

Prevention of Succinylcholine-induced Fasciculation and Myalgia

A Meta-analysis of Randomized Trials

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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 succinylcholine (compared with 1 mg/kg). 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.

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 myalgia⁸; 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

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Received from the Department of Anesthesiology and Critical Care Medicine, University Hospital of the Saarland, Homburg, Germany; the Département d'Anesthésie et de Réanimation, Centre Hospitalier Universitaire Nancy/Brabois, Nancy, France; and the Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland. Submitted for publication November 24, 2004. Accepted for publication June 17, 2005. Supported by grant No. 3233-051939.97 from the Swiss National Science Foundation, Bern, Switzerland (to Dr. Tramèr). Presented in part as an abstract at the 13th Annual Meeting of the European Society of Anaesthesiology, Euroanaesthesia 2005, Vienna, Austria, May 28–31, 2005.

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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 performed 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 cluster⁶³ of which we considered the older report as the original⁵⁷ and excluded the duplicate.⁶⁴ One pediatric study was excluded,⁶⁵ because all other trials were in adults.

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

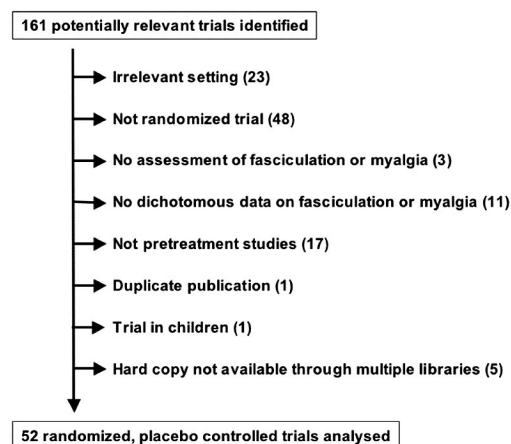


Fig. 1. Flowchart of retrieved, excluded, and analyzed trials.

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

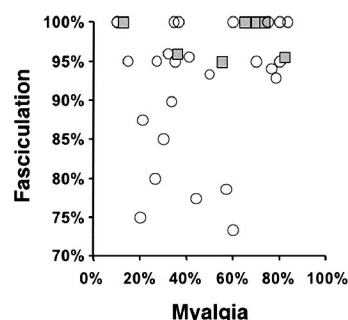


Fig. 2. Incidence of fasciculation and of myalgia in control patients who received a placebo or no treatment (*i.e.*, control event rate). Each symbol represents one trial. Data are shown for 35 trials that reported on both fasciculation and myalgia, and where the dose of succinylcholine was 1 mg/kg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

§ Details of the trials are available at: <http://www.hcuge.ch/anesthesie/data>. Accessed May 13, 2005.

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 SCh	227/231 (98.3)	1.07	16	145/231 (62.8)	1.41	6
1.5 mg/kg 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.

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.

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).

Fentanyl,^{3,16,21,26,33,41,44,45,50,51,61} methadone,³⁶ or meperidine²⁹ 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).

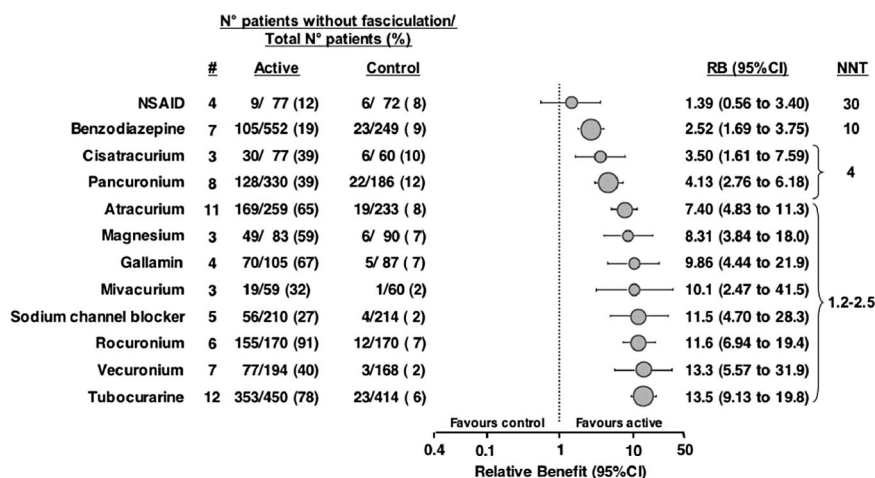
In 9 trials, the dose of succinylcholine was 1 mg/

kg,^{16,21,23,26,32,36,46,54,55} and in 25 trials, the dose was 1.5 mg/kg.^{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 succinylcholine. The average incidence of fasciculation was 98.3% with 1 mg/kg succinylcholine and 92.0% with 1.5 mg/kg. The average incidence of myalgia at 24 h was 62.8% with 1 mg/kg succinylcholine and 44.6% with 1.5 mg/kg. Both differences were statistically significant; for prevention of fasciculation with 1.5 mg/kg succinylcholine compared with 1 mg/kg, 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} phenytoin²⁹), 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} C²⁸), magnesium sulfate,^{17,36,58} calcium chloride,⁴² dantrolene,¹⁹ dexamethasone,⁵⁵ chlorpromazine,^{22,42} and succinylcholine.^{15,48,62}

Fig. 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.



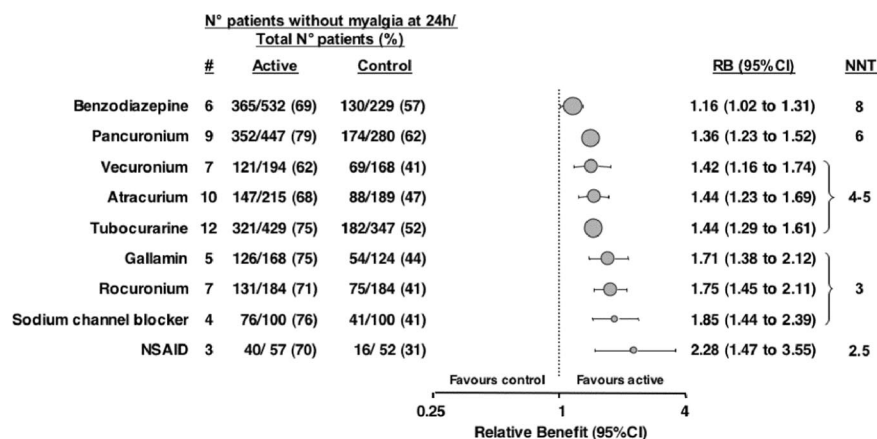


Fig. 4. Prevention of succinylcholine-related myalgia at 24 h. For each intervention that was tested in at least three trials, a meta-analysis was performed (# = number of analyzed trials). Symbol sizes are proportional to the number of analyzed patients. CI = confidence interval; NNT = number needed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

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.#

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.#

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.

Adverse Effects

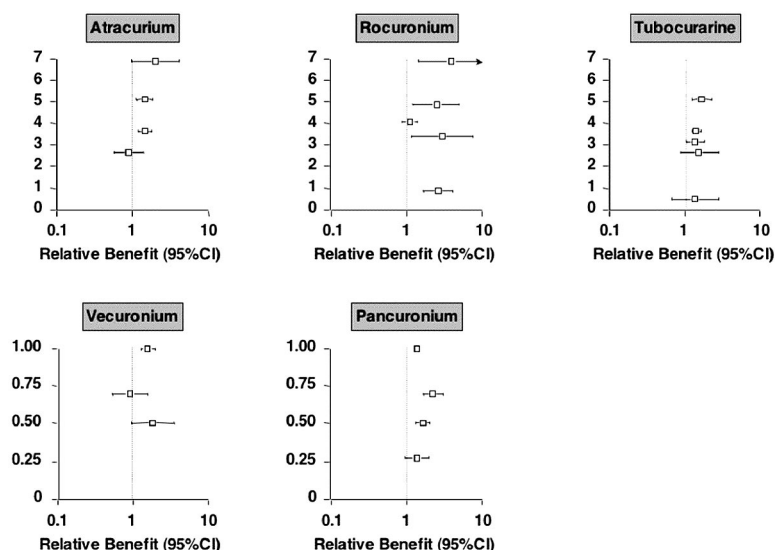
Nine trials reported on adverse effects.^{3,17,19,23,38,44,51,59,61} Blurred vision, diplopia, heavy eyelids, muscle weakness, difficulty in swallowing, and voice disorder were significantly more often reported in patients who received a nondepolarizing muscle relaxant (table 2). With pancuronium, dose-responsiveness 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 µg/kg, 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

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

Details of the meta-analyses are available at: <http://www.hcuge.ch/anesthesia/data>. Accessed May 13, 2005.

Fig. 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.



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.

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
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 μ g/kg, respectively, for 70 kg body weight); medium dose 0.42–0.49 mg (6–7 μ g/kg, respectively); high dose 0.63–0.70 mg (9–10 μ g/kg, respectively). Dose ranges were arbitrarily chosen.

CI = confidence interval.

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 prejunctional agonistic action of succinylcholine on nicotinic receptors that results in rapid firing.⁶⁸ Nondepolarizing muscle relaxants effectively 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 pancuro-

nium 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 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 $\mu\text{g/kg}$. Approximately 15 of 100 patients are symptomatic at 7 $\mu\text{g/kg}$. 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 ED_{95} . 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 succinyl-

choline-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.

The authors thank Nazan Afan, B.S. (Graduate Student, Medical School, University of the Saarland, Homburg, Germany), and Emanuela Morinello, M.D. (Resident in Anesthesia, Department of Anesthesiology and Critical Care Medicine, University Hospital of the Saarland), for their help in translating Turkish and Italian reports.

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