and myalgia was made with a meta-analysis on different pretreatments published by Pace in 1990 [22]. According to his results diazepam, lidocaine, and various non-depolarizing neuromuscular blocking agents such as atracurium, pancuronium, d-tubocurarine, and gallamine were effective in reducing the incidence of postoperative myalgia by about 30%.

In the 1990s new non-depolarizing neuromuscular blockers (rocuronium, mivacurium, cisatracurium) were introduced into clinical practice. Meanwhile, all of these drugs have been tested on their effect in preventing postoperative myalgia. Furthermore, more recent studies found that the concept of 'precurarization' and the avoidance of succinylcholine itself could not reduce the incidence of myalgia in ambulatory patients [23,24].

Even more than 50 years after the introduction of succinylcholine there is still a lack of knowledge about the pathogenesis of postoperative myalgia, an optimal pretreatment to avoid this undesirable adverse effect, and possible side effects of

the various pretreatment strategies. Therefore, the aim of this thesis was to give some new insights in the problem of myalgia and to find answers on the following research questions:

Is succinylcholine a suitable drug for ambulatory anaesthesia in comparison to a modern non-depolarizing neuromuscular blocking agent (i.e. rocuronium) with respect to postoperative myalgia?

Does succinylcholine-associated myalgia have an inflammatory origin and can it be avoided through the preoperative use of a glucocorticoid?

Is pain due to 'precurarization' with rocuronium an issue and are there gender related differences?

What is the optimal intervention to prevent succinylcholine-associated myalgia according to current standards in evidence-based medicine?

Is a pretreatment with a selective cyclooxygenase-2 inhibitor effective in reducing the incidence of succinylcholine-associated myalgia?

In chapter II, this thesis provides a general overview about the 'state of the art' in using neuromuscular blocking agents and neuromuscular monitoring. In chapter III the first research question is discussed in a randomized controlled trial that was performed in ambulatory patients at the University Hospital of the Saarland, Homburg, Germany. Chapter IV contains a randomized controlled trial that investigates a possible inflammatory component of succinylcholine-associated myalgia with a laboratory and a clinical approach. The question of rocuronium-associated pain following a 'precurarization' dose of this compound is discussed in chapter V. To the aim of an evidence-based approach in finding an optimal pretreatment on succinylcholine-associated myalgia a meta-analysis of randomized controlled trials was performed in co-operation with the Division of Anaesthesia at Geneva University Hospitals and the Department of Anaesthesia and Critical Care at the University Hospital of Nancy-Brabois. The results can be found in chapter VI. Finally, the effect of the selective cyclooxygenase-2 inhibitor parecoxib on postoperative myalgia was tested in a randomized controlled trial. The findings of this trial are discussed in chapter VII.

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Chapter 2

Neuromuscular blocking agents and monitoring: state of the art

Jan-Uwe Schreiber, Thomas Fuchs-Buder, Claude Meistelman

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Requirements on neuromuscular blocking agents.

The primary aims for the use of neuromuscular blocking agents during a general anaesthesia are twofold. Besides optimizing the surgical conditions during procedures where a relaxation of the skeletal muscles is required muscle relaxation may improve the intubation conditions for the anaesthesiologist and, thus, may reduce the incidence of postoperative laryngeal and pharyngeal trauma associated with endotracheal intubation [1]. The use of neuromuscular blocking agents requires a sufficient depth of anaesthesia and can not replace an insufficient administration of anaesthetics and analgesics. The ideal neuromuscular blocking agent should have a rapid onset with a reliable duration of action and recovery. Furthermore, it is desirable that the agent does have a profile that includes no drug-related adverse effects, a low anaphylactic potential, and no interaction with other compounds. None of the currently available neuromuscular blockers fulfils these requirements completely.

Pharmacology

The main effect side of all neuromuscular blocking agents is the acetylcholine receptors of the neuromuscular junction. These are situated in opposition to the acetylcholine storage vesicles of the presynaptic membrane. The acetylcholine receptor contains five subunits (2 alpha, beta, delta, and epsilon) and has the shape of a channel in form of a rosette. The channel works in accordance to the “all or nothing” principle and opens if acetylcholine or another depolarizing agent (succinylcholine) activates the two alpha-subunits. The opening is caused by an allosteric change of shape of the receptor which is now penetrable for sodium and potassium cations. If a sufficient count of receptors has been opened by acetylcholine a contraction of the skeletal muscle occurs after reaching the threshold. Subsequently, acetylcholine releases from the receptor and will be metabolized into acetate and choline. The channel closes for repolarisation (figure 1).

Thus, there are two different pharmacological options to avoid that threshold potential may be reached which results in a muscular contraction: Pharmacological block of the alpha-subunits of the receptor (non-depolarizing block). The agent competes against acetylcholine for the subunits. The opening of the channel can be avoided if one of the alpha-subunits has been blocked against acetylcholine. Basically, non-depolarizing neuromuscular blocking

agents can be antagonised with cholinesterase inhibitors or, in case of aminosteroid relaxants, also with the cyclodextrin sugammadex.

Pharmacological stimulation of the receptor with an agonist of the α -subunits that imitates the effect of acetylcholine and avoids re-polarisation of the muscle cell due to its persistent presence at the neuromuscular junction (depolarizing block). This is the mechanism of action of succinylcholine. All other neuromuscular blocking agents that are currently in use are non-depolarizing neuromuscular blockers. In contrary to a non-depolarizing block it is not possible to reverse a depolarizing block with choline esterase inhibitors or sugammadex.

Figure 1. Schematic illustration of the neuromuscular junction (1=axon, 2=synapse, 3=vesicle containing acetylcholine, 4=acetylcholine receptor, 5=mitochondrium)

With the exception of mivacurium redistribution terminates the relaxing effect of the drugs at first order. Further metabolism occurs due to specific profile of the compound with involvement of organ dependent metabolism or not.

The pre-ganglia neurons of the autonomic nerve system are cholinergic and contain nicotinic acetylcholine receptors (as well as the skeletal muscles). Furthermore, the post-ganglia neurons of the parasympathic system are cholinergic but these are muscarinic receptors. Among others the clinical impact of hemodynamic side effects of the different neuromuscular blocking agents

depends on the affinity of the single compounds on nicotinic and muscarinic acetylcholine receptors. The proportion of the blocking effect on ganglia compared to the neuromuscular blocking effect is known as the autonomic margin of safety. An increasing margin describes a lower probability of an autonomic block. Hemodynamic side effects from neuromuscular blocking agents might be also caused by a decreased nor-epinephrine re-uptake (i.e. pancuronium) or by histamine release.

Definitions for the characterization of neuromuscular blocking agents

The potency of the neuromuscular blocking effect of a single agent can be defined with the so called *ED95*. The *ED95* represents the dose of a neuromuscular blocking agent in mg kg^{-1} or $\mu\text{g kg}^{-1}$ which causes a 95% blockade of the neuromuscular receptors. Commonly, a dose twice the *ED95* has been accepted as an adequate dose for endotracheal intubation.

The *onset time* has been defined as the time between the administration of a neuromuscular blocking agent and its peak effect. The *clinical duration* (*DUR25*) describes the time in minutes between injection of the agent and the reversal of the then occurring block up to 25% of normal values. In this period the relaxation should be sufficient for most of the surgical procedures. The term has been also used in the description of the different agents regarding their classification in ultra short (*DUR25* < 15 min), short (*DUR25* < 25 min), medium (*DUR25* 20-50 min), and long (*DUR25* > 50 min) duration of action, respectively. Analogous, the *DUR95* represents the time for a 95% reversal of the block. The latter times depend directly from the initial dose that was administered.

The *recovery index* describes the time between a recovery of 25% and 75% from the neuromuscular block. In contrast to the *DUR25* and *DUR95* the recovery index is more likely to be a variable that is independent from the administered dose.

The *Train-of-four-Ratio (TOF-Ratio)* specifies the proportion of the fourth response compared to the first response. This technique of neuromuscular monitoring will be described in detail in the part “Neuromuscular monitoring” of this article. The TOF-Ratio provides information about the neuromuscular recovery and a possible residual curarization. In this context a TOF-Ratio < 0.6 represents a profound and a TOF-Ratio between 0.7 and 0.9 a minimal residual

block, respectively. Sufficient neuromuscular recovery has been reached with a TOF-Ratio of 0.9 (ideally 1.0).

Profound residual curarization (TOF < 0.6) Although this grade of residual paralysis can not be detected through clinical signs or with a simple neuromuscular monitoring device there might be a significant impact on ventilatory parameters such as forced vital capacity, pharyngeal function, integrity of the upper airway, and hypoxic ventilatory response. Tidal volume and breathing frequency can be expected within normal ranges.

Minimal residual curarization (TOF-Ratio 0.7 – 0.9) At this grade of neuromuscular recovery forced vital capacity, expiratory flow, and hypoxic ventilatory response have reached the ranges as equal as prior to the neuromuscular blockade. However, there is still a dysfunction of the upper airway with a decreased inspiratory airflow, difficulty in swallowing, decrease volume of the upper airway, and dysfunction of the airway dilating musculus genioglossus. Thus, an increased risk for pulmonary aspiration in the extubated patient should be taken into account. Therefore, a TOF-Ratio < 0.9 does not represent a sufficient recovery of the integrity of the upper airway and the respiratory function.

Margin of safety of neuromuscular transmission. This term describes the percentage of acetylcholine receptors that has to be covered by a neuromuscular blocking agent to detect first clinical signs of muscular weakness. Commonly, this percentage is around 70 – 75%. Thus, several clinical consequences appear for onset, repetitive administration, and neuromuscular recovery. Typically, a twofold ED₉₅ is administered for endotracheal intubation. This dose makes sure that the margin of safety of neuromuscular transmission will be bridged rapidly and reliably. In case of an intraoperative necessity for a repetition normally 25% of the initial intubation dose of a neuromuscular blocking agent is adequate to restore a complete neuromuscular block because the major percentage of receptors is still covered by the blocking agent at this time. This effect also explains the comparably long effect of the short-acting mivacurium whether this compound is used for the enhancement of a pancuronium-induced block. The effect-side profile of pancuronium dominates the neuromuscular block at the majority of receptors.

Furthermore, there are clinical consequences in neuromuscular recovery. Situations with 25 – 30% of not-covered receptors can not be detected reliably with common qualitative stimulation patterns (Train of four or Double-burst stimulation) or with clinical signs. At this time no margin of safety exists and

small changes in the relation between acetylcholine and the blocking agent at the neuromuscular junction may lead to a significant blockade again. In this context it was found that small doses of magnesium - which are normally without any neuromuscular effect - may cause a clinically relevant recurarization. Magnesium inhibits the pre-synaptic acetylcholine release and, thus, may interact with the proportions of acetylcholine and the compound. Similar effects can be observed with aminoglycosid antibiotics and calcium channel inhibitors [2]. Consequently, this effect might be harmful for extubated patients in the early postoperative period (figure 2).

Figure 2. Neuromuscular recovery following vecuronium injection (1) and recurarization after injection of magnesium (2).

Depolarizing agents – succinylcholine

Mechanism and indication. Succinylcholine is the only depolarizing neuromuscular blocking agent that is currently used by clinicians. Moreover, it is the oldest neuromuscular blocking agent that is currently available; succinylcholine was introduced into clinical practice in 1952. Due to its pharmacological properties with a rapid onset and a short duration of action this agent is still unique. The ED₉₅ has been described with 0.3 mg kg⁻¹ [3]; to facilitate endotracheal intubation a three- to fivefold ED₉₅ (1 – 1.5 mg kg⁻¹) is commonly used. Optimal intubation conditions can be achieved within 45 – 60 s in 90% of all patients following this dosage. The duration of action is 9 to 12 minutes until a complete recovery has been accomplished. Spontaneous breathing of the patient returns gradually after 5 minutes. A repetitive administration within a short period may cause a prolonged duration of action due to a so called phase-2-block (or dual block). It has been suggested that the cause might be an additional blockade of pre-synaptic acetylcholine receptors. Contrary to a depolariz-

ing block the phase-2-block is suitable for antagonising with cholinesterase inhibitors.

Due to its pharmacological profile succinylcholine has been the agent of choice in short during procedures for a long time and it is still the most commonly used neuromuscular blocker for the 'rapid sequence induction'.

Side effects. Succinylcholine has been commonly associated with huge variety of side effects. In 1996 the German Society for Anesthesia and Critical Care published an advise that succinylcholine should be avoided in children undergoing elective surgery [4]. In 2002 adult patients were also included in this recommendation [5]. Succinylcholine is one of the drugs that may trigger a malignant hyperthermia and has to be avoided in patients with a known disposition. Due to activation of nicotinic and muscarinic acetylcholine receptors the agent may cause severe cardiac arrhythmias especially in children that may also include bradycardia and cardiac arrest. Therefore, it has been recommended to administer a small dose of a vagolytic agent in children prior to succinylcholine. Furthermore, an increasing intraocular and intragastric pressure as well as post-operative myalgia can be observed following succinylcholine.

Rhabdomyolysis and hyperkalemia must be seen as severe and life-threatening complications. These may occur more frequently in immobilized patients, patients with major burns, denervation, and several days after major trauma. It has been suggested that these adverse effects are caused by peri- and extrajunctional acetylcholine receptors which has been newly constituted in those patients. These new receptors are being consistent with embryonal acetylcholine receptors and are different from the adult form due to one subunit. Furthermore, the newly constituted receptors do provide a prolonged channel opening and, consequently a potassium efflux from the myocyte that is increased twofold. Thus, an up-regulation on the sensitivity to succinylcholine might appear within 3 to 5 days in patients who suffer from the mentioned conditions. Therefore, succinylcholine should be absolutely avoided in those patients.

Degradation of succinylcholine occurs through plasmatic cholinesterase. In case of a genetic variation the effect of succinylcholine can be prolonged for hours. Activity of this cholinesterase might be also reduced in patients with hepatic diseases, cytotoxic therapy, during pregnancy, and undergoing cardiopulmonary bypass.

Non-depolarizing agents

Non-depolarizing neuromuscular blockers are commonly quaternary ammonium molecules. The compounds can be grouped into aminosteroids (i.e. rocuronium, pancuronium, vecuronium) and benzylisoquinolines (i.e. atracurium, cisatracurium, mivacurium) [6]. Alcuronium, doxacurium, and pipecuronium are not frequently used or no longer available and, thus, will not be part of this review.

Pancuronium

Pancuronium was introduced into clinical practice in 1967. Therefore, it is one of the oldest non-depolarizing agents available. The agent represents the group of neuromuscular blockers with a long duration of action. The single ED₉₅ has been described as 0.06 – 0.07 mg kg⁻¹ bodyweight. If a dose of 0.15 mg kg⁻¹ was used for intubation a DUR₂₅ of 100 min and a DUR₉₅ of 150 min should be expected. The onset time with this dose will be around 3 minutes. Pancuronium is degraded mainly through hepatic metabolism and renal elimination. Biliary metabolism is of minor importance. The agent does not cause any histamine liberation. Impairments of the mentioned organs systems may cause a delay in metabolism and a prolonged effect. Pancuronium interacts with the norepinephrine re-uptake which consequently may result in tachycardia and increasing blood pressure. Pancuronium was also accused to increase the risk of postoperative pulmonary complications following surgery of long duration [7]. This might be related to an insufficient neuromuscular recovery following repetitive administrations of pancuronium [8].

Due to its lack of controllability even after repetitive administration pancuronium does not have a place in “fast-track surgery”. The agent might be an alternative for long-during procedures that require a sufficient neuromuscular block. Patients should be scheduled for a postoperative ventilator therapy then.

Vecuronium

Vecuronium was introduced in the 1980s. It is an aminosteroid with an intermediate duration of action. Contrary to other neuromuscular blocking agents this agent is basically available as a powder for the preparation of a solution

with saline and does not require being stored at 8-10° C. Therefore, vecuronium is a suitable agent for disaster and emergency services. The ED95 of vecuronium is 0.05 mg kg⁻¹. The DUR25 has been described with 30 min and the DUR95 with 50 min, respectively. Following a twofold ED95 the onset time will be around 2.5 min and the recovery index 13 min, respectively [6]. Even higher doses of vecuronium do not cause histamine liberation or sympathetic activation. Thus, Vecuronium offers a good hemodynamic stability. Degradation of vecuronium occurs mainly due to hepatic metabolism; a minor part is eliminated by the kidneys. Vecuronium is metabolized into three different metabolites. One of them, 3-OH-vecuronium, has neuromuscular blocking properties with a potency of 80% of vecuronium. Without any impairment in organ function 3-OH-vecuronium does not reach clinically relevant concentrations. In case of an impaired renal or hepatic function the duration of a neuromuscular block might be prolonged.

Due to a lack of hemodynamic effects vecuronium still does have its place into clinical practice if hemodynamic stability is wanted during anaesthesia.

Rocuronium

The chemical structure of rocuronium that was introduced into clinical practice in 1994 is comparable with vecuronium. The ED95 of rocuronium has been described as 0.3 mg kg⁻¹. The potency of the neuromuscular blocking effect is fivefold less in comparison to vecuronium; even the distribution volume of rocuronium is smaller [6]. These pharmacological properties allow a faster onset. The higher dose leads to an increased concentration of rocuronium molecules at the neuromuscular gap. The onset time following an intubation dose (i.e. 0.6 mg kg⁻¹) varies in dependence of the evaluation technique between 60 and 150 seconds. However, even using a two- to threefold ED95 may produce acceptable or excellent intubation conditions after 60 seconds in up to 90% of the patients [9].

Reducing the intubation dose to 0.4 mg kg⁻¹ leads to an increased onset time (i.e. 3 min) and to a decreased clinical duration (i.e. 20 min), respectively. Therefore, rocuronium might be an agent with a relatively short duration of action in case of a dose reduction [10].

Following an intubation dose of rocuronium both the DUR25 and the DUR95 are comparable to vecuronium. Its primary metabolism is hepatic and biliary; even a small part undergoes renal elimination. No active metabolites are

produced during degradation. An increase of heart frequency and blood pressure might be observed following higher dosages of rocuronium. These effects like to be vagolytic due to a lack of increased histamine plasma concentrations. The fastest onset in comparison to all other non-depolarizing neuromuscular blockers is the most outstanding property of rocuronium. Furthermore, rocuronium offers hemodynamic stability and a lack of histamine liberation. Due to its specific pharmacological properties rocuronium can be taken as an alternative agent for the 'rapid sequence induction' in case of contraindications against succinylcholine. When using a reduced dosage rocuronium offers a comparatively short duration of action.

Atracurium

Atracurium is a non-depolarizing neuromuscular blocker that belongs to the group of benzyloquinolines. As vecuronium atracurium was introduced into clinical practice in the early 1980s. It is also a neuromuscular blocker with an intermediate duration of action with an ED₉₅ of 0.25 mg kg⁻¹. If the intubation dose was used an onset time of 3 to 4 minutes should be taken into account. Then, the clinical duration is around 35 minutes; the recovery index is between 12 and 15 minutes. Mainly, atracurium is degraded organ independently by Hoffmann elimination and ester hydrolysis via unspecific esterases [6]. The Hoffmann reaction is a chemical reaction that occurs spontaneously under physiological conditions. One of the products from degradation is laudanosine which was potentially neurotoxic in animal studies. However, induction of seizures in animals required doses that can not be matched if common clinical doses of atracurium are used. In addition, laudanosine induces vasodilatation. Laudanosine is eliminated via the kidney. Therefore, laudanosine potentially may cumulate in case of renal insufficiency.

Through direct interaction with mast cells atracurium can induce histamine liberation. This may lead to a decrease in blood pressure, tachycardia, and generalized erythema. These adverse effects occur in particular following rapid injection and increased dosage.

Cisatracurium

Cisatracurium is one of the ten stereo isomers of atracurium. It was introduced into clinical practice as 1R-cis,1'Rcisatracurium in 1996. The agent is four to five times more potent in its neuromuscular blocking effects than atracurium. Therefore, the ED₉₅ is 0.05 mg kg⁻¹. The onset time after an intubation dose has been described as long as 3 to 5 minutes, the DUR₂₅ as 45 minutes, and the recovery index as 15 minutes, respectively [6].

Degradation of cisatracurium occurs solely through Hoffmann reaction. In comparison to atracurium less laudanosine arises after degradation. Also histamine liberation is significantly reduced which means that there are no histamine associated symptoms even after rapid injection or high doses of cisatracurium. The hemodynamic stability has been improved when compared to atracurium.

The main advantage of atracurium and cisatracurium is the more or less organ independently degradation that results in a low risk of accumulation. Both agents are suitable for continuous infusion. Basically, the problem of direct induced histamine liberation following atracurium does not appear after cisatracurium. A drawback might be the onset time that is quite longer than those of rocuronium. Therefore, cisatracurium and atracurium are no suitable drugs for use during a 'rapid sequence induction'.

Mivacurium

Mivacurium is the most recent agent from the group of benzylisoquinolines. It has received its approval for clinical use in 1996 from the German authorities. The compound is a mixture of three different isomers, predominantly of the cis-trans and the trans-trans isomer (around 96%) which are responsible for relaxing properties. The molecule is degraded and inactivated by plasmatic cholinesterase. It has been already mentioned that the primary termination of the neuromuscular effects does not depend on redistribution but on metabolism which is contrary to other non-depolarizing neuromuscular blocking agents. The metabolites are neither toxic nor does they have muscle relaxing effects. In case of a genetic variation that results in an atypical plasmatic cholinesterase a prolongation of the duration of action up to 15 to 30 minutes may occur in patients with an heterozygous form. If the homozygous form is present (incidence 1 over 3000) the clinical effects of mivacurium may last for hours. In

patients with terminal renal failure or impaired liver function the concentration of plasmatic cholinesterase might be decreased which may result in a prolongation of action.

Mivacurium has been classified as a muscle relaxant with a short duration of action. The estimated ED₉₅ is 0.08 mg kg⁻¹. A dose of at least 0.2 mg kg⁻¹ (2.5*ED₉₅) should be used to reach good or excellent intubation conditions in most of the patients after 2 to 3 minutes [6]. Several authors have recommended the usage of higher doses (3*ED₉₅) for induction. The DUR₂₅ following an induction dose (2.5*ED₉₅) is between 20 to 25 minutes. The recovery index was estimated with 5 to 10 minutes independently from the technique of administration (bolus or continuous). Regarding these characteristics mivacurium should be an appropriate drug for continuous infusion with a dose of 4 - 6 µg kg⁻¹ min⁻¹ to maintain a sufficient block. However, infusion requirements may vary widely (4 - 20 µg kg⁻¹ min⁻¹). Thus, continuous neuromuscular monitoring is recommended for an optimal maintenance.

Similar to atracurium rapid injection of higher doses of mivacurium may induce a relevant histamine liberation that results in tachycardia, hypotension, and erythema.

Mivacurium has become a successor of succinylcholine in elective patients who are scheduled for surgical procedures of short duration. The agent offers an excellent controllability. Therefore, mivacurium is the ideal agent for continuous infusion. The main disadvantages of the compound are the prolonged onset time and potential histamine liberation.

Neuromuscular monitoring

In a recent survey covering 12 anaesthesia departments in the UK Grayling and Sweeney revealed that around 10% of anaesthetists applied routinely neuromuscular monitoring and more than 60% never used such a monitor. Moreover, these authors stated that there was an “apparent overall confusion among clinicians as to be the best method to confirm recovery from neuromuscular blockade”. In addition, they found limited knowledge regarding the minimum train-of-four ratio which should be observed prior to extubation and insufficient reliance upon the use of quantitative monitors [11]. Similar results are reported in Germany, where a recently published nation wide survey showed that in around 18% of the anaesthesia departments only neuromuscular monitoring was routinely applied [12].

In view of these disappointing results current standards need to be reassessed in the light of recent improvements in neuromuscular monitoring. In the first part of the following article we will present an update of the basic considerations on neuromuscular monitoring. The second part will focus on current developments and ongoing discussions in that area.

Basic considerations

Nerve stimulation

Using nerve stimulation as an indicator for a neuromuscular block has been described in 1941 by Harvey and Masland for the first time [13]. In 1958 Christie and Churchill-Davidson presented the first device for the estimation of a neuromuscular blockade in a clinical setting [14]. The basic principles of neuromuscular monitoring have not been changed since the clinical introduction of neuromuscular monitoring devices. Stimulating a peripheral motor nerve with an electric impulse results in a muscular response following the all-or-nothing principle. The force and intensity of the response depends upon the count of activated muscular fibres. In case of a sufficient stimulating intensity all fibers of the innervated muscle should contract and a response at a maximum level should result. At this level, an additional increase of stimulating intensity will not lead to an increase of the muscular response. For clinical application of neuromuscular monitoring it is widely recommended to use an electrical stimulus that is 15-20 % above the level of maximum muscular response, i.e. a supramaximal stimulus [15]. This is to ensure that factors, such as variability in skin impedance, do not have a significant influence on the muscular response and, therefore, on the quality of measurement.

Stimulating electrodes

Even the preparation and the placement of the stimulating electrodes may have an influence on neuromuscular monitoring. Before placing the electrodes the skin should be cleaned with an alcoholic solution and rubbed afterwards. The electrodes should be placed correctly at the site to ensure that the current stimulates the target nerve in an appropriate way. It is less important whether Ag/AgCl ECG electrodes or special neuromuscular monitoring electrodes are intended for use. When using ECG electrodes the distance between the two electrodes should be less than 6 cm. Moreover, it is recommended to place the

negative electrode at the distal site [16]. To avoid interrogation of the measurement, through hypothermia-related increase of skin impedance, skin temperature should be maintained at 32° C.

Sites of nerve stimulation

Choosing the site of neuromuscular monitoring depends on several factors. Firstly, the site should allow easy access. Secondly, interrogation through other nerve-muscle units should be avoided, and, thirdly, it is recommended to choose a nerve-muscle-unit that allows a quantitative monitoring. The most common used nerve-muscle-unit for neuromuscular monitoring is the N. ulnaris with the M. adductor pollicis as the responding muscle. The distal stimulating electrodes should be placed at the Sulcus ulnaris, while the second electrode can be situated 3-5 cm proximal of this site. In case of quantitative accelerographic monitoring the probe can be placed at the tip of the thumb. For optimal results in quantitative monitoring the four other fingers should be fixed. It might be also helpful to use an arm cast as well as a special thumb adapter.

A couple of surgical procedures do not allow free access to the arms of a patient, e.g. during ENT surgery or if the patient is situated in a prone position. For the last setting the use of N. tibialis posterior/M. flexor hallucis brevis nerve-muscle-unit might be an alternative. The electrodes have to be placed next to the medial malleolus. For accelerographic quantitative measurement the probe of the device can be fixed at the plantar tip of the big toe. It has been shown that quantitative measurement of neuromuscular recovery at this site does not differ significantly from measurements at the N. ulnaris/M. adductor pollicis [17]. However, the estimation of the neuromuscular response might be interfered by flexion of the foot sole through additional stimulation of the plantar muscles.

Another option for neuromuscular stimulation is the N. facialis. The indicating muscles are then either the M. orbicularis oculi or the M. corrugator supercilii [18]. Moreover, the required current intensity at the N. facialis seems to be less compared to the other sites of stimulation. When using the M. corrugator supercilii or the M. orbicularis oculi as indicators for neuromuscular response it is important to remind that even the mimic muscles may interfere with the measurement. The accelerographic probe tip should take place either just above the medial part (M. corrugator supercilii) or at the lateral part below the eyebrow (M. orbicularis oculi).

Muscle groups differ in onset, offset and peak effect of neuromuscular blocking agents. Therefore, monitoring of one nerve-muscle-unit can only provide limited information about other major muscle groups. It is important to choose the monitored nerve-muscle-unit dependently from the goal of observation. It would be appropriate to use the N. facialis/M. corrugator supercilii for monitoring optimal intubation conditions or paralysis of the diaphragm and the abdominal wall muscles following neuromuscular blocking agents whereas the N. ulnaris/M. adductor pollicis would be the better choice if information about the pharyngeal recovery is wanted [18].

Stimulation patterns

Clinically used stimulation patterns are the single twitch stimulation, the Train-of-four stimulation (TOF), the tetanic stimulation, the Post-tetanic count stimulation (PTC), and the Double-burst stimulation (DBS) (table 1). Independently from the type, the characteristics of pulse wave form and duration are the same in all stimulation patterns. A monophasic impulse with a rectangular wave form and a duration of 0.2 ms is recommended and implemented in almost all nerve stimulators.

Single twitch

It consists of application of supramaximal stimuli on the target nerve with a frequency between 0.1 Hz and 1.0 Hz. Choosing a frequency > 0.15 Hz may result in a decrease of muscular response due to fading. In a clinical setting single twitch stimulation has only limited relevance. Without using suitable monitoring equipment (e.g. a mechanomyograph or an electromyograph) the technique does not provide reliable information neither about the neuromuscular recovery nor the onset of a neuromuscular block. However, in neuromuscular research single twitch stimulation may play an important role when investigating the onset of neuromuscular blocking agents.

Table 1. Recommendations for the use of the single stimulation patterns for the estimation of a neuromuscular block in different clinical situations*

Stimulation pattern	Onset block	Deep block (TOF=0)	Moderate block (TOF>0)	Recovery
TOF	Adequate	Not adequate	Adequate	Intermediate (a) Adequate (b)
DBS	Intermediate	Not adequate	Not adequate	Intermediate
PTC	Intermediate	Adequate	Not adequate	Not adequate
Tetanus (50/100 Hz)	Not adequate	Not adequate	Not adequate	Intermediate

* Modified from Fuchs-Buder T. Neuromuskuläres Monitoring in Klinik und Forschung. Heidelberg. Springer 2008: 44. TOF=Train of four; DBS=Double burst stimulation; PTC=Post tetanic count; (a)=tactile estimation; (b)=quantitative estimation

Train of four (TOF)

Train-of-four stimulation was introduced into clinical practice in the early 1970s by Ali and colleagues [19]. Compared to single twitch stimulation, TOF allows a more reliable tactile assessment of a neuromuscular block. The stimulation pattern contains four twitches of 2 Hz over a period of 2 sec. A stimulation free interval of at least 10 sec should be allowed between two TOF stimulations to avoid a fading associated bias in measurement. Train of four count describes the number of noticeable responses following a TOF stimulation pattern. Without a neuromuscular block all four responses are present with equal intensity. Loss of the fourth response represents a 75-80% neuromuscular block. The disappearance of response three, two, and one can be associated with a block of 85%, 90%, and 98-100%, respectively [20]. A sufficient neuromuscular block for surgical procedures can be assumed until the reappearance of the fourth twitch response.

Train of four ratio describes the relation of the amplitude between the fourth and the first twitch response. This relation that results from dividing the amplitudes of the fourth to the first twitch and can be taken as a parameter for neuromuscular recovery following non-depolarizing neuromuscular blockade. For exact estimation of the TOF ratio a device that supports mechanomyographic, acceleromyographic, or electromyographic recordings is necessary. Tactile estimation allows detecting a fading during TOF stimulation only if TOF ratio is below 0.4 [21]. An objectively measured TOF ratio of 0.7 represents adequate

recovery of the diaphragm. However, to ensure sufficient return of the function of the pharyngeal muscles, a TOF ratio of 1.0 is mandatory.

Tetanic stimulus

Tetanic stimulation is a high-frequency (50-200 Hz) stimulation pattern that applies for 5 sec. Due to the high frequency an estimation of single twitches is not possible. The muscular response will be perceived as a single, forceful contraction. In case of an incomplete neuromuscular recovery following non-depolarizing neuromuscular blockers a fading effect can be observed while stimulating. Baurain and colleagues found a visual fading effect of 100 Hz, 5 sec tetanic stimulation up to a comparable TOF ratio of 0.85 [22]. However, recent studies on this topic have shown that the sensitivity of using a tetanic stimulation in detecting residual curarisation is about 70% but with a low specificity of only 50% [21].

Post-tetanic count (PTC)

Post-tetanic count allows the tactile or visual evaluation of a deep non-depolarizing neuromuscular block that does not respond on a train-of-four stimulation [23]. During a PTC stimulation a 50 Hz tetanic stimulation applies for 5 sec. 1 Hz supramaximal single stimuli follow after a break of 3 sec. The PTC results in the number of responses following the 1 Hz stimulation and should be ideally at 0 if a deep neuromuscular block is desired. If, however, 5 – 7 responses are detectable, return of TOF is imminent.

Double-burst stimulation (DBS)

DBS was introduced for clinical use in 1989 by Engbaek and colleagues [24]. The technique allows a better tactile evaluation of minor neuromuscular blocks than tactile evaluation of the Train of four ratio. During DBS two bursts of 50 Hz with an interval of 750 ms apply. A burst consists of two or three impulses. The bursts are combined as a series of 3 and 3 impulses or 3 and 2 impulses, respectively. In clinical practice DBS 3,2 is currently used. A fading of the second impulse series compared to the first correlates with an incomplete neuromuscular recovery with a comparable TOF ratio < 0.6. Therefore, the method is more sensitive in tactile evaluation of a residual blockade in comparison with a tactile evaluation of the fading during a train-of-four stimulation [25]

Equipment

Monitoring equipment for the surveillance of neuromuscular block can be divided into two groups. Nerve stimulators that allow a quantitative monitoring of the blockade and devices that do not, respectively. The last group of devices is most common in hospitals of several countries. However, the use of nerve stimulators without an option for quantitative measurement does not allow the detection minor levels of neuromuscular block (i.e. a TOF ratio between 0.7 and 1.0) reliably. Therefore, the use of an objective monitoring is generally recommended [26]. The most widely used methods are acceleromyography, electromyography, and mechanomyography. Kinemyography that was recently introduced by GE Healthcare is a procedure that works based on the measurement of the thumb movement. Currently, there are only few data about comparability with other types of measurement available.

Acceleromyography

Acceleromyography is one of the most popular quantitative monitoring techniques in daily clinical use because it is comparably cheap, handy, and easy to install. After placing the stimulating electrodes at the target nerve a piezo-electric element has to be placed over a muscle. Acceleromyography measures the isotonic acceleration of the end-organ (e.g. the thumb) when moved by the stimulated muscle. Basis for the method is Newton's second law ($\text{force} = \text{mass} \times \text{acceleration}$). If mass is constant, muscle contraction can be calculated if acceleration is measured. The movement of the end-organ generates voltage in the piezo-electric element that correlates proportional with the acceleration of the muscle. The generated voltage is used for calculation by the connected device.

Acceleromyography has been shown as a well correlating procedure in comparison to the techniques such as mechanomyography but intraoperative measurements with acceleromyography can be influenced by artifacts, patients' movement, and unstable twitch responses. Therefore, the fixation of fingers and forearm is recommended when using the thumb as end-organ. Moreover, the use of devices that produce a small elastic preload at the thumb, and therefore may decrease the variability of measurements, is recommended [15].

Mechanomyography

Mechanomyography measures the isometric contraction of a muscle following nerve stimulation. A force transducer is placed at the end-organ that converts the muscle force into an electric signal. Most commonly the N. ulnaris and the M. adductor pollicis are used for stimulation with this technique. For stabilization of the signal a preload of 200 g must be applied. Moreover, the limb of the end-organ has to be immobilized.

Due to the stringent precautions, time consuming preparation, and the large scale design of the monitoring equipment mechanomyography is not used in daily clinical practice. However, when investigating new neuromuscular blocking agents the technique still remains as the “gold standard”.

Electromyography

Electromyography is the oldest technique for the estimation of a neuromuscular blockade. Based on the fact that the force of muscular contraction is proportional to the compound action potential of the muscle, the device records the electric activity of the stimulated muscle (i.e. the compound action potential) following the stimulation of the corresponding nerve. The device records the amplitude of the signal as a sum of the compound action potential. The recorded results show a good correlation with mechanomyography but can not be used interchangeably. Electromyography can be used not only at the limbs but also at other muscular sites of interest (e.g. the diaphragm or the larynx). However, a careful skin preparation and maintaining the skin temperature at a constant level may improve quality of signal. The equipment is not as bulky as for mechanomyography recordings but not even handy. Therefore, electromyography has been primary used for scientific matters in the last time.

Current developments

Neuromuscular Monitoring & PORC

There is a large consensus in the literature that neuromuscular monitoring in general and objective neuromuscular monitoring in particular may reduce the incidence of postoperative residual curarization (PORC). However, the results of a meta-analysis published 2007 by Naguib, Kopman, and Ensor were more

than surprising [27]. These authors conclude that they “could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of PORC“. However, serious remarks on both the design and the methodology of their meta-analysis soon arise. Indeed, it has been criticized that no distinction between objective and non-objective monitoring methods were made in this meta-analysis. The chosen methodology to select articles - included comparative and not comparative studies – and therefore was questionable [28].

Moreover, in the meantime Claudius and colleagues published a systematic review about the role that plays acceleromyography in research and clinical practice [29]. This complete overview over the place of AMG found also good evidence that acceleromyography improves the detection of postoperative residual paralysis and it confirmed that recovery of the AMG TOF-ratio to unity indicates with a high predictive value recovery of pulmonary and upper airway function from residual neuromuscular blockade.

Baillard and colleagues have chosen another approach to point out the impact of neuromuscular monitoring on the incidence of residual paralysis [30]. An initial survey in their department revealed an incidence of residual paralysis of about 62%; at that time quantitative monitoring was applied in just 2% and reversal in 6% of patients undergoing general anaesthesia. This gives rise to the suspicion of a link between the high incidence of residual paralysis and the poor application of monitoring and reversal. Consequently, these authors made quantitative neuromuscular monitoring available in all OR and also implemented guidelines for monitoring and reversal of neuromuscular block. In the following 10 years the incidence of residual paralysis in their PACU decreased successively from initially 62% to 3%! In the same period the proportion of patients being intraoperatively monitored with AMG increased from 2% to 60%; and in 42% of patients neuromuscular block was now reversed at the end of the case compared to initially only 6%! Moreover, these data also revealed that the absences of neuromuscular monitoring as well as the absence of pharmacological reversal were independent risk factors for postoperative residual paralysis.

Thus, these recent reports further confirmed that neuromuscular monitoring and the large use of reversal agents are key elements for any successful strategy to prevent postoperative residual paralysis.

Performance of Acceleromyography

Convincing evidence indicates that even low levels of residual paralysis corresponding to a mechanomyographically (MMG) measured TOF-ratio between 0.7 and 0.9 may be potentially harmful. Especially impaired laryngeal function and pharyngeal function with an increasing risk of an upper airway obstruction and/or pulmonary inhalation may contribute to residual paralysis-associated morbidity and mortality [31]. In the view of these recent findings the question arises whether in clinical practice acceleromyography (AMG) may detect low levels of residual paralysis, reliably. Moreover, AMG is increasingly used for research purpose, too. Thus, it must be clarified whether AMG-derived values and MMG-derived values can be used interchangeably. Consequently, the performance of AMG was in the focus of current research activity over the last years.

Acceleromyography for use in clinical practice

In clinical practice different ways to assess neuromuscular recovery with AMG can be seen: punctually at the end of surgery or continuously - with or without initial calibration. In addition, normalization of AMG values, i.e. dividing the value of TOF recovery by the control value determined before the injection of the neuromuscular blocking agent, has also been proposed. Unfortunately, the impact of these different AMG set up to detect low but potentially harmful levels of residual paralysis has not yet been systematically evaluated. Whilst the baseline train-of-four (TOF) ratio measured with MMG is usually close to 1.0, the average baseline TOF ratio assessed with AMG is most often significantly higher than 1.0. A similar situation is found during recovery. AMG TOF-recovery is most often significantly higher than 1.0 contrary to MMG TOF-recovery which normally is situated near 1.0. Therefore AMG and MMG cannot be used interchangeably and the TOF ratio assessed by MMG should be regarded as a real TOF ratio. By consequence it may be essential to correct raw AMG TOF-parameters to avoid overestimation of neuromuscular recovery and thus, to miss low levels of residual paralysis.

Capron and co-workers first asked the question how to detect under routine clinical conditions with acceleromyography low levels of residual paralysis reliably [32]. These authors measured MMG TOF-recovery of the m. adductor pollicis and compared it with the corresponding AMG TOF-recovery of the contralateral arm. This set-up allowed assessing concomitantly AMG and

MMG recovery in the same patient. In their study AMG was applied either calibrated or uncalibrated and the uncalibrated AMG recovery values were expressed with or without normalization. The results of that study confirmed that independently of the set-up AMG overestimates neuromuscular recovery compared to MMG and thus, despite an AMG recovery of 0.9 laryngeal function and pharyngeal function may still be significantly impaired. The negative predictive value (NPV) in that context indicates the percent of patients without residual paralysis, i.e. with a MMG TOF-ratio ≥ 0.9 , at a given level of AMG TOF-recovery. As indicated in table 2 recovery of the TOF ratio to unity and initial calibration or normalization of the final TOF values are mandatory to detect low levels of residual paralysis reliably with AMG. Without initial calibration, however, even an AMG TOF-recovery to unity is insufficient to exclude low levels of residual paralysis (table 2).

Table 2. Negative Predictive Values of Different Acceleromyographic (AMG) TOF Ratios; adapted from reference [21].

AMG TOF ratio	Negative Predictive Value		
	Calibrated data	Uncalibrated data, not normalized	Uncalibrated but normalized data
0.9	37 (20 – 56)%	40 (23 – 59)%	89 (70 – 98)%
0.95	70 (51 – 85)%	60 (41 – 77)%	92 (75 – 99)%
1.0	97 (83 – 100)%	77 (58 – 90)%	96 (80 -100)%

Presuming that AMG is often used as an isolated test at the end of surgery Samet et al compared the performance of DBS, 100 Hz tetanus and a single, and thus uncalibrated, AMG TOF to detect residual neuromuscular blockade at the end of surgery [11]. The NPV of these tests were between 29% (DBS) and 47% (single AMG TOF) with the tetanus in between (38%) and thus are not appropriate to detect low levels of residual paralysis reliably. These results further support that AMG monitoring should be continuously applied from the induction of anaesthesia until the end of surgery rather than only punctually. By consequence appropriate monitoring devices should be available at any anaesthesia workplace. Moreover, recovery to unity and calibration or normalization is mandatory to detect low levels of residual paralysis with AMG.

Calibration in clinical practice

There exist two different calibration programs for the current AMG devices, depending on the respective model (i.e. TOF-Watch®, TOF Watch S® or TOF Watch SX®). The first one applies only several single twitches and then sets the T1 response to 100%. This calibration modus sets the current automatically at 50 Hz. Calibration with this program needs approximatively 10 s. The second program not only calibrates the T1 response but also determined the supra-maximal current. It is available only in TOF-Watch S® and TOF-Watch SX® monitors and needs about 30 s to be correctly applied. Both calibration programs are user friendly and can easily be applied during induction of anaesthesia.

Normalization in clinical practice

As suggested by the data from Capron et al normalization of the final TOF ratio's may be an other option to correct raw AMG recovery parameters to improve the detection of residual paralysis [32]. Kopman and colleagues as well as Suzuki and colleagues have both confirmed the potential interest of normalization to improve the performance of AMG [33,34]. However, baseline control TOF determined before the administration of the neuromuscular blocking agent is also a prerequisite for normalization. In addition, the automatically calculated TOF-value given by most monitor devices loses of its usefulness as today manual calculation is still required to normalize TOF-parameters. Thus, actually normalization is not appropriate for routine application under clinical conditions. Nevertheless, it should be feasible for the manufacture to integrate in a future software-update of the TOF-Watch series a program allowing automatic calculation of normalized TOF ratio's by taking into account the baseline control TOF.

However, it must be emphasized that both, calibration and normalization, require a reference value before the administration of the neuromuscular blocking agent. This reference value is specific for the respective nerve/muscle unit. Therefore an intraoperative switch of the monitoring site, s.a. from the corrugator supercili during onset to the adductor policis during recovery, as sometimes proposed when simple qualitative monitoring devices are applied, cannot be recommended when AMG is used.

Acceleromyography for scientific use

Since many years mechanomyography is considered as the “gold standard” for precise quantification of neuromuscular block. This method should still be considered as the standard when new neuromuscular monitoring techniques or new compounds are under evaluation. However, acceleromyography is now increasingly used for research purpose, too. Nevertheless, despite good concordance between acceleromyography and mechanomyography as indicated by the Bland and Altman analysis (figure 3), TOF-values from both monitors cannot be directly compared. Indeed, the difference in TOF between AMG and MMG showed a bias of -6.6% and the limits of agreement were -22.3 and 9.1. These values are still too wide to allow both monitors to be used interchangeably.

Not all commercially available acceleromyographs are suitable for research. For instance, in two of the three acceleromyographs commercialized by Schering Plough (TOF-Watch® and TOF Watch® S) a special algorithm is used to calculate the TOF ratio. If the value of T2 is higher than the value of T1, the TOF ratio will not be calculated as T_4/T_1 but as T_4/T_2 and if this value is also above 1.0, the TOF Watch® (S) will only display a TOF ratio of 1.0. Although this method of calculating the TOF ratio has yet not been evaluated systematically, it is probably of little real importance when used in the clinical context. However, such devices are not appropriate when used for research studies. In contrast, the actual TOF Watch® SX device, does not have this special algorithm built-in and can therefore be used in the research setting.

Originally, unrestricted movement of the thumb was considered a prerequisite for the use of this measurement method, but there is increasing evidence that a small elastic preload in the range of 75 - 150 g on the thumb may decrease the variability. An appropriate preload device from the manufacturer is commercially available. Finally, because AMG is prone to errors as a result of artefacts, unstable twitch responses and movements (including those caused by the surgeon or other personnel in the operating room) more often than MMG and EMG, it is advised to fix the fingers and the forearm when the m. adductor pollicis is used for AMG monitoring.

Details about the used of AMG for research purpose are summarized in the last update of the guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents [15].

Figure 3. (AMG) and (MMG) with 95% limits of agreement, adapted from reference [33].

Neuromuscular monitoring & PONV

Several randomized and controlled clinical trials confirmed that the stimulation of the acupuncture point P6 effectively reduce the incidence of postoperative nausea and vomiting (PONV). In 2004 a systematic review including 26 trials with more than 3000 patients further confirmed this [35- 37]. The efficacy of the P6 stimulation to reduce PONV was independently of the technique chosen for its stimulation, i.e. with a classical acupuncture needle or with electro-pressure respectively acupressure. However, despite its proven efficacy this approach to prevent PONV never gained widespread popularity in clinical routine. It is likely that it may be difficult to assume continuous stimulation intraoperatively. However, according to a recent publication by Arnberger and colleagues things could change. Indeed, these authors reported that intraoperative P6 acupuncture point stimulation with a conventional nerve stimulator significantly reduces the incidence of PONV over 24 h and the efficacy of this non-pharmacological approach to PONV was similar to that of commonly used antiemetic drugs in the prevention of PONV [38]. To perform this study, the authors used a TOF-Watch S AMG monitor for the P6 stimulation, this acupuncture point being located proximal to the wrist crease between the tendons of the palmaris longus and the flexor carpi radialis muscles of the forearm and thus close to the course of the n. medianus. One might speculate whether stimulation of the P6 could allow both, assessment of neuromuscular blockade

and prevention of PONV. Unfortunately until today only one single study evaluated the n. medianus as a stimulation site for neuromuscular monitoring and more comparative information about the stimulation characteristics of the P6 but also about the evaluation of the muscular response is needed [39].

Thus, before changing current practice and abandon the n. ulnaris as reference site for neuromuscular monitoring stimulation it has to be proven that the n. medianus is also appropriate for neuromuscular monitoring [40]!

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Chapter 3

Pretreatment before succinylcholine for outpatient anesthesia

Thomas Mencke, Jan-Uwe Schreiber, Christine Becker, Marion Bolte, Thomas Fuchs-Buder.
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Abstract

This study aims to evaluate whether precurarization reduces the incidence or the severity of myalgia after succinylcholine in outpatient anesthesia. To this end, 120 patients undergoing ambulatory knee arthroscopy were randomized as follows: Group A: pretreatment with rocuronium 0.06 mg kg⁻¹, 4 min later succinylcholine 1.5 mg kg⁻¹; Group B: pretreatment with saline, 4 min later succinylcholine 1.5 mg kg⁻¹; Group C (control): pretreatment with saline, 4 min later rocuronium 0.6 mg kg⁻¹. Three min after pretreatment, the patients were asked for signs of muscle weakness. After induction of anesthesia the following parameters were assessed: incidence and severity of fasciculations and myalgia and cardiac side effects. Postoperative care and pain management were standardized. The incidence and severity of postoperative myalgias did not differ significantly between the three treatment groups; the overall incidence in the groups A, B and C was 25, 30 and 17.5 %, respectively. Pretreatment with rocuronium (group A) led to signs of muscle weakness compared with the other two groups (B and C): 36 patients (90 %) vs 9 patients (22.5 %) and 6 patients (15 %), respectively; $p < 0.001$.

Implications

This study demonstrated that pretreatment of succinylcholine with rocuronium failed to decrease the incidence or the severity of postoperative myalgia. However, in most patients, pretreatment was associated with muscle weakness before loss of consciousness. Thus, there is no convincing evidence supporting routine pretreatment with succinylcholine.

Introduction

Succinylcholine is a popular muscle relaxant for ambulatory anesthesia [1]. Unfortunately, postoperative myalgia (POM) may frequently occur after the use of succinylcholine [2–7] and this myalgia may be particularly troublesome in outpatients [3,5,6]. Although pretreatment with succinylcholine with nondepolarizing myorelaxants seems to be effective in decreasing muscle fasciculation, its effectiveness in reducing POM is controversial [5,6]. Moreover, pretreatment may produce muscle weakness preceding loss of consciousness [8]. Interestingly, increasing evidence suggests that POM is multifactorial in its origin, with succinylcholine being only one contributing factor [3,5,9,10]. Therefore, it is of clinical relevance in the context of ambulatory anesthesia to quantify the specific contribution of succinylcholine on POM, thus allowing clinicians to decide whether strategies to prevent succinylcholine-induced myalgia pretreatment are worth their side effects. To this end, this study was designed to compare the incidence and severity of POM after succinylcholine—with and without pretreatment—with those observed in a control group not receiving succinylcholine but using a nondepolarizing myorelaxant. Moreover, the side effects of pretreatment were also systematically assessed.

Methods

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 120 adult, ASA physical status I or II patients, undergoing ambulatory knee arthroscopy under general anesthesia. Pregnant patients, patients with neuromuscular disease or medications known to interact with neuromuscular function were excluded.

Patients were randomly assigned to one of three groups ($n = 40$ for each) by random number: Group A: rocuronium 0.06 mg kg^{-1} and 4 min later succinylcholine 1.5 mg kg^{-1} ; Group B: saline 4 min before succinylcholine 1.5 mg kg^{-1} ; and Group C (control): saline 4 min before rocuronium 0.6 mg kg^{-1} . Pretreatment was administered in a double-blinded manner, and syringes were adjusted to a 3-mL volume. One hour before arrival in the operating room, patients were premedicated with midazolam 7.5 mg orally. The induction regimen was standardized for all groups as follows. At time 0, injection of fentanyl $1\text{--}2 \text{ }\mu\text{g kg}^{-1}$ and the pretreatment regimen according to the patient's group; 4 min later, anesthesia was induced with thiopentone $4\text{--}7 \text{ mg kg}^{-1}$ IV and succinylcholine

1.5 mg kg⁻¹ (Group A and B) or rocuronium 0.6 mg kg⁻¹ (Group C); 60 s later, the patient's trachea was intubated. Afterward, patients received a diclofenac suppository 100 mg. Anesthesia was maintained with remifentanyl 0.25 µg · kg⁻¹ · min⁻¹ and desflurane 2%–3% in O₂/air; 15 min before the end of surgery, patients received 1.0 g metamizol as a short infusion and a bolus of piritramid 3.0 mg IV. For the first postoperative hour, patients received piritramid 3.0 mg IV, if requested.

An investigator blinded to the patient's group assignment assessed the following variables:

Fasciculation: recorded according to a 4-point rating scale (6): 0 = absent (no fasciculation), 1 = mild (fine fasciculation of the eyes, face, neck, or fingers but without limb movement), 2 = moderate (fasciculation involving limbs and/or trunk), 3 = severe (fasciculation with movement of one or more limbs and/or movements requiring forceful retention).

Muscle weakness: patients were asked 3 min after injection of the pretreatment whether they had one or more of the following symptoms: diplopia, heavy eyelids, misarticulation (i.e., "voice disorder"), difficulty in swallowing, or dyspnea. The severity of muscle weakness was defined as the number of these symptoms (0–5) mentioned by the patients.

The incidence of bradycardia (decrease of heart rate of at least 20% or heart rate <60/min) and irregular rhythm were assessed after the intubating dose of the myorelaxant.

Severity and intensity of POM: an investigator unaware whether patients fasciculated asked them specific questions 1 h and 24 h after surgery [11]; see Appendix.

Comparisons among groups were performed by using Fisher's exact test, or the Kruskal-Wallis analysis of variance test, followed by the Duncan's post test (versus Control group) or Dunn's post test (pairwise comparison) as appropriate. Demographic data were analyzed by using the Mann-Whitney *U*-test. Results were presented as mean (SD or percentage) or as median (25th and 75th percentiles). Results were considered statistically significant at $P < 0.05$. Sample-size estimation was based on the results of a meta-analysis [4].

Results

Patient characteristics and surgical duration did not differ among groups (Table 1). Six patients in Group A, 3 in Group B, and 4 in Group C received a bolus of 3 mg of piritramide IV in the postanesthesia care unit (not significant).

The incidence and the severity of myalgias did not differ among groups (Table 2).

The incidence and severity of muscle fasciculation were significantly reduced by pretreatment with succinylcholine with rocuronium instead of saline (2.5% versus 80% Group A versus B; $P < 0.001$). Fasciculations were not observed when succinylcholine was avoided (Group C). In the 120 patients studied, there was no correlation between the fasciculation score and POM.

Table 1. Patient Characteristics and Incidence of Patients Requesting Analgesics (Piritramide 3.0 mg) in the Postanesthesia Recovery Room (PACU)

	Group A Pretreatment with rocuronium n = 40	Group B Pretreatment with saline n = 40	Group C Rocuronium 0.6 mg/kg n = 40
Age (yr)	38.8 ± 13.7	40.3 ± 13.1	41.7 ± 9.7
Weight (kg)	76.6 ± 12.2	71.6 ± 13.1	73.9 ± 8.3
Height (cm)	174.8 ± 8.6	173.4 ± 9.8	173.7 ± 9.5
Male/Female	28/12	26/14	24/16
Patients requesting piritramide	6	3	4

Values are mean ± SD; Values are numbers (patients requiring piritramide).

Pretreatment with rocuronium (Group A) was associated with a significantly more frequent incidence of signs of muscle weakness compared with both groups pretreated with saline, i.e., Group B and C (90% versus 22.5% versus 15%, respectively; $P < 0.001$). In Group A, the severity of muscle weakness was also significantly increased (Table 3).

After succinylcholine administration, bradycardia requiring atropine IV occurred in six patients (three in each group, A and B).

Table 2. Incidence, Severity, and Localization of Myalgia

Pretreatment	Group A (<i>n</i> = 40)	Group B (<i>n</i> = 40)	Group C (<i>n</i> = 40)
Muscle Relaxant	Rocuronium 0.06 mg/kg, Succinylcholine 1.5 mg/kg	Saline 0.9%, Succinylcholine 1.5 mg/kg	Saline 0.9%, Rocuronium 0.6 mg/kg
Myalgia in PACU			
Incidence	4 (10)	2 (5)	2 (5)
Severity	0 (0–1)	0 (0–1)	0 (0–1)
Myalgia at 24 h			
Incidence	7 (17.5)	11 (27.5)	7 (17.5)
Severity	0 (0–2)	0 (0–3)	0 (0–3)
Overall myalgia			
Incidence	10 (25)	12 (30)	7 (17.5)
Localization			
Neck	5	6	4
Shoulder	2	6	5
Throat	4	3	3
Other	4	6	4

Incidence of myalgia = number (percentage) of patients; Severity of myalgia = median (range) according to a 4-point rating scale (11): 0=none, 1=slight, 2=moderate, 3=severe.; PACU = Postanesthesia Care Unit

Table 3. Incidence, Symptoms, and Severity of Muscle Weakness After Pretreatment

Pretreatment	Group A (<i>n</i> = 40)	Group B (<i>n</i> = 40)	Group C (<i>n</i> = 40) Saline
Muscle Relaxant	Rocuronium 0.06 mg/kg, Succinylcholine 1.5 mg/kg	Saline 0.9%, Succinylcholine 1.5 mg/kg	0.9%, Rocuronium 0.6 mg/kg
Incidence	36 (90)*	9 (22.5)	6 (15)
Symptoms			
Heavy eyelids	31*	7	6
Diplopia	18*	3	2
Voice disorder	6*	0	0
Dyspnea	3	1	0
Swallowing difficulty	8*	1	0
Severity			
Once	13*	6	4
Twice	16*	3	2
Three or more	7*	0	0

Values are numbers (percentage). Severity = number of paralytic symptoms (0–5) presented

* $P < 0.001$ compared with Group B or C.

Discussion

Increasing evidence suggests that eliminating succinylcholine may not eliminate POM in outpatients. Pretreatment with different nondepolarizing myorelaxants did not affect the incidence of succinylcholine-induced myalgia [6]. Substituting vecuronium for succinylcholine failed to decrease the incidence of POM after outpatient laparoscopy and similar findings were reported for atracurium [3,5,10]. To assess the specific contribution of succinylcholine on POM in outpatients, we standardized the perioperative management, and the type of surgery was uniform (all patients underwent ambulatory knee arthroscopy). Thus, anesthesia- and surgery-related factors contributing to POM were controlled; demographic data were also comparable among groups (Table 1). In this clinical setting, the incidence and the severity of POM did not differ whether 2xED95 rocuronium or succinylcholine—with or without pretreatment—was used to facilitate intubation (Table 2). These observations further support the claim that there may be a baseline incidence of POM in outpatients that is unrelated to the choice of muscle relaxant [3,5,9,10]. Pretreatment of succinylcholine, however, led to muscle weakness in most patients (Table 3). Whereas Martin et al. [8] reported a similarly frequent rate of muscle weakness after pretreatment, some other studies observed those symptoms only rarely [6,9]. This discrepancy may be explained by the manner in which side effects were assessed. Similarly to Martin et al., we asked all patients systematically for the occurrence of weakness symptoms. Most studies reporting an infrequent incidence assessed weakness by observation. However, diplopia or heavy eyelids may be difficult to quantify by observation, thus leading to an underestimation of their incidence. Surprisingly, some patients being pretreated with saline (Groups B and C) also complained of signs of muscle weakness. This may be related to the prior administration of fentanyl because drowsiness and dizziness were reported after opioids, and some patients may have interpreted these symptoms as weakness [12].

A significant limitation of this study is that POM was assessed only up to 24 h. However, it has been reported that 92% of patients who complained of POM reported it within 24 hours after surgery. Another study reported no difference in the incidence 24 versus 48 hours after surgery [13,14]. Therefore, we expect that our methodology would have identified most cases of severe POM.

In conclusion, in the present study, pretreatment with rocuronium failed to decrease the incidence or severity of POM. Pretreatment, however, was regularly associated with muscle weakness before loss of consciousness. In light of these

results, there is no convincing evidence supporting routine pretreatment with succinylcholine for outpatients.

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Appendix: Assessment of postoperative myalgia

Do you have any pains and aches or stiffness in your muscles other than the knee wherein the arthroscopy was performed?

If the answer was no, myalgia was graded 0 = none (no pain); if the answer was yes, the location (i.e., neck, shoulder, arm, throat, abdomen, buttocks), the severity of pain, and the necessity for pain medication were recorded:

- A: If the pain was confined to one location, myalgia was graded 1 = slight (pain confirmed to one site but causing no disability).
- B: If the pain was affecting more than one location, myalgia was graded 2 = moderate or 3 = severe.

Does the muscle pain restrict your normal activity? Restriction of normal activity was assessed as follows: Can you get out of bed? Are you able to turn your head? Can you cough without distress or pain?

- A: If the answer was yes, myalgia was graded 2 = moderate (pain affecting more than one site but causing no disability).
- B: If one of these questions was answered with no, myalgia was graded 3 = severe (pain affecting more than one site and causing disability).

Chapter 4

Postoperative myalgia after succinylcholine

No evidence for an inflammatory origin

Jan-Uwe Schreiber, Thomas Mencke, Andreas Biedler, Oliver Fürst, Stefan Kleinschmidt, Heiko Buchinger, Thomas Fuchs-Buder
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Abstract

A common side effect associated with succinylcholine is postoperative myalgia. The pathogenesis of this myalgia is still unclear; inflammation as a cause has been suggested but without convincing evidence. The present study was designed to investigate whether an inflammatory reaction contributes to this myalgia. The incidence and severity of succinylcholine-associated myalgia was determined in 64 patients pretreated with saline or dexamethasone prior succinylcholine ($n = 32$ for each). Incidence and severity of myalgia did not differ significantly between the two groups: 15 patients in the dexamethasone group complained of myalgia, compared to 18 patients in the saline group, and severe myalgia was reported by 5 patients and 3 patients, respectively (n.s.). At 48 hours postoperatively 12 patients in both groups still suffered from myalgia; n.s. In addition, interleukin-6 (IL-6) as an early marker of inflammation was assessed in a subgroup of 10 patients pretreated with saline. We found an increase of IL-6 for only three patients but only one patient reported myalgia; no relationship between myalgia and the increase of IL-6 was found. In conclusion, there is no evidence for an inflammatory origin of succinylcholine-associated myalgia.

Implications

Administration of dexamethasone before succinylcholine was not effective in decreasing the incidence or the severity of succinylcholine-induced postoperative myalgia. Furthermore, there was no significant relationship between postoperative myalgia and time course of interleukin-6 concentrations, a marker of inflammation. Pretreatment with dexamethasone is not justified to prevent postoperative myalgia after succinylcholine.

Introduction

A common side effect associated with succinylcholine is postoperative myalgia (POM) [1]. The pathogenesis of this myalgia is still unclear but pretreatment with non-depolarizing neuromuscular blockers apparently fails to decrease the incidence or intensity of POM [2-5]. Interestingly, POM is clinically similar to a well known phenomenon following physical exertion, that is, delayed onset muscular soreness [6]. A recent study in sports medicine found an increase of inflammatory variables such as interleukin-6 (IL-6) in direct correlation to the incidence and severity of muscle soreness after unaccustomed muscular stress [7]. Inflammation as a cause for succinylcholine-associated myalgia has been also suggested by several authors but without convincing evidence [8-12].

The present study was designed to investigate whether an inflammatory reaction contributes to POM. The incidence and severity of POM in patients pretreated with saline or dexamethasone prior to succinylcholine was determined. Dexamethasone is a glucocorticoid with a powerful anti-inflammatory potency. In addition, in a subgroup receiving succinylcholine pretreated with saline, interleukin-6 concentrations as a marker of inflammation were determined.

Material and Methods

After obtaining approval from the institutional ethics committee and informed consent, we included 64 adult patients (ASA physical status I-II) undergoing elective ENT-surgery. Exclusion criteria were: Inflammatory disease, obesity (body mass index >30), diabetes, and intake of steroids and non-steroidal anti-inflammatory drugs (NSAID). During the premedication visit, a postoperative pain questionnaire and the system of numeric analogue scale (NAS) for verbal pain and stiffness rating were discussed with the included probands [2]; Appendix A. To simplify data analysis the 11 muscle groups were divided in three regions (head/neck/shoulder, trunk, and limbs), myalgias were graded as none, mild (NAS 1-3), moderate (NAS 4-6), or severe (NAS 7-10). The highest rating of pain in this three regions determined the severity of myalgia.

All patients received midazolam 7.5 mg orally for premedication. Before induction of anesthesia, two groups were randomized receiving either dexamethasone 8 mg iv (DEX group) or saline iv (SAL group). 3 minutes later, a continuous infusion of remifentanyl $0.25 \mu\text{g kg}^{-1} \text{ min}^{-1}$ followed by thiopental

5-7 mg kg⁻¹ iv, and succinylcholine 1.5 mg kg⁻¹ iv, 60s later, tracheal intubation was performed. Fasciculations were evaluated as follows [5]: None = absent, Mild = fine fasciculations of the eyes, face, neck, or fingers but without limb movement, Moderate = fasciculations involving limbs and/or trunk, Severe = fasciculations with movement of one or more limbs and/or movements requiring forceful retention. Anesthesia was maintained with remifentanyl 0.15 - 0.25 µg kg⁻¹ min⁻¹ and 0.5 minimal alveolar concentration isoflurane. Twenty minutes before the expected end of surgery, all patients received piritramide 3 mg IV, which is a synthetic opioid with pharmacodynamic properties similar to morphine [13,14]. After surgery piritramide 0.05 mg kg⁻¹ iv was given by request for the first 24 hours, and thereafter also diclofenac.

All patients were visited postoperatively for four times (6h, 24h, 48h, 72h) on the ward by an investigator blinded to the group assignment. Besides the number of patients with POM and severity of POM, the cumulative incidence (total number of episodes of myalgia during the first 72 h) was determined. Duration of anesthesia and doses of additional taken analgetic drugs because of muscular pain were documented.

From ten patients of the SAL group, who underwent an additional randomization, blood samples for the assay of interleukin-6 were taken. Samples were obtained before induction, twenty minutes after induction, at the end of anesthesia, 6 and 24 hours after the end of anesthesia. Blood samples were drawn in EDTA-tubes and kept on melting ice until separation of plasma by centrifugation. After centrifugation plasma was aspirated in 1-mL aliquots and stored at -70°C for later analysis. IL-6 concentrations were determined with a commercially available enzyme-linked immunosorbent assay (ELISA)-Kit (Bio-source Europe SA, Nivelles, Belgium. Detection limit: 2 pg ml⁻¹).

All data were presented as mean (± SD). For statistical analysis Fisher's exact test or Chi-Square-Test and t-test for unpaired groups were used. Demographic data were compared with Mann-Whitney-U-test. Numbers-needed-to-treat (NNT) were calculated [15]. A positive NNT indicated how many patients had to be exposed to the intervention (i.e. pretreatment with dexamethasone) in order to prevent one particular event (i.e. POM) in one patient. According to pre-set criteria a NNT between 1 and 5 was considered as clinically relevant. A P Value of <0.05 was considered significant. The estimation of the sample size was based on the results of the study of Naguib and co-workers [8]. For an 80 % power to detect a 55% difference in the incidence of myalgia

between the groups with an $\alpha = 0.05$, 62 patients were needed. We enrolled 64 patients, i.e. 32 patients in each group, if not all patients completed the study.

Results

Groups were comparable in age, weight, height, and sex distribution. Also duration of anesthesia did not differ significantly (Table 1). Analgesic requirements were comparable between the two groups.

Table 1. Demographic data

	DEX (n=32)	SAL (n=32)	<i>P</i>
Age (y)	38.2 ($\pm$ 13.9)	37.8 ($\pm$ 12.1)	NS
Gender (M/F)	23/9	21/11	NS
Height (cm)	174.4 ($\pm$ 9.5)	175.8 ($\pm$ 9.1)	NS
Weight (kg)	77.3 ($\pm$ 12.3)	76.9 ($\pm$ 13.3)	NS
Duration of Anesthesia (min)	93.3 ($\pm$ 30.3)	97.9 ($\pm$ 40.9)	NS

Incidence and severity of myalgia did not differ significantly between the two groups: At the assessment of myalgia, i.e. 6, 24, 48, and 72 hours postoperatively, 15 patients in the DEX group complained 25 times of myalgia, compared to 18 patients with 31 episodes of myalgia in the SAL group (not significant). Severe myalgia was reported by 5 patients in the DEX group versus 3 patients in the SAL group and the study groups did not differ in the localization of myalgia (Table 2). At 48 hours after surgery 12 patients in both groups still suffered from myalgia; (not significant). To treat POM with dexamethasone, a NNT of 11 (confidence interval, 6.7 - -3) was calculated. We found an increase of IL-6 more than the lower limit of detection for only three patients but only one patient reported myalgia. No relationship between POM and the increase of IL-6 was found (Table 3).

Table 2. Incidence, severity, and localisation of postoperative myalgia.

	DEX (n=32)	SAL (n=32)	<i>P</i>
Myalgia at 6 h			
Incidence	1	4	NS
Severity#	6	4.3 (3-5)	NS
Myalgia at 24 h			
Incidence	11	11	NS
Severity#	5.4 (2-10)	3.7 (1-6)	NS
Myalgia at 48 h			
Incidence	12	12	NS
Severity#	4.7 (2-8)	4.1 (1-8)	NS
Myalgia at 72 h			
Incidence	1	4	NS
Severity#	3	3,5 (1-9)	NS
Overall Incidence			
Patients w. myalgia§	15 (47%)	18 (56%)	NS
Cumul. incidence+	25 (20%)	31 (24%)	NS
Localisation*			
Neck/Shoulder	10	15	NS
Trunk	12	8	NS
Limbs	4	2	NS

§ Number of patients who had at least one episode of myalgia during follow-up. + Count of episodes with myalgia during follow-up. # Median (range) of highest ranking of severity according to NAS. *Multiple notifications were allowed.

Table 3. List of SAL subgroup with additional IL-6 quantification.

Patient-No.	Gender	Myalgia	Fasciculations+	IL-6 Conc.*
1	M	None	Moderate	n.d.
2	M	Moderate	Severe	n.d.
3	M	Mild	Severe	n.d.
4	M	None	Mild	n.d.
5	M	None	Moderate	n.d.
6	M	None	Mild	72
7	M	None	Moderate	32
8	M	None	Moderate	n.d.
9	F	Moderate	Mild	n.d.
10	F	Moderate	Mild	87

*post-induction concentration maximum in pg ml⁻¹ / "n.d." = not detectable, IL-6 concentration all times less than 2 pg ml⁻¹

+ Grading of fasciculations (5): None = absent, Mild = fine fasciculations of the eyes, face, neck, or fingers but without limb movement, Moderate = fasciculations involving limbs and/or trunk, Severe = fasciculations with movement of one or more limbs and/or movements requiring forceful retention.

Discussion

POM occurs frequently after succinylcholine and is particularly troublesome in outpatients [1,2]. This study was designed to investigate whether inflammatory processes cause POM. Naguib et al. were first to shown that the preoperative administration of cyclo-oxygenase inhibitors, i.e. salicylates could reduce the incidence of POM [8]. Then McLaughlin et al. postulated an activation of phospholipase A2 and the synthesis of prostaglandins, both pro-inflammatory, after succinylcholine [9]. Finally, Kahraman et al. reported a significant decrease of prostaglandine E2-like activity and a reduced incidence of POM in patients pretreated with diclofenac [11]. Despite the fact that ketorolac acts in a similar way as salicylates, pretreatment with the more potent ketorolac could not decrease the incidence and severity of POM [12]. The authors speculated that the relatively short duration of action of ketorolac, which is only 6 to 8 hours, might explain this discrepancy.

To differentiate succinylcholine-induced myalgia from other causes of post-operative myalgia, perioperative management was standardized and the type of surgery was uniform (all patients underwent elective ear-nose-throat surgery). Moreover, demographic data and duration of anesthesia were also comparable

between the groups (Table 1). Thus, anesthesia- and surgery-related factors contributing to POM were controlled. In this clinical setting, the incidence and severity of myalgia did not differ whether patients were pretreated with dexamethasone or saline before succinylcholine. Based on the results of the present study, there are several explanations why the inflammatory reaction is not the cause of succinylcholine-induced myalgia: first, dexamethasone was chosen for pretreatment because it has the highest antiinflammatory activity of all adrenocortical steroids and thus a much stronger potency than NSAID to reduce both the synthesis of prostaglandins and inflammatory stimulation [16]; as an effective dose for its antiinflammatory action dexamethasone 8 mg iv has been proposed [17]. Moreover, its effective half-life of approximately 48-60 hours should cover the entire postoperative period effectively with a single dose. Thus, if an inflammatory process contributes to succinylcholine-induced myalgia, dexamethasone 8 mg iv, should abolish it and thus reduce the intensity of POM. That hypothesis is not supported by our study (Table 2). Whether an earlier administration of dexamethasone would improve its efficacy in reducing succinylcholine-induced myalgia remains speculative. Second, interleukin-6 is a pro-inflammatory cytokine and plays a key role in human acute phase protein synthesis. It contributes to the early stages of the acute inflammatory response. The kinetics of clearance is biphasic and consists of a rapid initial elimination corresponding to a half-life of about 3 minutes and of a second lower decrease corresponding to a half life of about 55 minutes [18]. Potential cytokine sources in injured skeletal muscles include infiltrating neutrophils and monocytes-macrophages, activated fibroblasts, and stimulated endothelial cells [19]. It is upregulated by other interleukins, interferons and tumor necrosis factor α and reaches its maximum 6 hours after physical exercise [7]. Under physiological conditions, cytokines are undetectable or are only found in small concentrations in the blood [20]. In the present study, any inflammatory origin of succinylcholine-induced myalgia should have led to an increase in the plasma concentration of IL-6 because the influence of general anesthesia for minor surgery on IL-6 production seemed to be only minimal [20] and opioids for postoperative pain management such as piritramide apparently did not modify the cytokine response [21]. Moreover, similar to recent findings in sports medicine reporting a significant correlation between muscle soreness after muscular exertion and the plasma concentration of IL-6 [7,19], this increase should be related to the severity of succinylcholine-induced myalgia. We measured the time course of IL-6 in the plasma of 10 patients from the SAL group. However, an increase in IL-6

could only be detected in three patients, but only one of them reported myalgia; no correlation was observed between severity of POM and increase of IL-6 (Table 3).

We conclude that pretreatment with dexamethasone 8 mg iv did not reduce succinylcholine-induced myalgia; no evidence for an inflammatory origin of POM was found.

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Appendix A; Postoperative Questionnaire for myalgia study.

Patient ID:

Date of surgery:

Type of surgery:

Follow-up: 6h 24h 48h 72h

1. Do you have any stiffness or soreness in your body besides headache and pain at the surgical side? yes___ no___
2. Have you been up? yes___ no___
3. Is there pain and stiffness in the muscles? yes___ no___
4. In which sites do you have the muscle pain/stiffness? Jaw___ Throat___ Neck___ Shoulders___ Arm___ Chest___ Abdomen___ Back___ But-tocks___ Thighs___ Calves___ Generalized___
5. When did you first noticed the pain? ____
6. Rate the muscle stiffness/pain on score (0 being no pain an 10 worst pain ever) only on the sites to be painful by the patient. Jaw___ Throat___ Neck___ Shoulders___ Arm___ Chest___ Abdomen___ Back___ But-tocks___ Thighs___ Calves___ Generalized___
7. What makes the muscle stiffness/pain worst? Movement___ Rest___
8. Describe the muscle pain/stiffness in your (patient's) own words.
9. Do you think the muscle pain is restricting your activity? yes___ no___
10. Is the muscle pain preventing you from getting out of bed? yes___ no___
11. How would you rate this limitation of activity on a scale of 0-10 (0 being no limitation of activity, 10 being muscle pain limiting the patient to bed all the time except for essential activity i.e., going to the bathroom.) ____
12. Have you ordered any extra pain medication because of the muscle pain? yes___ no___
13. Are you taking your prescribed pain medication to help your surgical pain___ or your muscle pain___?

Chapter 5

Women report more pain on injection of a precurarization dose of rocuronium

A randomised, prospective, placebo-controlled trial

Thomas Mencke, Jan-Uwe Schreiber, Heike Knoll, Christian Stracke, Stefan Kleinschmidt, Hauke Rensing, Malte Silomon.
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Abstract

Background. The purpose of this study was to investigate whether gender influences the perception of pain on injection of rocuronium.

Methods. In this prospective, placebo-controlled trial 120 patients were randomised in 4 groups to receive rocuronium 0.03 mg kg⁻¹ (40 female and 40 male patients) or saline (20 female and 20 male patients). The incidence and severity of the injection pain after administration of the study drug was compared between female and male patients by using a numerical rating scale (0-10). Signs of local irritation, i.e. erythema and thrombophlebitis were assessed up to 48 hours after surgery.

Results. In 26 (32.5%) of the 80 patients receiving rocuronium, pain on injection was observed. This occurred significantly more frequent in female compared with male patients: 18 (45%) vs. 8 (20%), respectively ($P=0.032$). The severity was more pronounced in women than in men ($P=0.020$). The incidence of the rocuronium-associated pain was significantly increased compared with the Saline groups ($P<0.001$). After surgery no patient complained of any residual pain and no local signs were observed in any patient during the study period.

Conclusions. Women experienced more pain on injection of rocuronium than men, moreover this is an additional evidence for gender-related differences in pain perception. When rocuronium is used as a precurarization agent, an analgesic pretreatment (e.g. opioids) should be considered especially for female patients.

Keywords

Neuromuscular blocking drugs, rocuronium; injection, pain, pain perception; gender, sex

Introduction

Gender differences have been identified in the perception of pain intensity and in the pharmacodynamics of anaesthetic drugs and neuromuscular blocking agents [1-4]. A previous study showed that the sensitivity of women to rocuronium was significantly higher compared with men, requiring 30 % less of the drug to achieve the same degree of neuromuscular block [5]. Pain on injection is one of the main disadvantages of this drug during induction of anaesthesia [6-10]. When administered in subparalyzing doses, 50-100% of patients reported a severe, burning pain [6,8-10]. Women have a lower pain threshold and a lower tolerance than men to most types of nociceptive stimuli [1,11]. However, the impact of gender on pain perception after injection of a precurarization dose of rocuronium has not been investigated to date.

Therefore, the purpose of this study was to investigate whether gender influences the perception of pain on injection of rocuronium 0.03 mg kg⁻¹ (i.e. 10% of ED₉₅). Thus, the incidence and severity of the injection pain between female and male patients was compared. Furthermore, we investigated the influence of the concentration of the solution of rocuronium on pain perception. Local irritations (i.e. erythema and thrombophlebitis) in the region of injection were assessed up to 48 hours after injection.

Methods

After obtaining approval from the Institutional Review Committee and written informed consent, we studied 120 patients, aged 18-70 years. The unpremedicated patients of ASA classification I or II underwent general anaesthesia for elective ear-nose-throat-surgery. Patients with analgesics, as were those with chronic pain and known allergy to the trial drug were excluded. Moreover, patients with obesity and pregnant patients were not included.

One hundred and twenty patients, i.e. 60 women and 60 men were randomised via random number draws in four groups as follows: rocuronium 0.03 mg kg⁻¹ (40 female and 40 male patients) or saline (20 female and 20 male patients). During the premedication visit, the system of numerical rating scale (NRS, 0 = no pain, 10 = worst pain imaginable) was explained to the patients.

On arrival in the operating room routine non-invasive monitoring was placed and the patients received two 20-gauge intravenous (IV) cannulas, one at each dorsum of the hand. Pretreatment was administered in a double-blind

fashion and syringes were prepared by an investigator who did not participate in the evaluation of injection pain. The calculated rocuronium doses were adjusted to a volume of 5 ml by saline, resulting in different concentrations of rocuronium in the study solution. Induction regimen was standardized as follows: At time 0, the study drug (rocuronium or saline) according to the patient's group assignment was injected over 5 s. Thereafter this cannula was flushed with 20 ml saline and maintained closed; no further drugs or fluids were injected in this cannula until its removal at the post-anesthesia care unit (PACU). Three minutes after administration of the study drug, anaesthesia was induced with alfentanil 10-20 $\mu\text{g kg}^{-1}$, thiopentone 4-7 mg kg^{-1} and succinylcholine 1.5 mg kg^{-1} . Anaesthesia was maintained with remifentanyl 0.25 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ and desflurane 2-3 % (end-tidal) in oxygen/air. At the end of surgery the patients were moved to the PACU.

Pain on injection of rocuronium was assessed as follows: Immediately after the end of the administration of the study drug, the patients were asked the following question: „Do you have any pain in the arm where the drug was injected?” If the answer was yes, the patients were asked to estimate the pain according to the system of the numerical rating scale (NRS, 0-10). Local signs were assessed on the arm immediately after the injection of rocuronium as well as 24 hours and 48 hours after recovery from anaesthesia as follows: Erythema = redness; Thrombosis = Hardness of the vein; Phlebitis = Tenderness on palpation of the vein; Thrombophlebitis = Tender and hard vein (12). Grading of the injection pain and the evaluation of local signs were performed by the same anaesthesiologist who was unaware of the patient's group assignment.

Statistical analysis: Statistical analysis was performed using the SigmaStat[®] for Windows Version 2.0 statistical software (1995, Jandel corporation, USA). Demographic data were analyzed using Mann-Whitney U-test, and results are presented as median (range). Comparisons between groups were performed using the χ^2 test, Fisher's exact test, or Kruskal-Wallis ANOVA test. Results were considered statistically significant when $P < 0.05$. To evaluate a possible role of the concentration of the solution of rocuronium on the severity of pain on injection, a correlation analysis (Pearson product moment correlation test) of these two variables was performed.

The required number of patients for the Rocuronium groups (female and male groups) was calculated in expectation of 40% injection pain in the Male group and a 35% increase of the absolute risk in the Female group. For an 80 % power and an $\alpha = 0.05$, 72 patients were needed. To compensate for

possible drop-outs, we enrolled 80 patients, i.e. 40 women and 40 men to receive rocuronium. These patients were compared with 40 patients (20 female and 20 male) of the Saline groups (Placebo).

Obesity = defined as weight of 20 % or more than the normal weight.

Normal weight (kg) = height in cm – 100.

Results

Data from all 120 patients enrolled in this study could be analyzed without dropouts (Fig. 1). Patient characteristics and doses of rocuronium are shown in Table 1.

Figure 1. Flow diagram of patient distribution

Table 1. Values are median (range). BMI = body mass index. Doses = total doses of rocuronium. Patient characteristics and doses of rocuronium.

	Rocuronium groups		
	n = 80		
	Female n = 40	Male n = 40	<i>p</i>
Age (years)	38 (19-69)	36 (18-68)	0.112
Weight (kg)	61 (46-98)	79 (60-114)	< 0.001
Height (cm)	165 (154-182)	176 (164-192)	< 0.001
BMI (kg m ⁻²)	23 (18-31)	25 (19-32)	0.054
Doses (mg)	1.8 (1.4-2.9)	2.3 (1.8-3.4)	< 0.001

One patient (2.5%) of the saline groups (female group) described pain on injection of rocuronium, this was significantly decreased compared with the rocuronium groups: one (2.5%) vs. 26 (32.5%), respectively; $p < 0.001$. The incidence and severity of pain on injection were significantly higher in female compared with male patients, $p < 0.05$ (Table 2). After surgery no patient complained of any residual pain, and no erythema or thrombophlebitis were observed. There was no significant correlation between the concentration of rocuronium and pain scores (Fig 2).

Table 2. Incidence, severity, and localisation of postoperative myalgia.

The incidence and severity of pain on injection.

	Rocuronium groups		
	n = 80		
	Female n = 40	Male n = 40	<i>p</i>
Incidence	18 (45)	8 (20)	0.032
Severity	3.0 (± 2.9)	0.5 (± 1.0)	0.020
Range	0-9	0-4

Figure 2. Correlation analysis of the applied concentrations of rocuronium and pain score; — = Male group ($r=0.08$, $P=0.62$); - - = Female group ($r=-0.09$, $P=0.56$)

Discussion

The major findings of the present study were: Women experienced more pain on injection of a precurarization dose of rocuronium than men. This is an additional evidence for sex differences in pain perception.

Rocuronium-associated side effects include pain on injection and the occurrence of sudden flexion and withdrawal movements of the wrist or arm where rocuronium is administered [6-10,13,14]. When rocuronium was injected in subparalysing doses, 50-100% of patients reported a severe, burning pain [6, 8-10]. The underlying mechanism, by which rocuronium induces pain, remains still unclear. A local release of mediators [8,15] or a direct activation of C-nociceptors [16] as a cause have been suggested. In the present study rocuronium was diluted with saline to an injection volume of 5.0 ml. Thus, the concentration in the solution was lower than in other studies investigating rocuronium-associated pain and therefore it might have been a weaker activator. The correlation analysis of the concentration of rocuronium and pain intensity revealed no significant relationship (Fig 2). However, the applied concentration (0.2-0.8 mg ml^{-1}) of the solution in the present study was lower compared to the commercial concentration of 10.0 mg ml^{-1} (Fig 2). This is a limitation of

the study, because we did not examine the higher concentration, and the range used was small.

The aim of the present study was to determine a possible gender-related difference in pain perception caused by injection of a precurarization dose of rocuronium. In fact, our data clearly demonstrate that the rocuronium-associated pain was sex-related, with women being significantly more sensitive than men ($P < 0.05$) (Table 2). The present study was designed as a placebo-controlled trial to show that the observed gender difference in pain perception was related to rocuronium; the sex-related differences did not occur among the placebo groups. Generally, women have a lower pain threshold and have a higher overall prevalence of pain than men [11]. In a previous study we demonstrated that female patients had significantly more frequent rocuronium-associated withdrawal movements than compared with men [14]. However, these patients received an intubating dose of rocuronium (0.6 mg kg^{-1} , i.e. $2 \times \text{ED}_{95}$) after induction of anaesthesia and therefore the injection pain could not be assessed clearly [14]. It was speculated that the spontaneous movements associated with rocuronium might be the direct consequence of pain on injection [8]. The results of the present study support this hypothesis because the differences in the incidences between female and male patients in both studies are very similar [14]. The possible mechanisms leading to higher pain scores in women as shown in the current study are not fully understood [17]. Females had lower cold pressor pain thresholds and pain tolerance levels, as well as reported greater sensory pain than males [2]. The authors suggested that females reported more negative pain experiences than males [2]. An influence of sex hormones on the neurochemical mediation of analgesia is discussed in the literature [1]. Moreover, female patients are more sensitive than males to opioids, such as morphine [4].

Many studies have investigated different strategies to prevent the injection pain, e.g. a pretreatment with opioids like fentanyl, alfentanil, or tramadol as part of the induction technique may decrease the incidence of pain on injection [6,13,15,18]. When rocuronium is used as a precurarization agent, an analgesic pretreatment with opioids should be considered for female patients. In conclusion, women experienced more pain on injection of rocuronium than men, moreover this is an additional evidence for gender-related differences in pain perception.

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Chapter 6

Prevention of succinylcholine-induced fasciculation and myalgia

A meta-analysis of randomized trials

Jan-Uwe Schreiber, Christopher Lysakowski, Thomas Fuchs-Buder, Martin R. Tramér
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Abstract

Fifty-two randomized trials (5,318 patients) were included in this meta-analysis. In controls, the incidence of fasciculation was 95%, and the incidence of myalgia at 24 h was 50%. Nondepolarizing muscle relaxants, lidocaine, or magnesium prevented fasciculation (number needed to treat, 1.2-2.5). Best prevention of myalgia was with nonsteroidal antiinflammatory drugs (number needed to treat, 2.5) and with rocuronium or lidocaine (number needed to treat, 3). There was a dose-dependent risk of blurred vision, diplopia, voice disorders, and difficulty in breathing and swallowing (number needed to harm, < 3.5) with muscle relaxants. There was evidence of less myalgia with 1.5 mg kg⁻¹ succinylcholine (compared with 1 mg kg⁻¹). Opioids had no impact. Succinylcholine-induced fasciculation may best be prevented with muscle relaxants, lidocaine, or magnesium. Myalgia may best be prevented with muscle relaxants, lidocaine, or nonsteroidal antiinflammatory drugs. The risk of potentially serious adverse events with muscle relaxants is not negligible. Data that allow for a risk-benefit assessment are lacking for other drugs.

Introduction

SUCCINYLCHOLINE is still the accepted standard for rapid sequence intubation [1,2]. It also seems to be a popular muscle relaxant for ambulatory anesthesia and short surgical procedures [3,4]. Perhaps no other drug used in anesthesia, however, is associated with a similarly high risk of complications [5]. Some complications are minor, but others are potentially life threatening. Fasciculation and myalgia are minor but frequent adverse effects of succinylcholine. Myalgia, which can be accompanied by muscle stiffness, can last for several days and can, at least in some patients, induce significant discomfort [6,7]. In 1990, a meta-analysis that included data from 45 randomized and nonrandomized trials concluded that atracurium, *d*-tubocurarine, gallamine, pancuronium, diazepam, and lidocaine all significantly decreased the frequency of myalgia by approximately 30% [8]. During the past 15 yr, many more trials that tested the efficacy of a large variety of pretreatments have been published. The aim of this quantitative systematic review was threefold: first, to update the previously published meta-analysis on the prevention of succinylcholine-related myalgia [8]; second, to include an analysis on the efficacy of pretreatments on succinylcholine-induced fasciculation; and finally, to quantify pretreatment-related adverse effects. This systematic review was performed following the Quality of Reporting of Meta-analyses (QUOROM) recommendations [9].

Materials and Methods

Search Strategy

A systematic search of the literature was performed without language restriction. We searched in MEDLINE, EMBASE, IndMED, and the Cochrane Controlled Trials Register using combinations of the free text terms *succinylcholine*, *suxamethonium*, *postoperative AND pain*, *randomized*, and *myalgia*. We did not use the term *fasciculation* because the primary aim was to study myalgia which is clinically more important. Electronic searches were conducted until February 2004 and were complemented by screening bibliographies of retrieved articles and reviews [7,8].

Study Selection

We considered published full reports of randomized controlled trials that tested the efficacy of pharmacologic regimens compared with placebo or no treatment for the prevention of succinylcholine-induced fasciculation or myalgia. Relevant trials had to report on dichotomous data on presence or absence of fasciculation or myalgia. We did not consider data from abstracts, letters, reviews, or animal research.

Assessment of Validity

Retrieved reports were screened for inclusion by two authors independently (J.-U. S., M. R. T.), who excluded irrelevant reports at that stage. Each author then independently scored all eligible reports for methodologic validity using the five-point Oxford scale, which takes into account randomization, blinding, and description of withdrawals [10]. The minimum score of an included randomized study was 1, and the maximum score was 5. Detailed information from each trial was entered into standard collection sheets. This was done by one investigator (J.-U. S.) and independently checked by the others. Consensus on quality scores and extracted data were reached by discussion. We converted all variable doses to fixed doses using average body weights of the study populations as reported in the original trials.

Data Synthesis

Because undue weight would have been given to pretreatments that were tested in one or two trials only, we restricted quantitative analyses to those pretreatments that were tested in at least three trials. We used a fixed effect model because the data seemed to be clinically homogenous. We calculated relative benefits as relative risks with 95% confidence intervals for efficacy data. Adverse effects were expressed as Peto odds ratios with 95% confidence intervals because many trials had zero cells (*i.e.*, they did not report on any event in one of the study groups). We calculated the number needed to treat (NNT) or to harm as an estimate of the clinical relevance of a treatment effect. The number needed to treat or to harm is the number of patients that must be treated with an experimental intervention to achieve a particular result (beneficial or harmful) in one of them which would not have been the case had they all received the control intervention (in this case, a placebo) [11]. Statistical analyses were per-

formed using RevMan 4.2 (Cochrane Library, Updated Software, Oxford, United Kingdom) and Microsoft® Excel 98 for Mac® (Microsoft Corp., Redmond, WA).

Results

Search Results

We identified 161 potentially relevant trials but subsequently excluded 109 (fig. 1). We eventually analyzed data from 52 randomized trials that were published between 1971 and 2003 and that included 5,318 patients [3,12-62]. From the previously published meta-analysis [8] we accepted 17 studies but rejected 28, primarily because they were not randomized. There was one duplicate cluster [63] of which we considered the older report as the original [57] and excluded the duplicate.[64] One pediatric study was excluded,[65] because all other trials were in adults.

Figure 1. Flowchart of retrieved, excluded, and analyzed trials.

The median number of patients per study was 71 (range, 20-587). The median quality score was 2; 13 trials scored 1; 24 scored 2; 11 scored 3; and 4 scored 4. Only 6 trials (12%) reported an appropriate method of randomization, and only 8 (15%) reported an adequate method of blinding.

Forty-six trials (88%) studied fasciculation, 49 (94%) studied myalgia, and 43 (83%) studied both. Most trials scored the degree of fasciculation and myalgia

on a four-point scale, ranging from, for example, none to mild, moderate, and severe. We extracted only data on complete absence of fasciculation and on complete absence of myalgia to avoid interpretation bias. The incidence of myalgia was most frequently reported at 24 h after surgery. Some studies reported on myalgia at 48 h, and a few reported on myalgia at 72 h.

Underlying Risk

We studied the relation between fasciculation and myalgia and tested the potential impact of the induction agent (propofol *vs.* thiopentone), dose of succinylcholine, and effects of opioids at induction on the incidence of fasciculation and myalgia. For that purpose, we selected the 35 trials that reported on both fasciculation and myalgia at 24 h [3,13-16,21-23,25-27,29,30,32-36,38,39,41,44-46,48,50-54,56-59,61]. In those, the average incidence of fasciculation in controls (*i.e.*, the control event rate) was 94% (range, 73-100%) and of myalgia at 24 h was 51% (range, 10-83%). Graphical display did not suggest any relation between the incidence of these two endpoints (fig. 2). The original data did not allow statistical testing for an association between severity of fasciculation and incidence of myalgia because severity of fasciculation was only inconsistently reported.

Figure 2. Incidence of fasciculation and of myalgia in control patients who received a placebo or no treatment (*i.e.*, control event rate). Each symbol represents one trial. Data are shown for 35 trials that reported on both fasciculation and myalgia, and where the dose of succinylcholine was 1 mg/kg (gray squares) or 1.5 mg/kg (clear circles). Number of symbols does not add up because some symbols are overlapping.

In four trials, induction of anesthesia was with propofol [26,33,41,61]; in one, it was with propofol or thiopentone [30]; and in the other 47, it was with thiopentone. The average incidence of fasciculation was 95.2% with propofol and 95.0% with thiopentone. The difference was not statistically significant. The average incidence of myalgia at 24 h was 65.4% with propofol and 49.2% with

thiopentone. This difference was statistically significant; for prevention of myalgia with thiopentone compared with propofol, the NNT was 6 (table 1).

Table 1. Impact of Induction Agent, Opioids, and Different Succinylcholine Doses on Myalgia and Fasciculation

	No. of Patients with Fasciculation/ Total No. of Patients (%)	Relative Risk (95% CI)	No. Needed to Treat (95% CI)	No. of Patients with Myalgia at 24 h/Total No. of Patients (%)	Relative Risk (95% CI)	No. Needed to Treat (95% CI)
Propofol	99/104 (95.2)	1.00		68/104 (65.4)	1.33	6
Thiopentone	725/763 (95.0)	(0.96–1.05)		391/795 (49.2)	(1.14–1.55)	(4–17)
Opiates at induction	324/340 (95.3)	1.01		182/340 (53.5)	1.09	
No opiates at induction	521/551 (94.6)	(0.98–1.04)		271/551 (49.2)	(0.96–1.24)	
1 mg kg ⁻¹ SCh	227/231 (98.3)	1.07	16	145/231 (62.8)	1.41	6
1.5 mg kg ⁻¹ SCh	521/551 (92.0)	(1.04–1.10)	(11–28)	268/601 (44.6)	(1.23–1.61)	(4–9)

Subgroup analyses were performed with data from control patients who received succinylcholine without any pretreatment. Data from trials that reported on both fasciculation and myalgia at 24 h are considered. Numbers needed to treat are shown for statistically significant results.
CI confidence interval; SCh succinylcholine.

Fentanyl [3,16,21,26,33,41,44,45,50,51,61], methadone [36], or meperidine [29] was given at induction in 13 trials. In the others, no opioids were used for induction. The average incidence of fasciculation was 95.3% with opioids and 94.6% without. The average incidence of myalgia at 24 h was 53.5% with opioids and 49.2% without. None of these differences were statistically significant (table 1).

In 9 trials, the dose of succinylcholine was 1 mg kg⁻¹ [16,21,23,-26,32,36,46,54,55], and in 25 trials, the dose was 1.5 mg kg⁻¹ [3,14,15,22,25,27,29,30,33-35,38,39,41,44,45,48,51,53,55-59,61]. The remaining trials used 1.3 or 2.0 mg kg⁻¹ succinylcholine. The average incidence of fasciculation was 98.3% with 1 mg kg⁻¹ succinylcholine and 92.0% with

1.5 mg kg⁻¹. The average incidence of myalgia at 24 h was 62.8% with 1 mg kg⁻¹ succinylcholine and 44.6% with 1.5 mg kg⁻¹. Both differences were statistically significant; for prevention of fasciculation with 1.5 mg kg⁻¹ succinylcholine compared with 1 mg kg⁻¹, the NNT was 16, and for prevention of myalgia, the NNT was 6 (table 1).

Pretreatments

A large variety of pretreatments were tested: nondepolarizing neuromuscular blockers (atracurium [16,21,30,37,40,41,46,49,50,53,57,61], cisatracurium [3,33,44], *d*-tubocurarine [12,13,23,25,29,33,39,41-43,45,51,56,57], gallamine [12,13,25,48,52], fazadinium [12,16] metocurine [13], mivacurium [18,41,60], pancuronium [12-14,21,25,31,38,48,59,62], rocuronium [26,33,35,41,54,61], vecuronium [21,22,25,26,35,41,45]), sodium channel blockers (lidocaine [24,32,43,52,53], phenytoin [29]), nonsteroidal antiinflammatory drugs (diclofenac [34], ketorolac [37], aspirin [42,46,56]) benzodiazepines (midazolam [27,45], diazepam [20,22,23,39,51]), vitamins (E [22,42], C[28]), magnesium sulfate [17,36,58], calcium chloride [42], dantrolene [19], dexamethasone [55], chlorpromazine [22,42] and succinylcholine [15,48,62].

Prevention of Fasciculation

The effect of 12 pretreatments on fasciculation was tested in at least three trials each (fig. 3). Nonsteroidal antiinflammatory drugs were not significantly different from placebo; all other pretreatments were. The NNT compared with placebo was approximately 10 with benzodiazepines and approximately 4 for cisatracurium and pancuronium. With magnesium, sodium channel blockers (four of five trials tested lidocaine), and the other nondepolarizing neuromuscular blockers, NNTs were between 1.2 and 2.5.

Figure 3. Prevention of succinylcholine-related fasciculation. For each intervention that was tested in at least three trials, a meta-analysis was performed (# = number of analyzed trials).Symbol sizes are proportional to the number of analyzed patients. CI = confidence interval; NNT = number needed to treat; NSAID = nonsteroidal antiinflammatory drug (aspirin, diclofenac, ketorolac); benzodiazepine (diazepam, midazolam); sodium channel blocker (lidocaine, phenytoin); RB = relative benefit.

Prevention of Myalgia at 24 h

The effect of nine pretreatments on myalgia at 24 h was tested in at least three trials each (fig. 4). Benzodiazepines had a weak but statistically significant effect on myalgia; the NNT was approximately 8. With all nondepolarizing neuromuscular blockers, there was a statistically significant effect on myalgia; NNTs were between 6 (pancuronium) and 3 (gallamine, rocuronium). With sodium channel blockers (three of four trials tested lidocaine), the NNT was approximately 3. Best efficacy was with nonsteroidal antiinflammatory drugs (two trials tested aspirin, one tested diclofenac); the NNT was 2.5.

Figure 4. Prevention of succinylcholine-related myalgia at 24 h. For each intervention that was tested in at least three trials, a meta-analysis was performed (# = number of analyzed trials). Symbol sizes are proportional to the number of analyzed patients. CI = confidence interval; NNT = number needed to treat; NSAID = nonsteroidal antiinflammatory drug (aspirin, diclofenac); benzodiazepine (diazepam, midazolam); sodium channel blocker (lidocaine, phenytoin); RB = relative benefit.

Myalgia at 48 and 72 h

Myalgia at 48 h was reported in 16 trials [12,14,15,22,25,29,32,35-38,41,49,53,59,61]. Of 374 controls, 189 (51%) reported myalgia at 48 h (range, 5-87%). Myalgia at 72 h was reported in 8 trials [16,22,29,30,38,45,49,59]. Of 185 controls, 51 (28%) still had myalgia at 72 h (range, 0-60%).

Dose-Response with Nondepolarizing Neuromuscular Blockers

With most nondepolarizing neuromuscular blockers, several doses corresponding to 10-30% of the respective ED₉₅ were tested. To test for dose-responsiveness, we selected those trials that tested neuromuscular blockers and that reported on myalgia at 24 h [3,12-14,16,21,23,25,26,29,30,33,35,38,39,41,44-46,48-54,56,57,59,61,62] and plotted doses *versus* relative benefits for prevention of myalgia. There was no clear evidence of dose-responsiveness for neuromuscular blocking agents (fig. 5). There were not enough data to allow for sensitivity analyses that addressed the time point of administration of neuromuscular blockers on efficacy.

Figure 5. Relation between doses of nondepolarizing neuromuscular blocking agents (in milligrams, y-axes) and efficacy in preventing myalgia at 24 h. Symbols are relative benefits with 95% confidence intervals (CI). A relative benefit greater than 1 indicates less myalgia compared with control. For regimens that have been tested in more than one trial, meta-analyses were performed.

Adverse Effects

Nine trials reported on adverse effects [3,17,19,23,38,44,51,59,61]. Blurred vision, diplopia, heavy eyelids, muscle weakness, difficulty in swallowing, and voice disorder were significantly more often reported in patients who received a nondepolarizing muscle relaxant (table 2). With pancuronium, dose-responsiveness could be tested with data from two trials [38,59]. For that purpose, we arbitrarily divided pancuronium regimens into low (0.21-0.28 mg), medium (0.42-0.49 mg), and high dose (0.63-0.7 mg), corresponding to approximately 4, 7, and 10 $\mu\text{g kg}^{-1}$, respectively, for a patient with 70 kg body weight. There was consistent evidence of dose-responsiveness for blurred vision, diplopia, heavy eyelids, and muscle weakness. Number-needed-to-harm values were 3.5 or lower (table 2) with the high-dose regimen. There were not enough valid data to allow for similar sensitivity analyses for other adverse effects and for other neuromuscular blocking agents. Adverse effects with other drugs were pain on injection and dizziness with diazepam [23,51], weakness and dizziness with dantrolene [19], and heat sensation with magnesium [17].

Table 2. Analysis of Adverse Effects after Pretreatment with Neuromuscular Blockers Blocking Agents

Adverse Effect	No. with Adverse Effect/ Total No. (%)		Odds Ratio (95% CI)	Number Needed to Harm	References
	Experimental Intervention	Control Intervention			
Blurred vision					
Any neuromuscular blocking agent	72/208 (34.6)	3/74 (4.1)	5.76 (3.0–11.1)	3	38,59,61
Pancuronium, low dose*	11/60 (18.3)	3/60 (5)	3.91 (1.25–12.3)	7.5	38,59
Pancuronium, medium dose	23/60 (38.3)	3/60 (5)	7.27 (3.04–17.4)	3	38,59
Pancuronium, high dose	38/60 (63.3)	3/60 (5)	17.6 (7.97–39.0)	2	38,59
Diplopia					
Any neuromuscular blocking agent	65/260 (25.0)	5/120 (4.2)	4.99 (2.80–8.88)	5	3,38,44,59
Pancuronium, low dose	4/60 (6.7)	1/60 (1.7)	3.62 (0.59–22.3)	20	38,59
Pancuronium, medium dose	16/60 (26.7)	1/60 (1.7)	8.00 (2.85–22.5)	4	38,59
Pancuronium, high dose	18/60 (30.0)	1/60 (1.7)	9.90 (3.58–27.4)	3.5	38,59
Heavy eyelids					
Any neuromuscular blocking agent	155/260 (59.6)	14/120 (11.7)	8.44 (5.38–13.2)	2	3,38,44,59
Pancuronium, low dose	15/60 (25.0)	1/60 (1.7)	7.89 (2.72–22.9)	4	38,59
Pancuronium, medium dose	33/60 (55.0)	1/60 (1.7)	14.0 (6.32–31.1)	2	38,59
Pancuronium, high dose	49/60 (81.7)	1/60 (1.7)	25.8 (12.6–53.1)	1.3	38,59
Weakness					
Any neuromuscular blocking agent	89/220 (40.5)	14/100 (14)	5.67 (3.31–9.72)	4	3,38,59
Pancuronium, low dose	7/60 (11.7)	5/60 (8.3)	1.45 (0.44–4.75)	30	38,59
Pancuronium, medium dose	16/60 (26.7)	5/60 (8.3)	3.50 (1.37–8.94)	5.5	38,59

Adverse Effect	No. with Adverse Effect/ Total No. (%)		Odds Ratio (95% CI)	Number Needed to Harm	References
	Experimental Intervention	Control Intervention			
Pancuronium, high dose	30/60 (50.0)	5/60 (8.3)	7.31 (3.34–16.0)	2	38,59
Difficulty in breathing					
Any neuromuscular blocking agent	154/308 (6.5)	20/308 (2.6)	2.23 (0.91–5.48)	26	3,38,41,44, 59,61
Difficulty in swallowing					
Any neuromuscular blocking agent	16/100 (16.0)	2/80 (2.5)	4.45 (1.65 to 12.0)	7	3,41,44
Voice disorder					
Any neuromuscular blocking agent	13/80 (16.3)	0/60 (0)	6.71 (2.08 to 21.6)	6	3,44

* Variable doses were converted to fixed doses using average body weights of the study populations as reported in the original trials. Low dose 0.21–0.28 mg (3–4 µg kg⁻¹, respectively, for 70 kg body weight); medium dose 0.42–0.49 mg (6–7 µg kg⁻¹, respectively); high dose 0.63–0.70 mg (9–10 µg kg⁻¹, respectively). Dose ranges were arbitrarily chosen.
CI confidence interval.

Discussion

Five main results emerge from this meta-analysis: Two confirm existing knowledge, and three challenge widespread opinion or provide new insights. First, the incidence of succinylcholine-induced myalgia is high, and symptoms sometimes last for several days. Second, small doses of nondepolarizing muscle relaxants (*i.e.*, approximately 10-30% of the ED95) prevent fasciculation and myalgia to some extent; however, the risk of potentially serious adverse effects is not negligible. Third, higher doses of succinylcholine decrease the risk of myalgia compared with lower doses, opioids for induction do not seem to have any impact, and, as to the choice of the induction agent, it cannot be excluded that there is less myalgia when thiopentone is used compared with propofol. Fourth, there is no clear relation between succinylcholine-related fasciculation and myalgia. Finally, pretreatment with sodium channel blockers (*i.e.*, lidocaine) or nonsteroidal antiinflammatory drugs (diclofenac and aspirin) may prevent myalgia.

Our meta-analysis has limitations. Most are related to weaknesses in the original trials. The average methodologic quality of the trials was low. For example, a minority only reported an adequate method of blinding, leaving room for observer bias. We do not know whether these trials were correctly performed but poorly reported. Also, the size of most trials was limited. This may partly explain the large variability in event rates, with some trials reporting less than 20% of controls having myalgia at 24 h and others reporting more than 80%. Follow-up was 24 h in most trials. This may not be long enough to provide an adequate view on the usefulness of pretreatment. Finally, many trials did not report on drug-related adverse reactions. However, lack of reporting of adverse reactions does not mean that none have occurred. For example, we would expect some cardiac adverse effects in susceptible patients with lidocaine. Also, the use of nonsteroidal antiinflammatory drugs such as aspirin may interfere with platelet function. In particular surgical settings, regular perioperative treatment with these analgesics may not be warranted [66]. Finally, potentially serious adverse effects such as difficulty in swallowing were reported with nondepolarizing neuromuscular blocking agents. Relevant data, however, came from only three studies, with a total of 100 patients who received pretreatment [3,41,44]. We were unable to provide reliable information on optimal regimens for each drug. Pretreatment intervals and tested doses were too diverse.

On average, one half of the patients who received succinylcholine without pretreatment had myalgia at 24 h and even at 48 h. After 3 days, approximately one third of patients still experienced muscle pain. It has been known for a long time that myalgia can last for up to 1 week [6,14]. The trials did not allow conclusions about the severity of muscle ache. However, as long as succinylcholine is used in daily clinical practice [67], there is a need for an effective treatment against this bothersome side effect, and this may explain the large number of published trials dealing with this subject.

Contrary to widespread belief, we were unable to find a clear relation between the incidence of fasciculation and myalgia. Clearly, the ability of nondepolarizing muscle relaxants to prevent both seems to link them tightly. However, benzodiazepines had a favorable effect only on fasciculation and almost no effect on myalgia, and nonsteroidal antiinflammatory drugs did not prevent fasciculation but were effective against myalgia. These data suggest that fasciculation and myalgia may have different origins. Fasciculation is thought to be related to a prejunctinal agonistic action of succinylcholine on nicotinic receptors that results in rapid firing [68]. Nondepolarizing muscle relaxants effec-

tively prevent fasciculation, presumably by blocking presynaptic nicotinic receptors. The etiology of succinylcholine-induced myalgia, however, remains obscure. The fact that very different drugs such as diclofenac, lidocaine, or pancuronium all attenuate myalgia to some extent provides indirect evidence that the origin of succinylcholine-induced myalgia must be, as previously suggested, multifactorial [7,69]. The beneficial effect of sodium channel blockers such as lidocaine may be explained through their cell membrane-stabilizing properties. The efficacy of nonsteroidal antiinflammatory drugs suggests that there is an inflammatory genesis and that prostaglandins may be involved [46,70]. This assumption, however, is contentious [55].

Patients who received a higher dose of succinylcholine were less likely to have myalgia compared with those who received a lower dose. A biologic basis for that differential effect may be that higher doses of succinylcholine reduce forces on muscle spindles and therefore produce more synchronous muscle contractions and subsequently less myalgia [7]. However, after administration of succinylcholine, biochemical markers of muscle damage, such as myoglobin or creatine kinase, did not correlate with the incidence of myalgia [71,72]. Recently published data suggested that succinylcholine doses as low as 0.6 mg kg⁻¹ still provided satisfactory intubation conditions with a shorter recovery and apnea period [73,74]. Clinicians will have to make the choice as to whether it is worthwhile to use a small dose of succinylcholine to shorten recovery and apnea period at the price of increasing the risk of postoperative myalgia. It has been suggested that a high induction dose of propofol decreases the risk of succinylcholine-induced myalgia [75]. We were unable to confirm this; however, results of the relevant subgroup analysis should be interpreted carefully because only a small number of trials that used propofol for induction could be included. Finally, whether an opioid was used for induction had no impact on myalgia.

Surprisingly, sodium channel blockers (most trials tested lidocaine) and nonsteroidal antiinflammatory drugs including aspirin were among the most efficacious drug classes to prevent myalgia. However, relatively small number of patients were tested, and, accordingly, 95% confidence intervals around the relative benefit point estimates were wide, reflecting some uncertainty in the degree of efficacy. Not unexpectedly, pretreatment with a small dose of a nondepolarizing muscle relaxant, perhaps the most popular technique in this setting, decreased the incidence of myalgia. Almost all manufactured muscle relaxants were tested in at least one study, and there was no obvious difference between specific drugs. All nondepolarizing muscle relaxants had NNTs for the

prevention of fasciculation and myalgia within a similar range, and 95% confidence intervals were overlapping. The degree of efficacy seems to be very similar for all nondepolarizing muscle relaxants. However, three issues must be discussed in this context. First, with this technique, the risk of potentially serious adverse effects is not negligible. Some may be minor, *e.g.*, heavy eyelids, blurred vision, or diplopia, at worst causing some discomfort. Others are potentially serious, *e.g.*, difficulty in breathing or swallowing. For pancuronium, the most frequently tested nondepolarizing muscle relaxant in these studies, a consistent and clinically relevant dose-response for adverse effects became apparent. Approximately 30 of 100 patients present symptoms of muscle weakness with $10 \mu\text{g kg}^{-1}$. Approximately 15 of 100 patients are symptomatic at $7 \mu\text{g kg}^{-1}$. The same degree of risk and a similar dose-response may apply to all other nondepolarizing muscle relaxants. This assumption is supported by a dose-response analysis for rocuronium that used a pharmacodynamic and pharmacokinetic model [76]. Second, and contrary to the data on adverse effects, there was no clear evidence of dose-responsiveness for efficacy with any of the nondepolarizing muscle relaxants. Therefore, if pretreatment with one of these drugs is chosen as a strategy to reduce succinylcholine-induced myalgia, the smallest dose of each agent that has shown efficacy in these randomized trials should be given. These doses are unlikely to be above 10% of the respective ED95. Finally, a standard dose of succinylcholine is likely to have a weaker paralyzing effect after pretreatment with a nondepolarizing muscle relaxant. Therefore, an increased dose of succinylcholine may be needed to achieve optimal intubation conditions [77].

Our meta-analysis provides rationale for future research. First, knowing that pretreatment with nondepolarizing neuromuscular blocking agents prevents myalgia to some extent but produces a finite risk of potentially serious adverse effects begs the question as to whether this method should still be recommended, and whether further research is actually warranted with this technique. It may be worthwhile to try to optimize the effect of dose and timing of administration of nondepolarizing muscle relaxants. Alternative drugs such as lidocaine or nonsteroidal antiinflammatory drugs seem promising. Among those, nonsteroidal antiinflammatory drugs are perhaps the most logical choice, considering their symptomatic analgesic efficacy in a variety of acute pain syndromes such as strains and sprains that strongly resemble succinylcholine-induced myalgia. However, the increased risk of surgical bleeding must be kept in mind. Second, it may be useful to test combinations of drugs with different

mechanisms to enhance efficacy. The origin of myalgia is likely to be multifactorial, and it may be naive to believe that one single drug can completely prevent it. The most effective prevention may be with a drug combination. Third, it may be a sensible option to treat muscle pain in patients who complain about it, rather than to try to prevent it in all patients. The myalgia is of minor harm only; not all patients, even if untreated, are affected; and none of the tested pretreatments are universally effective. There is no rationale why treatment of myalgia should be less effective than prevention. None of the retrieved trials examined the treatment of established myalgia symptoms with, for example, a single dose of a nonsteroidal antiinflammatory drug. Finally, the importance of pretreatment in the prevention of more serious succinylcholine-induced adverse effects, such as hyperkalemia or an increase in intraocular or intracranial pressure, remains unclear. There is some evidence that with low-dose mivacurium, succinylcholine-induced increase in intraocular pressure may be prevented [18]. However, there is no clear evidence that succinylcholine increases intracranial pressure in patients with brain injuries [78], and only limited data are available for patients with brain tumors [79]. If muscle fasciculation was a causative factor of these effects, the prevention of succinylcholine-induced fasciculation may be an important goal.

In conclusion, nondepolarizing muscle relaxants, lidocaine, or magnesium may be used for the prevention of succinylcholine-induced fasciculation. Myalgia may best be prevented with nondepolarizing muscle relaxants, lidocaine, or nonsteroidal antiinflammatory drugs. Nondepolarizing muscle relaxants should be used cautiously because the risk of potentially serious adverse effects is not negligible. There is a lack of relevant data to allow for a rational risk-benefit analysis for other pretreatments.

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Chapter 7

Does preoperatively administered parecoxib prevent succinylcholine- associated myalgia?

A randomized, placebo-controlled trial

Jan-Uwe Schreiber, Thomas Mencke, Sascha Pradarutti, Silke Jeblick, Thomas Fuchs-Buder
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Abstract

Background and objective:: Data from several studies implicate that pretreatment with non-selective cyclooxygenase inhibitors such as aspirin or diclofenac may decrease the incidence of postoperative succinylcholine-related myalgia. We tested the influence of a preoperatively administered selective cyclooxygenase 2 inhibitor, parecoxib, on postoperative myalgia.

Methods:: After Ethics Committee approval, 68 patients were randomized into two groups ($n = 34$ each). Group 1 received parecoxib 40 mg intravenously 3 min before induction of anaesthesia, and Group 2 received saline (in a double-blinded manner). Incidence and severity of myalgia was evaluated systematically with a standardized questionnaire 24, 48 and 72 h after anaesthesia. We also assessed the number of patients who felt limited in their activity due to myalgia.

Results:: Seven patients in the parecoxib-treated group complained of myalgia compared with 11 in the control group (not significant). No significant difference in the severity of myalgia or in the limitation of patients activity was found between the groups.

Conclusion:: Intravenous parecoxib 40 mg, when administered before induction of anaesthesia, did not reduce incidence and severity of postoperative myalgia and did not improve activity in those who suffered from myalgia.

Introduction

Due to its unique pharmacological properties, succinylcholine still keeps its place in anaesthetic practice [1]. A frequent adverse effect of succinylcholine is myalgia that can last for several days in varying intensity. Myalgia may cause discomfort and can delay normal activity. This has led to the implication that succinylcholine may not be a suitable drug for ambulatory anaesthesia [2]. Results of a recent meta-analysis showed that parenteral pretreatment with non-selective cyclooxygenase inhibitors such as aspirin or diclofenac may reduce the incidence of succinylcholine-related myalgia 24 h after anaesthesia [3]. In contrast, preoperative administration of intravenous (i.v.) ketorolac or oral aspirin did not lead to a decreased rate of myalgia 48 h after surgery [4,5].

Adverse effects may limit the use of non-selective cyclooxygenase inhibitors for the prevention of postoperative myalgia. Due to their pharmacological mechanism, agents as diclofenac may interfere with haemostasis and may cause an increase in intraoperative blood loss compared with selective cyclooxygenase 2 inhibitors [6]. For use in the ambulatory setting, an agent for parenteral administration with a rapid analgesic onset would be favourable.

The aim of this randomized, placebo-controlled trial was to test the effect of pretreatment with parecoxib, a parenteral, selective cyclooxygenase 2 inhibitors, on incidence and severity of succinylcholine-associated myalgia over 72 h after anaesthesia. In addition, impairment of patients' activity was evaluated.

Material and Methods

After Ethics Committee (Chamber of physicians of Saarland) approval and informed consent, 68 adult patients (ASA I-II) scheduled for minor surgery were planned for inclusion. Types of surgery were hernia repair, implant removal after osteosynthesis of the lower ankle and inguinal lymph node dissection. Exclusion criteria were chronic intake of non-steroidal anti-inflammatory drugs, obesity (body mass index (BMI) > 30 kg m⁻²), neuromuscular disease, acute or chronic inflammatory diseases and contraindications for parecoxib.

Incidence and severity of myalgia was evaluated with a standardized questionnaire [7]. During the premedication visit, patients were informed about the questionnaire and the methodology of the numeric analogue scale (0 = no pain to 10 = worst pain). On the day before surgery, patients were allocated according to a computer generated randomization list to a pretreatment group (group

COX) or to a control group (group SAL). Midazolam 7.5 mg orally was used for premedication 1 h preoperatively. After placing an i.v. cannula, group COX received 40 mg parecoxib in 2 mL saline i.v. (Dynastat®; Pfizer, Karlsruhe, Germany); group SAL (control group) received 2 mL saline. For administration of the study drug, unlabelled syringes were used. These were prepared preoperatively by an assistant and according to the randomization scheme. The performing anaesthetist was blinded to the group assignment. Three minutes after administration of the study drug, induction of anaesthesia started with 1 $\mu\text{g kg}^{-1}$ fentanyl i.v. Five minutes later, propofol 2 mg kg^{-1} i.v. was administered followed by succinylcholine 1 mg kg^{-1} after loss of consciousness. Sixty seconds later the patient's trachea was intubated. Anaesthesia was maintained with remifentanyl 0.25 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ and desflurane 0.5 minimal alveolar concentration (MAC). All patients received piritramide 3 mg i.v., a synthetic opioid for postoperative pain therapy, 20 min before the expected end of surgery. Postoperative pain therapy was standardized with oral diclofenac 50 mg twice a day and, if additional medication was needed, piritramide 0.05 mg kg^{-1} i.v.

All patients were visited at 24, 48 and 72 h after surgery by an investigator who was not aware of the group assignment. According to a standardized questionnaire, incidence, severity, and location of myalgia, and impairment of activity were assessed. To simplify data analysis, postoperative myalgia was graded as none, mild (numeric analogue scale 1-3), moderate (4-6) and severe (7-10). Muscle groups were divided into three regions (head/neck/shoulder, trunk and limbs).

Data are presented as means ($\pm\text{SD}$) or absolute values. χ^2 -test, Fisher's-exact test, and *U*-test were used as appropriate. A $P < 0.05$ was considered significant. The number-needed-to-treat (NNT) was calculated [8]. The NNT indicated how many patients have to receive pretreatment with parecoxib to prevent postoperative myalgia in one of them who would have had myalgia had they all received saline. We regarded an $\text{NNT} < 5$ as clinically relevant. For statistical calculations SigmaStat® 2.0 for Windows® (Jandel Corporation, San Rafael, CA, USA) and Microsoft Excel® X for Macintosh® (Microsoft Corporation, Redmont, WA, USA) were used. Calculation of sample size was based on previous studies [9,10]. When assuming a myalgia incidence of 60% in the control group, 34 patients per group were needed to detect a 55% reduction in myalgia with pretreatment ($\alpha = 0.05$, $\beta = 0.2$).

Results

Due to protocol violation (unexpected major surgery) one patient of the COX group was excluded from data analysis; consequently, data from 67 patients were analysed. Patient characteristics data, duration of anaesthesia and consumption of additional analgesic medication were comparable between the two groups (Table 1). In the COX group, seven patients reported myalgia compared with 11 patients in the SAL group; $P = 0.2$. The number of episodes of myalgia in the COX group did not differ significantly from the SAL group (13 vs. 21 episodes, $P = 0.175$) (Table 2). In the SAL group, one patient requested additional analgesics due to myalgia. In the COX group, no such requests were reported. The number of patients who felt limited in their activity due to myalgia, and the severity of myalgia was not significantly different between the two groups; $P = 0.11$ (Table 3). The NNT to prevent myalgia in one patient compared with saline was 9 (95% confidence interval, 3 to -10). No adverse drug reactions that could possibly be related to parecoxib were observed.

Table 1. Patient characteristics data

	COX ($n = 33$)	SAL ($n = 34$)
Age (yr)	36.9 (± 13)	44.6 (± 15.4)
Gender (M/F)	23/10	26/8
Height (cm)	174.3 (± 7.2)	172.3 (± 8.4)
Weight (kg)	73.5 (± 13.3)	75.9 (± 13.0)
Duration of anaesthesia (min)	114.7 (± 48.5)	114.3 (± 55.3)
Additional piritramide dose (mg)	7.5 (± 7.5)	9.3 (± 7.8)

Data are numbers or mean ($\pm$ SD). There were no significant differences.

Table 2. Incidence of postoperative myalgia

	COX ($n = 33$)	SAL ($n = 34$)
24h	7	9
48h	4	10
72h	2	2
Overall		
Patients with myalgia*	7 (21%)	11 (32%)
Number of episodes†	13	21

* Number of patients who had at least one episode of myalgia during follow-up.

† Number of episodes with myalgia during follow-up.

There were no significant differences.

Table 3. Severity and location of myalgia, and impairment of activity

	COX-patients with myalgia (n = 7)	SAL-patients with myalgia (n = 11)
Severity of myalgia*		
Mild	3	5
Moderate	2	4
Severe	2	2
Impairment of activity [†]	0	4
Localization of myalgia [‡]		
Neck/shoulder	6	7
Trunk	5	7
Limbs	0	4

*Highest ranking during follow-up reported by patients with myalgia.

[†]Number of patients who reported a limitation of activity due to myalgia.

[‡]Multiple notifications were allowed.

There were no significant differences.

Discussion

The present study examined for the first time whether parecoxib might reduce succinylcholine-related myalgia. The main finding was that preoperatively administered parecoxib failed to reduce incidence and intensity of myalgia over 72 h after anaesthesia.

Several studies have shown a significantly decreased incidence of myalgia following preoperative administration of a parenteral non-selective cyclooxygenase inhibitor such as aspirin or diclofenac [9,11]. In contrast, a preoperatively administered dose of intravenous ketorolac failed to reduce myalgia over 48 h after anaesthesia [4]. The authors of this study explained their result through the short duration of action of ketorolac. Another reason might have been the limited dose of ketorolac i.v. (10 mg) that was used in this study. Thus, the rationale to use parecoxib in our study was that this agent has a longer duration of action but a comparable onset of analgesic activity compared with ketorolac [12,13]. We used a bolus dose of parecoxib 40 mg. This corresponds to the highest single bolus dose that is recommended by the manufacturer, and we assumed that this dose had comparable analgesic properties as 30 mg of ketorolac. Moreover, parecoxib does not impair platelet function [14], and it was at least as efficient or even superior to ketorolac in different pain models [15,16]. It was also analgesic following preoperative administration [17].

It has been reported that the incidence of succinylcholine-related myalgia varies between 1.5% and 89% [18]. A variety of other factors may influence the incidence and severity of myalgia (e.g. type and location of surgery, ambulation, intubation trauma). To minimize any confounding factors on succinylcholine-induced myalgia, we limited the type of surgery to minor interventions. Postoperative evaluation of succinylcholine-associated myalgia was done with an established questionnaire that allows distinction between succinylcholine-associated myalgia and other forms of postoperative myalgia [7]. Also postoperative pain therapy was standardized.

The incidence of myalgia in the control group was lower compared with our recent study on patients undergoing minor eyes, nose, throat surgery [10]. This difference may be due to the different surgical settings. Other factors as the method of evaluation of postoperative myalgia and postoperative pain therapy were comparable between the two trials.

It could be hypothesized that the use of diclofenac for postoperative pain therapy interfered with the incidence of postoperative myalgia. So far, no data are available on the effect of non-steroidal anti-inflammatory drugs on established succinylcholine-associated myalgia. Moreover, it is unclear whether cyclooxygenase inhibitors have advantages compared to other regimens (e.g. opioids) regarding a decreased rate of postoperative myalgia. To avoid any dose-related effect of diclofenac on myalgia, a standard dose was used in all patients. Due to the design, our study should be sensitive enough to detect a prophylactic effect of parecoxib if there was one.

Postoperative myalgia has been described as a complex mechanism with different steps [18]. Furthermore it has been postulated that succinylcholine-related tissue damage and myalgia are separate entities [5]. In the study by Laurence, no relationship between the usage of succinylcholine, changes in biochemical markers as creatine kinase, and the incidence of myalgia was found [19]. Recent data showed that there is no evidence for a significant inflammatory reaction contributing to myalgia [10]. This led to the assumption that the primary effect of cyclooxygenase inhibitors on myalgia is not directly related to damage of muscular tissue and subsequent inflammatory reaction but to the influence on the effect of prostaglandines in nociception. Kahraman and colleagues observed a decrease of prostaglandin E₂-like activity in patients pre-treated with the cyclooxygenase inhibitor diclofenac before succinylcholine compared with a control group [11]. Additionally, there is some evidence for a pre-emptive analgesic effect of non-selective cyclooxygenase inhibitors as ke-

torolac and selective cyclooxygenase 2 inhibitors [20,21]. In this context, a preventive administration of an intravenous long-acting cyclooxygenase 2 inhibitor to avoid myalgia might be rationale. Our data show that the administration of parecoxib 40 mg i.v. immediately before induction of anaesthesia does not lead to a clinically relevant reduction of myalgia at any time during the follow-up. This result is in contrast to the findings of a recent meta-analysis that found a clinically relevant effect of preoperatively administered non-selective cyclooxygenase inhibitors on postoperative myalgia 24 h after anaesthesia [3]. Moreover, neither the severity of myalgia nor the limitation of patients' activity related to myalgia was significantly influenced by the pretreatment. Also the consumption of piritramide as an additional analgesic was comparable in both groups.

We cannot exclude that earlier administration of parecoxib would improve its efficacy; however, in an ambulatory setting, a longer pretreatment interval might be impracticable.

Recent reports about severe adverse effects with parecoxib in different surgical settings suggested that this agent could possibly be harmful in patients with an increased perioperative risk [22,23]. This begs the question as to whether the use of parecoxib is generally justified to avoid a comparatively minor problem as postoperative myalgia. However, in our study no parecoxib-related adverse effects were observed.

In conclusion, the results of this trial show that preoperatively administered parecoxib does not significantly reduce succinylcholine-related myalgia over 72 h. The use of parecoxib for the prevention of postoperative myalgia does not seem to be justified.

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Appendix: Postoperative questionnaire for myalgia study

Patient ID:

Date of surgery:

Type of surgery:

Follow-up: 24h 48h 72h

1. Do you have any stiffness or soreness in your body besides headache and pain at the surgical side? yes___ no___
2. Have you been up? yes___ no___
3. Is there pain and stiffness in the muscles? yes___ no___
4. In which sites do you have the muscle pain/stiffness? Jaw___ Throat___ Neck___ Shoulders___ Arm___ Chest___ Abdomen___ Back___ Buttocks___ Thighs___ Calves___ Generalized___ Buttocks___ Thighs___ Calves___ Generalized___
5. When did you first noticed the pain? ____
6. Rate the muscle stiffness/pain on score (0 being no pain and 10 worst pain ever) only on the sites to be painful by the patient. Jaw___ Throat___ Neck___ Shoulders___ Arm___ Chest___ Abdomen___ Back___ Buttocks___ Thighs___ Calves___ Generalized___
7. What makes the muscle stiffness/pain worst? Movement___ Rest___
8. Describe the muscle pain/stiffness in your (patient's) own words.
9. Do you think the muscle pain is restricting your activity? yes___ no___
10. Is the muscle pain preventing you from getting out of bed? yes___ no___
11. Have you ordered any extra pain medication because of the muscle pain? yes___ no___
12. Are you taking your prescribed pain medication to help your surgical pain___ or your muscle pain___?

Chapter 8

Discussion

Many advances in anaesthesia techniques have been made over the last 50 years. However, during acute situations, anaesthesiologists still trust a drug with a lot of adverse effects. Efforts were made to find a successor for succinylcholine with comparable properties. Rocuronium, introduced in the 1990, seemed to be the first non-depolarizing agent with an onset profile that was comparable to succinylcholine. However, the dose of rocuronium for a succinylcholine-like onset is huge ($3\text{--}4 \times \text{ED}_{95}$), which results in a duration of action that is 10 to 15 times longer than the duration of action of succinylcholine.

In 2000 the non-depolarizing rapacuronium was introduced in the USA, and only for the US market. The pharmacological properties of this agent were promising and with a rapid onset and offset almost mimicking succinylcholine. Unfortunately, several fatalities were associated with the use of rapacuronium and, therefore, it was withdrawn from the market shortly after its introduction.

The last agent that has been dedicated to be a potent successor for succinylcholine, until now, was the benzylisocholine gantacurium (GW280430A, AV430). But the agent is still undergoing clinical testing and it is not predictable if it will ever enter the market and become a place in clinical practice [1].

In 2008 sugammadex, a specific binding agent for steroidal neuromuscular blockers such as rocuronium and vecuronium was introduced in clinical practice. Due to its mechanism of action this cyclodextrin provides a rapid reversal even of a deep neuromuscular block within minutes. Therefore, it has been suggested that succinylcholine should be withdrawn from clinical practice and might be replaced by a combination of rocuronium with sugammadex, which now offers a rapid onset combined with a rapid offset due to the antagonist [2]. However, when focusing on intubation conditions during a rapid sequence induction, succinylcholine still offers intubation conditions which are superior in comparison to rocuronium. This has been implied by a recent systematic review in the field of anaesthesia [3] and was also stated in the field of emergency medicine [4]. Consequently, one can expect that succinylcholine still will claim its place in clinical anaesthesia. Probably, the rapid sequence induction will be a small niche for the agent, but a very important one. Another clinical field where succinylcholine is commonly in use until today is the field of electroconvulsive therapy [5]. Furthermore, succinylcholine, as a very inexpensive agent in comparison to rocuronium/sugammadex, will play a role, when the budget is tight for example in underdeveloped areas, but also in our crisis ridden situation.

Two main aspects emerge from today's situation.

Firstly, there is still a necessity for clinical research on succinylcholine, its effects, and its side effects.

Secondly, the need for a non-depolarizing successor of succinylcholine with a beneficial side-effects profile is still existent.

The present thesis focuses on the problem of postoperative myalgia. As stated before, the aetiology of this problem seems to be multifactoral and it might be an illusion to find an universal strategy in preventing this adverse effect. However, some new insights can be taken from this work with respect to the emphasized research questions. In the future, this may improve the clinical use of succinylcholine.

Several factors such as gender, age, type of surgery, and ambulation have been associated with an increased incidence and severity of succinylcholine-associated myalgia [6].

However, an underlying baseline risk for postoperative myalgia specifically for outpatients for several neuromuscular blockers has been already described [7-9]. Thus, the first trial of the present thesis estimates the baseline risk of myalgia for outpatients at the institution the research took place (University Hospital of the Saarland, Homburg, Germany). The study could confirm the findings that episodes of myalgia were also present in patients who did not receive succinylcholine but received rocuronium (chapter 3). Therefore, the implication that, because of postoperative myalgia, succinylcholine might not be an appropriate drug for ambulatory anaesthesia seems to be questionable [10]. Furthermore, it remains speculative whether the use of rocuronium/sugammadex for outpatients may decrease the incidence of postoperative myalgia in this specific group of patients.

Postoperative myalgia has some clinical similarities with muscle pain following unaccustomed muscular stress, i.e. delayed onset muscular soreness (DOMS). Soreness normally occurs 24 hours after muscular stress, the characteristics of pain are comparable, and also the exact aetiology of DOMS is also still unknown. A number of theories have been proposed to be associated with the origin of DOMS. These included lactate acidosis, muscle spasm, connective tissue and cell damage, enzyme efflux, and inflammation [11]. Some of these aetiologies were also investigated in patients receiving succinylcholine. But neither electrolytes nor enzymes as a marker for cell damage could be successfully linked with the intensity of postoperative myalgia following succinylcholine. Data from sports medicine implied that an inflammatory process might take part in the aetiology of DOMS due to an increase of pro-inflammatory cyto-

kines following exercise and, therefore, also in postoperative myalgia [12]. The findings in sports medicine were confirmed in various settings of exercise by several authors. Due to the fact that interleukin-6 is produced in the skeletal muscle this cytokine has been termed as an “inflammation-responsive” myokine [13]. Consequently, it should be highly specific for trauma and inflammation in the muscular tissue. However, a significant increase of inflammatory parameters such as interleukin-6 could not be observed in patients with succinylcholine-associated myalgia. Furthermore, an anti-inflammatory agent with a strong potency (i.e. dexamethasone) did not influence the incidence or intensity of succinylcholine-associated myalgia (chapter 4). Thus, in contrast to the well known soreness phenomenon following unaccustomed exercise it might be concluded that inflammation does not play a key role in the pathogenesis of succinylcholine-associated myalgia. However, anti-inflammatory agents such as diclofenac were found effective in reducing postoperative myalgia when administered before succinylcholine [14]. Basically, these clinical findings were confirmed in a meta-analysis (Chapter 6) and might be best explained by inhibiting the production of pain mediating prostanoids. The cited meta-analysis also showed that data on the prophylactic use of non-steroidal anti-inflammatory agents and aspirin in the prevention of myalgia are currently limited.

Due to the lack of data about non-steroidal anti-inflammatory drugs in the prevention of postoperative myalgia a trial was initiated where the effect of a selective cyclooxygenase-2 inhibitor was tested. Cyclooxygenase-2 inhibitors are offering some advantages regarding postoperative bleeding complications when compared with non-selective cyclooxygenase inhibitors such as diclofenac [15]. In this trial parecoxib failed to be efficient in the prevention of myalgia following succinylcholine (chapter 7). A calculated number-needed-to-treat of 9 reflects this issue. Regarding a lack of efficacy and in the light of several reports about adverse cardiac events following the use of parecoxib does not seem to be justified in the prophylaxis of a comparable minor problem such as myalgia. The results of the trial also emphasize the question if a concept of preemptive analgesia does promise success for postoperative soreness. However, it remains unclear if a postoperative treatment of myalgia with a cyclooxygenase inhibitor (selective or non-selective) will be successful.

Another aspect of this thesis regards the side effects of different pretreatments. As stated in the meta-analysis (chapter 6) pretreatment with different agents may lead to adverse effects associated with these agents. The available data allowed a risk-analysis for adverse effects following a pretreatment with

non-depolarizing neuromuscular blocking agents. These adverse effects included weakness, shortness of breath, diplopia, and difficulties in swallowing. Beside these there are side effects which are more specific for the single agents. Rocuronium has been described as the most efficient non-depolarising blocking agent in the prophylaxis of succinylcholine-associated myalgia (chapter 6). However, rocuronium itself may cause pain during injection even in sub-paralyzing doses. Thus, the effect of a dose of $0.1 \times \text{ED}_{95}$ rocuronium was tested in a randomized controlled trial in 120 patients (Chapter 5). In this trial 32% of the patients felt injection pain following rocuronium. Women were significantly more affected than men (45 vs. 20%). It was already suggested that gender may have an influence onto pain tolerances and sensation of pain [16]. But this gender-related effect might also depend on the type of pain initiation [17]. It seems that not even the perception of myalgia shows gender-related differences, but also those following rocuronium. During the last years several strategies have been published to avoid injection pain after rocuronium which included lidocaine, opioids, sodium bicarbonate, and esmolol [18,19]. It might be a recommendation to consider one of these strategies before the use of rocuronium, even before using a pretreatment dose.

In conclusion, four main results are emerging from the present thesis. Firstly, myalgia does not appear exclusively after the use of succinylcholine but also following non-depolarizing neuromuscular blockers. Secondly, it does not seem that an inflammatory component takes a significant part in the pathogenesis of succinylcholine-associated myalgia. Thus, the usefulness of anti-inflammatory agents in the prevention of succinylcholine-associated myalgia might be limited. Thirdly, non-depolarizing neuromuscular blocking agents and sodium channel inhibitors are effective in the prevention of succinylcholine-associated myalgia, according to an evidence-based approach. This might be also the case for non-steroidal anti-inflammatory drugs. However, data are limited for this class of agents. And fourthly, gender-related differences of pain perception are not restricted to postoperative myalgia but may occur also after pretreatment with rocuronium.

Finally, the exact aetiology and pathogenesis of succinylcholine-associated myalgia still remains unknown. However, this clinical problem continues to be important for clinicians and patients as recent publications have shown [20,21]. Thus, there is still a need for future research on the field of the prevention and, maybe more important, the therapy of succinylcholine-associated myalgia.

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Chapter 9

Summary

The depolarizing neuromuscular blocking agent succinylcholine was introduced in 1952 into clinical practice. Despite its high rate of possible adverse effects the agent has become very popular in clinical anaesthesia due to its unique pharmacological properties such as rapid onset and offset. Like every drug, succinylcholine has side effects. Some of the known side effects of the agent might be life threatening such as malignant hyperthermia or bradycardia. Others are relatively minor but may cause discomfort to the patient such as postoperative myalgia (POM) which is associated with the use of succinylcholine and may last for several days.

Many efforts were undertaken in the prevention of POM since the introduction of succinylcholine and several techniques were tested regarding their efficacy. Most of these were pharmacological pretreatments with different agents such as non-depolarizing neuromuscular blockers. However, none of the tested techniques seems to be completely reliable in the prevention of POM. One of the difficulties in finding an optimal prevention might be that there is still a lack of knowledge about the aetiology of POM.

Therefore, one of the aims of this thesis was to find some new insights in the aetiology of POM investigating the hypothesis of an inflammatory reaction that possibly contributes to myalgia. Further, the efficacy and side effects of different pretreatment regimens were analysed and the effect of cyclooxygenase-2 inhibitors on POM was tested.

Chapter 1 introduces the problem of postoperative myalgia following succinylcholine. It briefly describes the history of succinylcholine in clinical anaesthesia. Further, several hypotheses over the aetiology of succinylcholine-associated myalgia and different strategies in its prevention are reflected.

Chapter 2 gives a general overview about the physiology and pharmacology of the neuromuscular junction. All neuromuscular blocking agents that are currently in use are discussed with their pharmacological properties and possible side effects. In a second part the various techniques of neuromuscular monitoring are described in detail. The chapter offers information about devices, stimulation patterns, and recent recommendations about the use of neuromuscular monitoring.

The basic incidence of POM in outpatients at the institution where all of the clinical trials in this thesis took place (University Hospital of the Saarland, Homburg, Germany) was estimated in a study that is presented in **chapter 3**. 120 patients were tested with three different regimens for neuromuscular blockade in a randomized controlled trial. The three regimens of neuromuscular block for

intubation included either the non-depolarizing agent rocuronium or the depolarizing agent succinylcholine. The third group of patients received succinylcholine after a precurarization dose of rocuronium ($0.1 \times \text{ED}_{95}$). All other anaesthetic conditions were standardized. Myalgia was assessed in all patients over 24 hours. There was no significant difference in the incidence of myalgia between the three groups. Moreover, the precurarization regimen led to an increased count of side effects such as heavy eyelids, diplopia, and difficulty in swallowing. Thus, routine precurarization in outpatients might be questionable.

In **chapter 4** the hypothesis if an underlying inflammation may contribute to succinylcholine-associated myalgia was tested. Therefore, 64 patients scheduled for ENT-surgery were included in a randomized controlled trial. The patients were randomized into two groups; group one received an anaesthetic pretreatment with dexamethasone 8 mg and group two a pretreatment with saline in a double blinded manner. The saline group underwent an additional subgroup randomization. Interleukin-6 which is a pro-inflammatory cytokine was estimated in the ten patients of this subgroup at different times of the perioperative period. Anaesthetic regimen included succinylcholine and was standardized in all patients. The incidence of POM was estimated in all patients over 72 hours postoperatively. Dexamethasone-pretreatment did not influence the incidence of POM significantly. In the subgroup no correlation between POM and an increase of plasma interleukin-6 concentrations was found. This led to the conclusion that there is no evidence for an inflammatory origin of succinylcholine-associated myalgia.

Chapter 5 describes a trial that investigates a side effect of rocuronium. Even in a small precurarization dose of $0.1 \times \text{ED}_{95}$ rocuronium may cause injection pain. The hypothesis was tested whether gender may influence the pain perception on a subparalyzing dose of rocuronium. 120 patients (60 women and 60 men) were included in the study. 80 (40 women and 40 men) of them received a subparalyzing dose of rocuronium following a randomization scheme. All others received saline for control. The main endpoints were pain on injection, thrombophlebitis, and other signs of local irritation. Women reported significantly more pain on injection even of a subparalyzing dose of rocuronium which might be taken as additional evidence in a gender-related difference in pain perception.

Since the introduction of succinylcholine a great variety of pretreatment strategies were tested on the efficacy. **Chapter 6** contains a meta-analysis that was done in accordance to current standards in evidence based medicine (QUORUM statement). The efficacy of different pretreatments in the prevention of

succinylcholine-associated myalgia and fasciculations was calculated based on the results of 52 randomized controlled trials with 5318 patients. Non-depolarizing neuromuscular blockers, lidocaine, and magnesium were efficient in preventing fasciculations with a calculated number-needed-to-treat of 1.2-2.5. Myalgia after 24 hours postoperatively was best prevented by non-steroidal anti-inflammatory drugs (NSAID), lidocaine, and rocuronium with a number-needed-to-treat of 2.5-3. There was a dose-dependent risk of side effects such as blurred vision, diplopia, heavy eyelids, and difficulty in swallowing if neuromuscular blocking agents were used for pretreatment. Furthermore, there was evidence that myalgia was less if a dose of 1.5 mg kg⁻¹ succinylcholine was used (instead of 1 mg kg⁻¹). Thus, myalgia may best be prevented with muscle relaxants, lidocaine, or non-steroidal antiinflammatory drugs. The risk of potentially serious adverse events with muscle relaxants is not negligible. Data that allow for a risk-benefit assessment were lacking for other drugs.

Due to the fact that NSAID were found efficient in the previous meta-analysis a follow-up trial was established to test the effect of a selective cyclooxygenase 2-inhibitor on POM. The results of this randomized controlled trial that included 67 patients are described in **chapter 7**. Non-selective NSAID may increase the risk of blood loss in the perioperative period; a side effect that should not be observed following a selective cyclooxygenase 2-inhibitor. Parecoxib was chosen as the testing drug. In contrast to the results of the previous meta-analysis parecoxib was not clinically efficient in the prevention of POM with a calculated number-needed-to-treat of 9. Further, no significant decrease in the impairment of activity due to POM was found in patients who were pretreated with parecoxib. Moreover, the use of cyclooxygenase 2-inhibitors in the prevention of a comparably minor problem such as POM remains questionable in the light of possible cardiovascular side effects which were associated with this class of agents.

Chapter 8 is the final one which highlights the main results of this thesis. The impact of recent developments in clinical anaesthesia such as the introduction of new agents and its relevance on the future use of succinylcholine are discussed. However, a successor of succinylcholine with a comparable pharmacological profile has not been found yet. Moreover, the exact pathogenesis remains unclear and is not fully understood. Therefore, no optimal pretreatment or treatments of succinylcholine-associated myalgia are available. This emphasizes the necessity for future research on succinylcholine-associated myalgia.

Samenvatting

De depolariserende spierverslapper succinylcholine werd geïntroduceerd in 1952 in de klinische praktijk. Ondanks de hoge waarschijnlijkheid van mogelijke negatieve effecten van deze substantie is hij zeer populair geworden in de klinische anesthesie, vanwege zijn unieke farmacologische eigenschappen zoals snelle onset en offset. Succinylcholine heeft bijwerkingen zoals elk ander geneesmiddel. Enkele van de bekende bijwerkingen van de agent zijn mogelijk levensbedreigend zoals bijvoorbeeld maligne hyperthermie of bradycardie. Andere geassocieerde bijwerkingen zijn relatief ongevaarlijk, maar leiden tot ongemak voor de patiënt, zoals postoperatieve spierpijn (POM). POM kan een week duren.

Sinds de invoering van succinylcholine werden een groot aantal onderzoeken verricht over de preventie van POM en verschillende technieken werden getest met betrekking tot hun effectiviteit. De meeste van deze waren farmacologische voorbehandelingen met verschillende middelen, zoals niet-depolariserende spierverslappers. Echter, geen van de beproefde technieken lijkt volledig betrouwbaar in de preventie van POM. Een van de moeilijkheden bij het vinden van een optimale preventie zou kunnen zijn dat er nog steeds een gebrek aan kennis is over de etiologie van POM.

Een van de doelstellingen van dit proefschrift was een aantal nieuwe inzichten in de etiologie van POM te vinden, met name het onderzoek naar de hypothese van een ontstekingsreactie die mogelijk bijdraagt aan de spierpijn. Verder werden de werkzaamheid en bijwerkingen van verschillende preventieve behandelingsschema's geanalyseerd en het effect van cyclooxygenase-2-remmers op POM werd getest.

Hoofdstuk 1 introduceert het probleem van postoperatieve spierpijn na succinylcholine. Het beschrijft de geschiedenis van succinylcholine in de klinische anesthesie. Verder werden er een aantal hypothesen over de etiologie van succinylcholine-geassocieerde spierpijn en verschillende strategieën in de preventie van POM behandeld.

Hoofdstuk 2 geeft een algemeen overzicht over de fysiologie en farmacologie van de neuromusculaire junctie. Alle spierverslappers die momenteel klinisch in gebruik zijn worden besproken met hun farmacologische eigenschappen en mogelijke bijwerkingen. In een tweede deel werden verschillende technieken van de neuromusculaire bewaking gedetailleerd beschreven. Het hoofdstuk biedt informatie over apparaten, stimulatie technieken, en de recente aanbevelingen over het gebruik van de neuromusculaire bewaking.

De incidentie van POM bij poliklinische patiënten in de instelling waar alle klinische studies in dit proefschrift hebben plaatsgevonden (Universitair Ziekenhuis Saarland, Homburg, Duitsland) werd bepaald door een studie die wordt gepresenteerd in **hoofdstuk 3**. 120 patiënten werden getest met drie verschillende regimes voor spierverslapping in een gerandomiseerde en gecontroleerde trial. De drie regimes van de neuromusculaire blokkade voor intubatie bevatte de niet-depolariserende agent rocuronium of de depolariserende agent succinylcholine. De derde groep patiënten kreeg succinylcholine na een precurarisatie dosis rocuronium ($0,1 \times \text{ED}_{95}$). Alle andere voorwaarden waren gestandaardiseerd. Myalgie werd onderzocht bij alle patiënten gedurende 24 uur. Er was geen significant verschil in de incidentie van spierpijn tussen de drie groepen. Bovendien leidde de precurarisatie regime tot een verhoogd incidentie van bijwerkingen zoals zware oogleden, diplopie, en moeite met slikken. Concluderend lijkt routine precurarisatie bij poliklinische patiënten twijfelachtig.

In **hoofdstuk 4** werd de hypothese getest of een onderliggende ontsteking kan bijdragen tot succinylcholine-geassocieerde spierpijn. Daarom werden 64 elective KNO-patiënten opgenomen in een gerandomiseerde gecontroleerde trial. De patiënten werden gerandomiseerd in twee groepen. Een groep kreeg een preoperatief voorbehandeling met dexamethason 8 mg en groep twee een voorbehandeling met zout (controle) op een dubbel blinde manier. De controle groep onderging een extra subgroep randomisatie. De pro-inflammatoire cytokine interleukine-6 werd bepaald in de tien patiënten van deze subgroep op verschillende tijdstippen van de postoperative periode. Het anesthesie regime was gestandaardiseerd bij alle patiënten. De postoperatieve incidentie van de POM werd geëvalueerd voor 72 uur. Dexamethason-voorbehandeling had geen

significante invloed op de incidentie van POM. In de subgroep werd er geen correlatie tussen POM en een toename van de plasma concentraties van interleukine-6 gevonden. Dit leidde tot de conclusie dat er geen aanwijzingen voor een ontstekingsreactie als oorsprong van succinylcholine-geassocieerde spierpijn zijn.

Hoofdstuk 5 beschrijft een studie die een neveneffect van rocuronium onderzoekt. Zelfs in een klein dosis voor precurarisatie van $0,1 * ED_{95}$ kan rocuronium injectie pijn veroorzaken. De hypothese werd getest of het geslacht van invloed kunnen zijn op der pijn perceptie na een subparalyserende dosis rocuronium. 120 patiënten (60 vrouwen en 60 mannen) werden opgenomen in de studie. Gerandomiseerd kregen 80 (40 vrouwen en 40 mannen) van hen een subparalyserend dosis rocuronium. Als controle kregen de anderen een zoutoplossing. De voornaamste eindpunten waren pijn bij injectie, tromboflebitis, en andere tekenen van lokale irritatie. Vrouwen meldde significant meer pijn bij injectie zelfs van een subparalyserend dosis rocuronium. Dit resultaat zou als aanvullend bewijs voor geslachtsgerelateerde verschil in pijn perceptie kunnen worden gezien.

Sinds de invoering van succinylcholine werd er een grote verscheidenheid van preventie strategieën getest op de werkzaamheid om succinylcholine-geassocieerde spierpijn te voorkomen. **Hoofdstuk 6** bevat een meta-analyse die werd gedaan in overeenstemming met de huidige normen in de evidence based medicine (QUORUM verklaring). De werkzaamheid van de verschillende voorbehandelingen in de preventie van succinylcholine-geassocieerde spierpijn en fasciculaties werd berekend op basis van de resultaten van 52 gerandomiseerde gecontroleerde studies met in totaal 5318 patiënten. Niet-depolariserende neuromusculaire blokkers, lidocaïne, en magnesium zijn efficiënt in het voorkomen van fasciculaties met een berekende number-needed-to-treat van 1.2-2.5. Spierpijn na 24 uur postoperatief werd het beste voorkomen door niet-steroïdale anti-inflammatoire geneesmiddelen (NSAID), lidocaïne, en rocuronium met een number-needed-to-treat van 2.5-3. Er was een dosis-afhankelijke risico op bijwerkingen zoals wazig zien, diplopie, zware oogleden, en moeite met slikken als neuromusculair blokkerende stoffen werden gebruikt voor de voorbehandeling. Bovendien waren er aanwijzingen dat spierpijn minder was als een dosis van $1,5 \text{ mg kg}^{-1}$ succinylcholine werd gebruikt (in plaats van 1 mg kg^{-1}). Zo kan spierpijn met spierverslappers, lidocaïne, of niet-steroïde anti-inflammatoire drugs best worden voorkomen. Het risico van potentieel ernstige ongewenste voorvallen met spierverslappers is niet te onderschatten. De ge-

vens die het mogelijk maken om een risico-benefit analyse te maken ontbraken voor andere voorbehandelingen.

Vanwege het feit dat NSAID efficiënt werden gevonden in de vorige meta-analyse, werd een follow-up studie opgezet om het effect van een selectieve cyclooxygenase 2-remmer op POM te onderzoeken. De resultaten van deze gerandomiseerde gecontroleerde studie met 67 geanalyseerde patiënten worden beschreven in hoofdstuk 7. Niet-selectieve NSAID's kunnen het risico van bloedverlies verhogen tijdens de perioperative periode, een bijwerking die na toediening van een selectieve cyclooxygenase 2-remmer niet zou gebeuren. Voor dit onderzoek werd parecoxib gekozen. In tegenstelling tot de resultaten van de vorige meta-analyse was parecoxib klinisch niet efficiënt in de preventie van POM met een berekende number-needed-to-treat van 9. Verder werd geen significante afname van een activiteitsbeperking als gevolg van POM gevonden bij patiënten die een voorbehandeling met parecoxib ontvingen. Bovendien blijft het gebruik van cyclooxygenase-2-remmers in de preventie van een relatief klein probleem, zoals POM bedenkelijk in het licht van mogelijke cardiovasculaire bijwerkingen die werden geassocieerd met deze klasse van agenten.

In de afsluitend **Hoofdstuk 8** worden de belangrijkste resultaten van dit proefschrift samengevat. De impact van de recente ontwikkelingen in de klinische anesthesie, zoals de invoering van nieuwe medicijnen en de relevantie daarvan voor het toekomstige gebruik van succinylcholine worden besproken. Er is echter nog geen opvolger van succinylcholine met een vergelijkbaar farmacologisch profiel gevonden. Bovendien blijft de exacte pathogenese nog niet volledig begrepen. Daarom is er geen optimale voorbehandeling of behandeling van succinylcholine-geassocieerde spierpijn beschikbaar. Dit benadrukt de noodzaak voor toekomstig onderzoek op succinylcholine-geassocieerde spierpijn.

Curriculum vitae

Jan-Uwe Schreiber was born on December 30, 1969 in Gütersloh, Germany. In 1989 he graduated from secondary school and worked as an Emergency Medical Technician for three years. In 1993 he started his medical studies at the Albert-Ludwigs-Universität Freiburg, Germany where he also earned his medical degree in May 2000. In the same year his doctoral thesis (Dr. med.) on “Escape rhythms in patients following His-bundle ablation and third-degree AV nodal block” was finished at the University of Freiburg and rated “cum laude”. He began his training in anaesthesiology in September 2000 at the Department of Anaesthesia and Critical Care Medicine at the University Hospital of the Saarland, Homburg, Germany (Prof. Dr. R. Larsen). After receiving board certification as an anaesthesiologist he became staff member of the department in 2005 and later Oberarzt. From 2007 to 2008 he completed his fellowship in intensive care medicine and got his board certification (“Zusatzbezeichnung Intensivmedizin”). In august 2008 he joined the staff of the Department of Anaesthesia and Pain Management at azM/Maastricht UMC.

His main scientific interests are the clinical pharmacology of neuromuscular blocking agents and evidence-based approaches in clinical anaesthesia. He is *ad-hoc* reviewer for several peer-reviewed journals such as *Anesthesia & Analgesia*, *Acta Anaesthesiologica Scandinavica*, and *Journal of Clinical Anesthesia* and active member of several national and international anaesthesia societies. Clinically, his main interests are cardiovascular anaesthesia and intraoperative transeophageal echocardiography.

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