2021년

대한신경근연구학회 춘계 학술대회

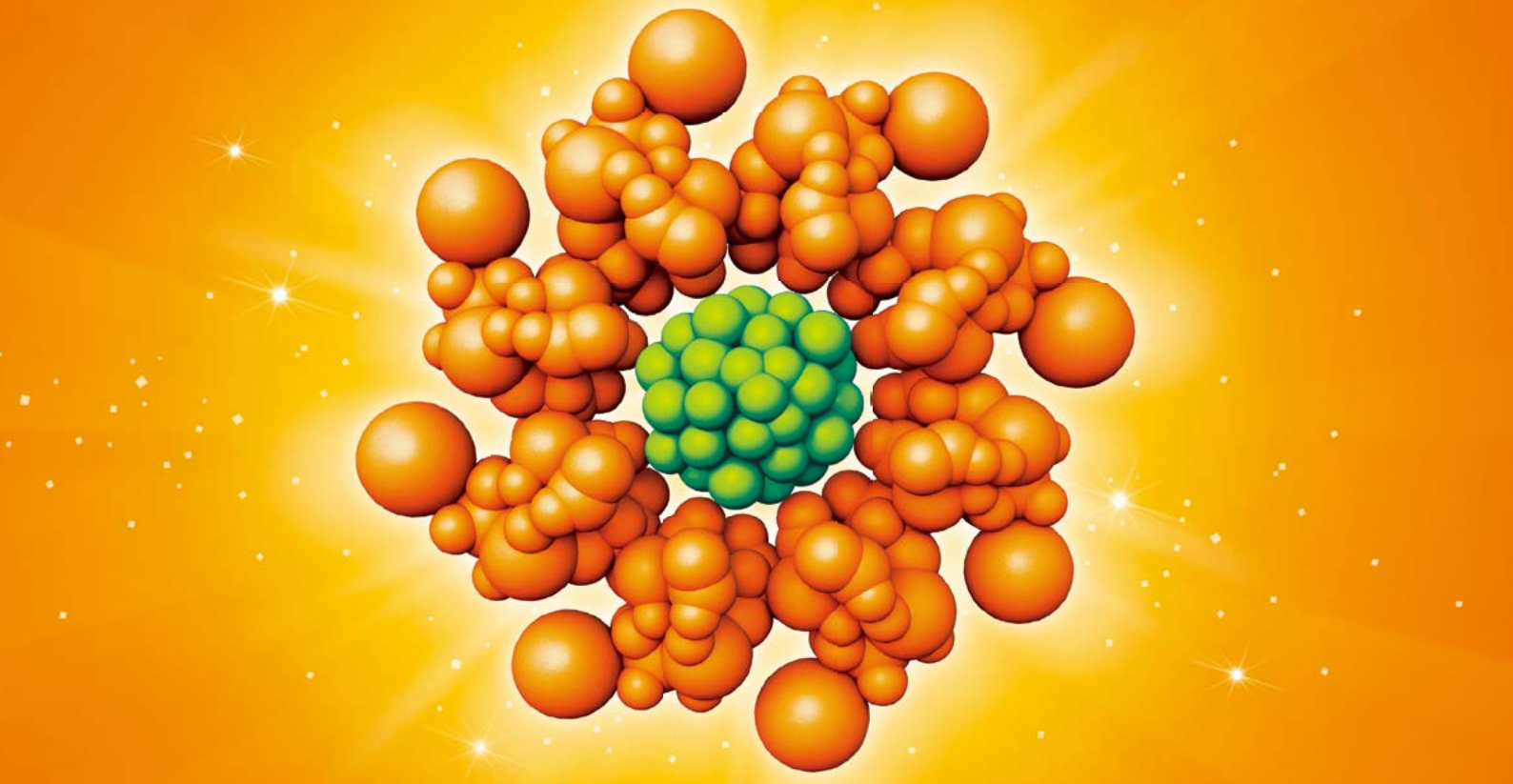
Online Web Seminar

일시 : 2021년 6월 26일(토)

Korean Neuromuscular Reserarch Society

대한신경근연구학회
Korean Neuromuscular Reserarch Society

EXPERIENCE THE BRIDION EFFECT[1,2]



Bridion (sugammadex) offered significantly fast and predictable recovery in most patients with moderate to profound rocuronium-induced neuromuscular blockade (NMB).[1,2]

Reappearance of T_2 for reversal of a NMB : 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. In comparison, it took 101 min for 98% of patients receiving neostigmine to recover to a TOF ratio of 0.9.[1]

Reappearance of 1-2 PTCs. : The median (range [interquartile range]) time to recovery of the TOF ratio to 0.9 was 2.7 (1.2-16.1 [2.1-4.1]) min in the Bridion (sugammadex) group versus 49.0 (13.3-145.7 [35.7-65.6]) min in the neostigmine group.[2]

Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium.[3]

The safety and efficacy of Bridion for pediatric and adolescents under the age of 18 has not been established.[3]

*** For more information, please refer to the full prescribing information.**

T_2 : The second twitch, **TOF :** Train-of-four, **PTC :** Posttetanic count

Bridion®(Sugammadex) 100 mg Selected Safety Information

[Indications and Usage] Reversal of neuromuscular blockade induced by rocuronium or vecuronium. **[Dosage and Administration] Adults:** Routine reversal: A dose of 4 mg/kg Bridion is recommended as IV injection if recovery has reached at least 1-2 post-tetanic counts(PTC) following rocuronium or vecuronium induced blockade. A dose of 2 mg/kg Bridion is recommended as IV injection, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. **Immediate Reversal of Rocuronium-Induced Blockade:** A dose of 16 mg/kg Bridion is recommended if there is a clinical need to reversal neuromuscular blockade soon(approximately 3 minutes) after administration of rocuronium as IV injection. The safety and efficacy with the use of Bridion for immediate reversal following vecuronium induced blockade has not been established. **Renal Impairment:** No dosage adjustment is necessary for patients with mild or moderate renal impairment(creatinine clearance ≥30 mL/min and <80 mL/min). Bridion is not recommended for use in patients with severe renal impairment(creatinine clearance <30 mL/min) or dialysis. **Elderly Patients:** Elderly patients tend to delay recovery from neuromuscular blockade, but dose adjustment is not necessary. **Obese Patients:** The dose of this drug in obese patients should be based on actual weight(ABW). **Hepatic Impairment:** No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Since no clinical studies have been conducted with patients with hepatic impairment, caution should be taken in patients with severe hepatic impairment or hepatic impairment with coagulation disorders. **[Warnings and Precautions] Contraindications:** Patients with known hypersensitivity to Bridion or any of its components. **Careful Administration:** 1) Patients with renal impairment 2) Patients with hepatic impairment 3) Patients with decrease of cardiac output 4) Patients with edema state 5) Patients with a history of allergic reaction 6) Patients with a history of pulmonary complications(Possible occurrence of bronchospasm) 7) Patients with coagulation disorders 8) Patients with arrhythmia 9) The elderly 10) Pregnant or women who may be pregnant. **Adverse Reactions:** 1) The safety of Bridion has been evaluated based on an integrated safety database of approximately 1,700 surgical patients and 120 healthy adult volunteers. The most commonly reported adverse reactions in patients who experienced surgery were anaesthetic complications. **Immune System:** 1) Hypersensitivity(≥1/1,000, <1/100), the others: Anaesthetic complications(body movement in the middle of anesthesia or operation, coughing, grimacing and sucking of the tracheal tube(≥1/100, <1/10), involuntary awakening during anesthesia(≥1/1,000, <1/100). 2) In clinical trials with surgical patients, hypersensitivity including anaphylaxis has been reported infrequently. The frequency of occurrence of hypersensitivity reactions in post-marketing surveys is unknown. Hypersensitivity reactions that occurred varied from isolated skin reactions to serious systemic reactions(i.e., anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to Bridion. Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, severe hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal. 3) Post-marketing clinical trials of obese patients(BMI ≥40 kg/m^2) showed that the adverse reaction profile was generally similar between patients who were administered actual body weight(ABW) and patients who were administered ideal body weight(IBW). **General Cautions:** 1) Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade. 2) In order to prevent recurrence of neuromuscular blockade, the recommended doses for routine should be used. 3) When drugs which potentiate neuromuscular blockade are used in the post-operative phase, special attention should be paid to the possibility of recurrence of neuromuscular blockade. 4) Recurrence of neuromuscular blockade may occur due to displacement of rocuronium or vecuronium from BRIDION by other drugs(i.e., Toremifene, fusidic acid). 5) When neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally(movement, coughing, grimacing and sucking of the tracheal tube). 6) In patients for whom intubation is expected to be difficult, the method of airway maintenance should be considered beforehand. If rocuronium-induced neuromuscular blockade cannot or does not allow airway intubation, it should be promptly restored from neuromuscular blockade. 7) Coagulation parameters should be carefully monitored in patients with known coagulopathies when sugammadex is administered. 8) In patients with severe renal failure(creatinine clearance <30 mL/min), the excretion of Bridion or the Bridion-rocuronium complex was delayed; however, in these patients there were no signs of re-occurrence of neuromuscular blockade. This drug is not recommended for use in patients with severe renal impairment. 9) Dedicated studies in patients with hepatic impairment have not been conducted. Patients with severe hepatic impairment or hepatic impairment with coagulation disorders should be cautious when administering this drug. 10) Bridion has not been studied for reversal following rocuronium or vecuronium administration in the ICU. 11) Do not use Bridion to reverse neuromuscular blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds, steroidal neuromuscular blocking agents, pancuronium other than rocuronium or vecuronium. 12) Conditions associated with prolonged circulation time such as cardiovascular disease, old age or edema state(i.e., severe hepatic impairment) may be associated with longer recovery times. 13) The patients should be carefully observed for the possibility of drug hypersensitivity reactions(including anaphylactic reactions). If any abnormality is observed, appropriate measures should be taken immediately. 14) Each 1 mL solution contains 9.7 mg sodium. If more than 2.4 mL(contain approximately 23 mg sodium) solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet. 15) In rare instances, cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of Bridion for reversal of neuromuscular blockade. **Drug Interactions :** 1) Toremifene: For toremifene, which has a relatively high binding affinity for Bridion and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with this drug could occur. 2) Fusidic acid: IV administration of fusidic acid in the pre-operative phase may give some delay in the recovery of the T_4/T_1 ratio to 0.9. No recurrence of neuromuscular blockade is expected in the post-operative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2-3 days. 3) Hormonal contraceptives: The interaction between 4 mg/kg Bridion and a progestogen was predicted to lead to a decrease in progestogen exposure(34% of AUC). **Pregnancy & Lactation Administration:** There are no clinical trial data for exposure to this drug during pregnancy. It is administered only if the benefits of administration exceed the risk. No data are available regarding the presence of Bridion in human milk, the effects of Bridion on the breast fed infant, or the effects of Bridion on milk production. Breastfeeding is not recommended during the administration of this drug. **Pediatric Administration:** The safety and efficacy of this drug in children aged younger than 18 years have not been established. **Elderly Administration:** Exercise caution when administering BRIDION to elderly patients who tend to delay recovery from neuromuscular blockade.(Revised: 2021.01.26)

※Before administering BRIDION, please read the full prescribing information.

Study design[1] : This randomised, multicentre, parallel-group trial included 98 adult patients. Patients received intravenous propofol for induction followed by sevoflurane maintenance anaesthesia. Neuromuscular blockade was monitored using acceleromyography and a train-of-four(TOF) mode of stimulation. Patients were randomly allocated to receive sugammadex 2.0 mg/kg or neostigmine 50 μg/kg(with glycopyrrolate 10 μg/kg) at reappearance of the second response of the TOF(mean 16% twitch height of first response) after the last dose of rocuronium. The primary endpoint was the time from sugammadex or neostigmine administration to recovery of the TOF ratio to 0.9.

Study design[2] : This phase Ⅲ, randomized study enrolled surgical patients, aged 18 year or older with American Society of Anesthesiologists physical status Ⅰ-Ⅳ. 74 patients were randomized to receive sugammadex(4.0 mg/kg) or neostigmine(70 μg/kg) plus glycopyrrolate(14 μg/kg). Anesthetized patients received an intubating dose of rocuronium(0.6 mg/kg), with maintenance doses(0.15 mg/kg) as required. Neuromuscular monitoring was performed by acceleromyography. Sugammadex or neostigmine was administered at reappearance of 1-2 posttetanic counts(profound neuromuscular blockade). The primary efficacy parameter was the time from sugammadex or neostigmine-glycopyrrolate administration to return of the train-of-four ratio to 0.9.

References : 1. Blobner M, *et al*. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur J Anaesthesiol*. 2010;27(10):874-881. **2.** Jones RK, *et al*. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology*. 2008;109(5):816-824. **3.** Bridion Product Label. Ministry of Food and Drug Safety.

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마약 | 전문 | 정주

원료약품 및 그 분량 울티바주1밀리그램 - 1바이알(16.1mg) 중 레미펜타닐염산염(별규) 1.1mg(레미펜타닐로서 1.0mg) / 울티바주2밀리그램 - 1바이알(17.21mg) 중 레미펜타닐염산염(별규) 2.21mg(레미펜타닐로서 2.0mg)울티바주5밀리그램 - 1바이알(20.53mg) 중 레미펜타닐염산염(별규) 5.53mg(레미펜타닐로서 5.0mg) **효능·효과** 1. 마취유도 및/또는 마취유지의 진통. 2. 기계적 환기를 실시중인 중환자의 진통 및 진정(18세 이상) **용법·용량** 이 약은 정맥내로만 투여해야만 하고, 경막외 및 경막내로 투여해서는 안된다. 이 약은 조제하여 멸균 주사용수, 5% 포도당 주사액, 5% 포도당 및 생리식염주사액의 혼합액, 생리식염주사액, 0.45% 염화나트륨 주사액 등의 정맥주사액으로 20~250㎍/mL 농도로 희석한 후 실온에서 보관할 때 24시간 동안 안정하다. 일반적인 마취를 위한 권장 희석농도는 성인의 경우 50㎍/mL, 1세 이상 소아의 경우 20~25㎍/mL이다. **1.** 일반마취 **1)** 성인: 투여량은 환자의 반응에 따라 개별적으로 결정되어야 한다. A) 마취유도: 정맥내 단회주입(㎍/kg)-1(30초 이상 투여)/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.5~1. B) 환기된 환자의 마취유지: • 아산화질소(66%): 정맥내 단회주입(㎍/kg) - 0.5~1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.4, 유지속도 0.1~2 • 이소플루란 (초회용량 0.5MAC): 정맥내 단회 주입(㎍/kg)- 0.5~1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.25, 유지속도 0.05~2 • 프로포폴(초회용량 100㎍/kg/분): 정맥내 단회주입(㎍/kg) - 0.5~1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.25, 유지속도 0.05~2. 정맥내 단회주입시에는 30초 이상 동안 투여해야 한다. C) 기도 확보 하에 자발적 호흡으로 마취된 환자에서의 마취: 기도 확보 하에 자발적 호흡으로 마취된 환자에서 호흡억제가 일어날 수 있다. 환자 투여량을 조절하기 위해 특별한 관리와 환기보조가 필요하다. 자발적 호흡으로 마취된 환자에서 보조 진통을 위한 권장 초기투여속도는 0.04㎍/kg/분이며 유효점까지 조절한다. 0.025~0.1㎍/kg/분 범위의 투여속도가 연구되었다. 자발적 호흡으로 마취된 환자에서 정맥내 단회주입은 권장되지 않는다. **2)** 소아(1~12세): A) 마취유도: 1~12세 소아에서의 유용한 자료가 없기 때문에 이 연령에서 이 약을 사용한 마취 유도는 권장되지 않는다. B) 마취유지: 마취유지를 위한 이 약의 권장용량은 다음과 같다. 병용투여 마취제* • 할로탄(초기용량 0.3MAC): 정맥내 단회주입(㎍/kg) - 1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.25, 유지속도 0.05~1.3 • 세보플루란(초기용량 0.3MAC): 정맥내 단회주입(㎍/kg) - 1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.25, 유지속도 0.05~0.9 • 이소플루란(초기용량 0.5MAC): 정맥내 단회주입(㎍/kg) - 1/ 정맥내 연속주입(㎍/kg/분) - 초기 투여속도 0.25, 유지속도 0.06~0.9. * 아산화질소/산소와의 병용투여 비율은 2:1. C) 수술 직후 환자 처치에 관한 기준/이 약 투여 중단 이전의 대체 진통제 사용: 이 약의 작용은 빠르게 소실되기 때문에, 투여중단 후 5~10분 이내에 잔류 아편양 효과는 나타나지 않는다. 수술 후 통증이 예상되는 수술환자에게는 이 약의 투여를 중단하기 전에 진통제를 투여하여야 한다. **3)** 신생아/영아(1세 이하): 신생아/영아(1세 이하)에서 이 약의 약물동력학은 체중 차이를 보정하면 성인에서와 유사하다. 그러나 1세 이하 소아에 대한 권장용량 설정을 뒷받침하는 자료는 충분하지 않다. 심장수술, 중환자, 고령자, 신경외과, ASA III/IV 환자, 비만환자, 신장애환자, 간장애환자에 관련한 자세한 사항은 제품정보전문 참고 **최종개정년월일** 2018. 05. 02

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- 강력한 **시너지 효과** (with other analgesic)
- 만성 신부전 환자에게도 쓸수있는 **안전한 진통제**

[효능/효과] 다음을 포함한 급성 및 만성통증의 완화 : 수술후 통증, 외상에 의한 통증, 골격근육통(염좌 및 타박상, 탈골 및 골절), 관절통, 치통, 암성통증 **[용법/용량]** 성인 : 이 약의 초기용량은 1일 3회, 1회 2캡슐씩 복용한다. 환자의 증상이나 치료반응에 따라 1일 3회, 1회 1~3캡슐씩 복용한다. **[사용상의 주의사항]** 1. 다음 환자에게 투여하지 말 것 1) 간질 환자 2) 심근경색 환자 3) MAO억제제를 투여받고 있는 환자 4) 이 약 또는 이 약의 구성성분에 대한 과민반응 환자 5) 경련 또는 경련의 병력이 있는 환자 6) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp유당분해효소 결핍증 (Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애 (glucos-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. 2. 다음 환자에는 신중히 투여할 것 1) 항콜린작용 약물을 복용중인 환자 2) 교감신경흥분작용 약물을 복용중인 환자 3) 간장애 및 신장애 환자 4) 고령자 또는 요폐 환자 3. 이상반응 1) 구역, 신경과민, 구강건조, 가벼운 두통, 요폐, 저혈압, 실신, 심계항진, 위장장애(복통,설사), 현기증, 감각이상, 경련, 떨림, 혼란, 환각, 혈관부종, 알레르기가 나타날 수 있으며 드물게 구토, 시야몽롱, 졸음, 발한, 불면증, 두통 및 심계항진이 일어날 수 있다. 2) 드물게 일시적이고 무해한 분홍색 착색뇨가 나타날 수 있다. 3) 이상반응은 용량의존성이므로 그 정도를 조절할 수 있으며 대개의 경우 반복투여로 소실된다. 4. 일반적 주의 1) 소염진통제에 의한 치료는 원인요법이 아닌 대증요법임에 주의한다. 2) 급성질환에 사용하는 경우에는 다음의 사항을 고려한다. ① 급성통증 및 발열의 정도를 고려하여 투여한다. ② 원칙적으로 동일한 약물의 장기투여는 피한다. ③ 원인요법이 있는 경우에는 실시한다. 3) 장기 투여시 또는 간장질환 환자에 투여시에 정기적으로 혈액 트란스아미나제를 측정하여야 한다. 4) 환자의 상태를 충분히 관찰하고 이상반응의 발현에 주의한다. 5) 이 약 투여시 감염증을 걸으로 나타나지 않게 할 수 있으므로 감염증이 합병된 환자의 경우에 적절한 항균제 또는 항진균제를 병용하고 관찰을 충분히 하여 신중히 투여한다. 6) 고령자에게 투여하는 경우 필요한 최소량으로 신중히 투여하고 부작용(특히 환각, 혼란 등 중추신경계 부작용)의 발현에 유의한다. 7) 간장애 및 신장애는 이 약의 대사와 배설에 영향을 미친다. 8) 이 약의 투여로 행동성이 저하되므로 작업 중 주의가 필요한 일(자동차 운전, 기계조작 등)에 종사할 경우에는 투여하지 않는 것이 바람직하다. 5. 상호 작용 1) 마약성진통제와의 병용투여는 아직 확립되지 않았다. 2) 아세트아미노펜 함유제제와의 병용투여시 간독성에 대한 세심한 관찰이 필요하다. 3) 다른 소염진통제와는 병용하지 않는 것이 바람직하다. 4) 삼환계 항우울제와 병용투여시 이 약의 이상반응 발생이 증가할 수 있으므로 주의해야 한다. 6. 임부 및 수유부에 대한 투여 1) 이 약을 임부에게 투여한 임상시험 자료는 없다. 2) 기형발생의 근거가 알려진 바 없으므로 임신 및 수유 중 투여를 권장하지 않는다. 7. 소아에 대한 투여 12세 이하의 소아에 대한 유효성 및 안전성이 확립되지 있지 않으므로 투여하지 않는다. 8. 고령자에 대한 투여 1) 고령자의 경우 대사가 느리므로 원칙적으로 성인용량의 최소량(1일 3회, 1회 1캡슐)부터 투약을 개시하여 관찰을 충분히 하면서 신중히 투여량을 결정한다. 2) 고령자에서 특히 환각, 혼돈과 같은 중추 신경계 부작용이 더 발생하는 것으로 보고되었다. 9. 과량 투여시의 처치 1) 이 약의 과량 투여 시 신경계(경련, 환각 및 불안) 및 심혈관계(과혈류 순환에 따른 심계항진)증상이 보고되었다. 2) 과량투여시 처치는 일반적인 보조요법을 시행하며, 즉시 위세척 등으로 과량 투여된약물을 제거해야 한다. 흡수를 제한하기 위해서 활성탄이 유용할 수 있다. 10. 보관 및 취급상의 주의사항 1) 어린이의 손이 닿지 않는 곳에 보관한다. 2) 직사광선을 피하고 될 수 있는 한 습기가 적은 서늘한 곳에 보관한다. 3) 의약품을 원래 용기에 꺼내 다른 용기에 보관하는 것은 의약품 오용에 의한 사고발생이나 의약품 품질 저하의 원인이 될 수 있으므로 원래 용기에 넣어 꼭 닫아 보관한다. **[저장방법]** 밀폐용기, 실온(1~30℃) 보관 **[포장단위]** 30캡슐, 300캡슐 **[사용기간]** 제조일로부터 36개월 ※ 올바른 복용법을 모르거나 의문사항이 있는 경우는 의사 / 약사와 상담하십시오.

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안녕하십니까?

저희 신경근연구학회는 회원들의 뜨거운 열정과 노력으로 지난 26년 동안 발전해 왔습니다.

안타깝게도 저희는 COVID19 유행으로 지난해 학술대회를 개최하지 못하였습니다. 아직도 COVID19 유행은 끝이 보이지 않고 진행 중이지만, 이러한 어려움 속에서도 많은 회원님들의 신경근 연구에 관한 새로운 지식에 대한 관심과 열망은 더욱 거세지는 것 같습니다. 따라서, COVID19가 지속되는 어려움에도 불구하고 춘계 학술대회를 온라인으로 개최하여 많은 회원 여러분들의 학술적 갈증을 해소할 수 있도록 준비하였습니다.

이번 춘계학술대회에서는 신경근 차단제 사용으로 인한 폐합병증의 실체와 예방 그리고 신경근 감시에 대한 최신지견 및 신경근 연구에 관한 최근 이슈와 Benzylisoquinolium 계열의 약제의 국내철수와 생산중단에 따른 대체약물은 무엇인가에 대한 특강 등이 준비되어 있습니다.

이번 대한신경근연구학회 학술대회에 많은 회원들과 전공의 선생님들의 관심과 참여가 학회발전에 큰 기여를 할 것이라 생각하며 이번 학술대회를 통하여 신경근연구에 대한 새로운 지식과 함께 임상에서 신경근 차단제와 Sugammadex 사용에 있어서 조금이나마 보탬이 되었으면 합니다.

비록 이번 춘계 학술대회는 비대면 온라인 학술대회로 진행이 되지만 COVID19가 조속히 극복되어 조만간 환히 웃으며 활기차고 변화된 모습으로 학술대회에서 다시 뵙기를 기원합니다.

감사합니다.

대한신경근연구학회 회장 **안 태 훈**

2021년
대한신경근연구학회 춘계학술대회
Online Web Seminar

일시: 2021년 6월 26일(토)
진행: Online Web Seminar

08:30 - 08:50	등록	
08:50 - 08:55	개회사 및 인사말	대한신경근연구학회 회장 조선의대 **안태훈**
08:55 - 09:00	축 사	대한마취통증의학회 이사장 고려의대 **김재환**

Session A. Preventing Postoperative Pulmonary Complications 좌장: 순천향의대 황경호, 조선의대 안태훈

09:00 - 09:30	What and Why	인제의대 **이원진** …… 3
09:30 - 10:00	Postoperative pulmonary complications : an update on risk assessment and reduction	건양의대 **성태윤** …… 6
10:00 - 10:30	Post-operative respiratory outcomes associated with the use of sugammadex	서울의대 **오아영** …… 9
10:30 - 10:40	Q & A	
10:40 - 10:50	Coffee Break	

Session B. Focuses on the Current Issues and Trends: Part I
좌장: 삼성메디 이비인후과 이수일, 충남의대 신용섭

10:50 - 11:20	Device & Technology Review: EMG vs AMG	조선의대 **정기태** …· 23
11:20 - 11:50	Management of Neuromuscular Blockade during Neurophysiologic Monitoring	충남의대 **임채성** …· 33
11:50 - 12:20	Hot topics in neuromuscular research area : Bibliometric Analysis of Last 5 year's top publications	인제의대 **이상석** …· 35
12:20 - 12:30	Q & A	
12:30 - 13:30	Lunch	

Session C. Focuses on the Current Issues and Trends: Part II

좌장: 을지의대 양홍석

13:30 – 14:00	Peri-operative administration of drugs and its neuromuscular consequences	울산의대 **최재문**	47
14:00 – 14:30	Farewell to Nimbex: What is the alternatives?	한양의대 **김규남**	71
14:30 – 14:40	Q & A		
14:40 – 14:50	Coffee Break		

Session D. Beyond Sugammadex: Still Remained Questions

좌장: 원광대 산본병원 김교상, 순천향의대 이정석

14:50 – 15:15	Safety and Efficacy of Sugammadex for Reversal of Neuromuscular Blockade in Pediatric Patients	가톨릭의대 **전진영**	87
15:15 – 15:40	Adequate dose of sugammadex beyond the guideline	고신의대 **김주덕**	90
15:40 – 16:05	Hypersensitivity: Still problem?	건국의대 **강운석**	100
16:05 – 16:30	The Future of Neuromuscular Blockade Antagonists	고려의대 **오석경**	105
16:30 – 16:45	Q & A		
16:45 – 16:50	폐회사 & 광고		

QR코드를 스캔하시면 각 사항을 확인 하실 수 있습니다.

Online Web Seminar

Q&A

초록집

2021년
대한신경근연구학회 춘계학술대회
Online Web Seminar

Session A

Preventing Postoperative Pulmonary Complications

좌장: 순천향의대 황경호, 조선의대 안태훈

Postoperative pulmonary complications
–What and Why?–

이 원 진

인제의대

정의와 위험성

Postoperative pulmonary complications (PPC)이라는 용어는 마취나 수술 후 호흡기에 영향을 미치는 거의 모든 합병증을 포함하는 의미이나, 현재까지 많은 연구에서 연구자의 편의 혹은 상황에 따라 다양하게 정의되었다. 2015년 유럽 마취과 학회에서는 다양하게 정의된 술 후 합병증을 통일하고자 European perioperative clinical outcome (EPCO) definitions에 대한 가이드라인 (Table 1)을 제시하였다. EPCO 가이드라인에서 PPC에 포함되는 것들은 respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonitis이며 PPC와 관련된 연구에서는 위 항목에 해당하는 것들을 상황에 맞게 조합하여 사용하고 있다.

Table 1. Postoperative pulmonary complications

Complication	Definition
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count > 12 x $10^9 l^{-1}$
Respiratory failure	Postoperative PaO_2 < 8 kPa (60 mmHg) on room air, a PaO_2:$FI0_2$ ratio <40 kPa (300 mmHg) or arterial oxyhemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows

Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

PPC의 빈도는 연구에 따라 1-23%로 다양하게 보고되고 있는데, 이는 연구에서 정의한 PPC의 범주가 다양하고 연구 대상자와 수술의 특성에 영향을 받아 그런 것으로 생각된다. PPC가 발생한 환자의 경우 그렇지 않은 환자에 비해 사망률이 높은 것으로 보고되고 있다. Canet 등은 PPC에 이환된 환자와 그렇지 않은 환자의 90일 사망률을 각각 24.4% 와 1.2%로 보고하였고, Khuri 등은 1년 사망률을 각각 45.9% 와 8.7%로 보고하였다. 또한 PPC가 발생한 환자의 경우 기관내 재삽관의 빈도와 재원기간 및 재입원빈도가 증가하는 것으로 보고되고 있으며 이에 따른 추가 의료비의 상승도 보고되고 있다.

수술 후 호흡기계의 변화와 회복

수술 중 전신마취제의 영향으로 호흡이 저하되고 고탄산혈증 및 저산소혈증에 의한 호흡 보상 반응이 저하된다, 대부분의 경우 적절한 기계환기로 큰 문제가 되지 않으나 환자의 호흡기 폐색 등의 문제가 있는 경우 술 중 고탄산혈증 및 저산소증이 심해질 수도 있다. 또한 신경근 차단제의 사용으로 흉곽의 근육 긴장도가 저하되면서 폐 용적, 특히 functional residual capacity (FRC)의 감소가 일어나고 대부분의 환자에서 atelectasis가 발생한다.

수술 직후에는 전신마취제 및 신경근차단제의 잔류효과와 마약성 진통제의 영향으로 respiratory failure의 위험이 높다. 수술 중 발생한 FRC의 감소와 atelectasis는 수술 직후 많은 수에서 지속되며, Strandberg 등은 수술 24시간 후에도 약 50%의 환자에서 atelectasis를 보고하였다. 특히 신경근차단제를 사용한 경우 그 위험도는 증가하며 Sundman 등은 신경근차단제 사용 후 train of four (TOF) ratio가 0.9 이상으로 회복된 경우에도 pharyngeal dysfunction을 보이는 경우가 13%라고 보고하였다. 이는 근력의 회복뿐만 아니라 신경근의 미세한 조절 작용의 회복 또한 중요하다는 점을 시사한다. 신경근차단으로부터 회복이 불완전한 경우(TOF ratio < 0.9)에는 forced vital capacity (FVC) 및 forced expiratory volume in 1s (FEV_1)등의 forced respiration이 유의하게 감소하며 Eikermann 등은 TOF ratio가 0.95이상 되어야 FEV_1 이 충분히 회복된다고 보고하였다.

수술 중 발생한 FRC의 감소는 minor surgery의 경우 술 후 수시간내에 정상으로 돌아오지만, major surgery의 경우 오랜 시간이 걸린다. Craig 등의 보고에 의하면 FRC는 술 후 1-2일째에 제일 많이 감소하며 이후 서서히 회복하여 술 후 5-7일에 정상치로 회복한다고 한다. 수술 후 atelectasis도 수일간 지속되며 Mavros는 수술 3일 후에도 50% 이상의 atelectasis를 보고하기도 하였다. Nieuwenhuijs 등은 major surgery 후 고탄산혈증, 저산소혈증에 의한 호흡 조절 작용이 6주까지 정상으로 회복되지 않는다고 보고 하였고 이를 통해 수술 후 호흡 조절 작용의 회복에 상당한 시간이 걸림을 유추할 수 있다. 정리하자면 마취 및 수술의 영향으로 FRC 감소, atelectasis의 발생, forced respiration의 저하, 비정상적인 호흡 조절 등이 발생하고 수술 후 저하된 호흡 기능에 의해 PPC가 발생하기 쉬운 상태가 된다.

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Postoperative pulmonary complications: an update on risk assessment and reduction

성 태 윤

건양의대

서론

수술 후 폐 합병증(Postoperative pulmonary complications, PPC)는 환자의 사망률, 이환율, 재원일수, 의료비용의 증가를 초래한다. 발생빈도는 general surgical population에서는 2.0%-5.6%, 상 복부, 흉부 수술에서는 20-70% 정도로, 환자군, 수술부위에 따라 다양하다. 수술 후 폐 합병증은 표준화된 정의(definition)가 없지만, 보통 호흡부전, 수술 후 48시간 이내의 기관내 튜브 재 삽관, weaning failure, 폐렴, 무기폐, 기관지 연축, 만성 폐쇄폐질환이나 천식의 악화, 기흉, 가슴막 삼출과 여러 형태의 obstruction을 포함한다.

전신마취후 central respiratory drive의 억제, 호흡근의 기능적 변화, 폐 용적 감소, 무기폐 발생은 수술 후 폐합병증을 유발할 수 있다. 또한 전신마취 중 사용한 신경근 차단제로 인한 잔류 근이완은 hypoxic ventilatory response, 호흡근 기능, 삼킴(swallowing)동안 기도 보호능력의 손상을 유발하여 결과적으로, 저산소증, 흡인, 폐부종, reintubation과 같은 폐합병증을 유발할 수 있다. 흉부나 횡격막 근처의 복부수술은 수술적 절개에 의한 호흡근 움직임의 functional disruption, 횡격막신경과 호흡근육을 자극하는 기타 신경의 reflex inhibition, 수술 후 통증을 초래하여 저 환기와 무기폐를 초래할 수 있다.

수술 후 폐 합병증의 위험인자

수술 후 폐 합병증의 위험인자는 크게 patient- or procedure-related risk factors 나눌 수 있다. 환자관련 위험인자에는 고령, 미국마취과학회 신체분류등급 2이상, functional dependence (frailty), 최근1개월이내의 급성 호흡기 감염, 흡연, 만성 폐쇄폐질환, 울혈성 심장질환, malnutrition (serum albumin <3 g/dl) 등이 있다. 시술관련 위험인자에는 수술부위, 긴 수술시간(>3h), 응급수술, 전신마취, 마약성 진통제의 사용, 신경근 차단제의 사용, (고용량) neostigmine 사용, 적절한 신경근 기능 감시의 실패 등이 있다.

잔류 신경근 차단은 train-of-four ratio <0.9로 정의되며, 이는 수술 후 폐합병증의 위험성 증가와 연관된다.

Preoperative risk stratification: Risk prediction models

수술후 폐합병증의 위험성을 예측하기 위한 많은 scoring system들이 있지만, 사용하기 위해 최적의 모델로 인정받은 것은 없으며, 대부분 임상환경에서 사용하기에 복잡하다는 단점이 있다. 1947년부터 2018년사이에 수술후 폐합병증의 예측모델을 보고한 21개의 논문을 분석한 결과, external validation에서 충분한 predictive power를 입증한 모델은 ARISCAT risk score가 유일하였다.

수술 후 폐합병증 감소를 위한 주술기 전략 (strength of evidence)

수술 전: Optimization of existing cardiorespiratory disease (fair), 조기 금연 (fair), Prehabilitation exercise programmes (insufficient data).

수술 중: Minimally invasive surgical techniques (fair), Selective use of nasogastric tubes (good), Lung-protective ventilation strategies (fair), Short acting NMBAs with quantitative monitoring (fair), Neuraxial blockade (insufficient data), Goal-directed fluid therapy (insufficient data).

수술 후: Adequate analgesia (good), Early mobilization (good), Postoperative epidural analgesia (insufficient), Lung expansion techniques (good).

잔류 신경근 차단으로 인한 수술 후 폐합병증의 감소를 위해서는 마취 중 신경근 차단제의 사용은 정량적인 신경근 감시 적용 하에 수술을 위해 반드시 필요한 용량의 신경근 차단제 투여가 필요하며, 수술종료시 역전제의 사용 역시, 정량적인 신경근 감시하에 신경근 차단 깊이에 따라 적정용량의 역전제가 투여되어 할 것이다

Summary

수술후 폐합병증은 환자의 사망률, 이환율, 재원일수, 의료비용의 증가를 초래할 수 있으므로 수술 전에 수술후 폐 합병증의 위험이 높은 환자의 선별 및 확인은 중요하다. 전신마취를 받는 환자에서 신경근 차단제와 역전제 (neostigmine)의 사용은 용량의존적으로 수술 후 폐합병증의 위험성을 증가시킬 수 있다. 신경근 차단제와 역전제 사용으로 인한 폐합병증의 감소를 위해서는 마취방법의 선택에 있어서 전신마취보다는 부위마취의 선택을 고려할 수 있다. 만약 전신마취를 시행한다면, 기관내 삽관보다는 성문상부기도 유지기의 선택이 신경근 차단제의 용량을 감소시킬 수 있을 것으로 기대된다. 신경근 차단제를 사용할 경우, 신경근 차단제 사용 후 잔류 신경근 차단과 이에 따른 폐합병증을 감소시키기 위해 수술 중 신경근 차단제와 수술종료시 역전제투여는 신경근 기능의 감시하에 적정용량을 투여하여야 한다.

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Postoperative Respiratory Outcomes associated with the Use of Sugammadex

오 아 영

서울의대

Sugammadex

- Significantly lower risk of residual NMB
- Fewer respiratory & cardiovascular events
- Less nausea & vomiting
- Fewer signs of residual paralysis

- No difference in serious advers events

Residual Neuromuscular Block (NMB)

- Increased risk for hypoxic ventilatory response impairment
- Unable to breathe deeply
- Experience airway obstruction
- Have diaphragmatic dysfunction
- Suffer impairment of airway protective reflexes
- Increase risk of aspiration

Sugammadex on Longer Term Outcomes?

Contents

- Recent large observational registry investigations
- Postoperative Pulmonary Complications (PPC)
- Previous studies on PPC
- Other outcome studies

Large Observational Registry Investigations

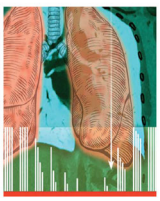
	Study Design	N	Sugammadex on PPC
Lancet Respir Med_19_Kirmeier E (POPULAR)	Prospective observational	22,803	NC
Anesthesiol 20_Kheterpal S (STRONGER)	Multicenter Retrospective	45,712	Improve
Anesth Analg 20_Krause M	Interrupted time series	7,316	Improve
Anesthesiol 21_Li G	Retrospective	10,491	NC

Anesthesiology *Jun* 2021

EDITORIAL

The "True" Risk of Postoperative Pulmonary Complications and the Socratic Paradox: "I Know that I Know Nothing"

Sorin J. Brull, M.D., F.C.A.R.C.S.I. (Hon), Glenn S. Murphy, M.D.



"…[What is the] relationship between neuromuscular antagonists and development of postoperative pulmonary complications[?]"

Lancet Respir Med 2019

Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study

Eva Kirmeier, Lars I Eriksson, Heidrun Lewald, Malin Jonsson Fagerlund, Andreas Hoeft, Markus Hollmann, Claude Meistelman, Jennifer M Hunter, Kurt Ulm, Manfred Blobner, and the POPULAR Contributors

- A prospective observational cohort study
- 22,803 patients, Jun 2014~April 2015, 211 hospitals in 28 European countries
- NMBAs increase PPCs: OR_{adj} 1.86 (95% CI, 1.53-2.26)
- Monitoring, reversal, sugammadex, extubation at TOFR≥0.9

  ⇒ fail to reduce PPCs

Lancet Respir Med 2019

			40%	24%	52%
	Anaesthetised patients (n=21 694)	Patients receiving NMBAs (n=17 150)	Patients with any NMM (n=6868)	Patients with quantitative NMM (n=4182)	Patients receiving a reversal agent (n=8795)
Outcomes*					
Any postoperative pulmonary complication	1658 (7·6%)	1441 (8·4%)	733 (10·7%)	441 (10·5%)	780 (8·9%)
Intermediate or severe postoperative pulmonary complication	1028 (4·7%)	884 (5·2%)	428 (6·2%)	245 (5·9%)	483 (5·5%)

Br J Anaesth 2020

Use of a train-of-four ratio of 0.95 *versus* 0.9 for tracheal extubation: an exploratory analysis of POPULAR data

Manfred Blobner[1,*], Jennifer M. Hunter[2], Claude Meistelman[3], Andreas Hoeft[4], Markus W. Hollmann[5], Eva Kirmeier[1], Heidrun Lewald[1] and Kurt Ulm[6]

- Patients with a quantitative NMM (n = 3,150)
- Extubating at TOFR>0.95 *vs* >0.9 reduced the adjusted risk of pulmonary complications by 3.5% (0.7-6.0%)

Anesthesiol 2020

ANESTHESIOLOGY

Sugammadex *versus* Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER)

A Multicenter Matched Cohort Analysis

Sachin Kheterpal, M.D., M.B.A., Michelle T. Vaughn, M.P.H., Timur Z. Dubovoy, M.D., Nirav J. Shah, M.D., Lori D. Bash, Ph.D., M.P.H., Douglas A. Colquhoun, M.B.Ch.B., Amy M. Shanks, Ph.D., Michael R. Mathis, M.D., Roy G. Soto, M.D., Amit Bardia, M.D., Karsten Bartels, M.D., Ph.D., Patrick J. McCormick, M.D., M.Eng., Robert B. Schonberger, M.D., M.H.S., Leif Saager, M.D., M.M.M.

Anesthesiology 2020; 132:1371–81

- A retrospective, observational, matched-cohort study
- 45,712 patients from Jan 2014 to Aug 2018
- Noncardiac surgical procedures
- ↓30% PPC
  - ↓47% pneumonia
  - ↓55% respiratory failure

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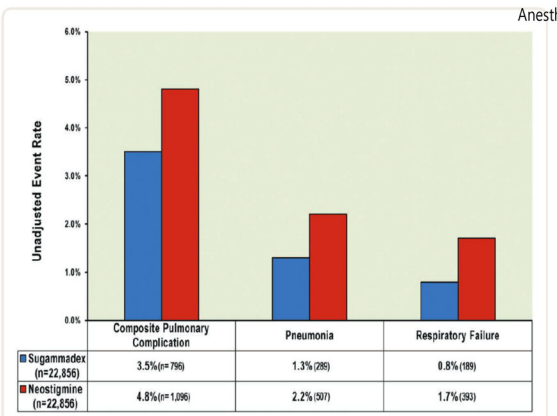

	Composite Pulmonary Complication	Pneumonia	Respiratory Failure
Sugammadex (n=22,856)	3.5%(n=796)	1.3%(289)	0.8%(189)
Neostigmine (n=22,856)	4.8%(n=1,096)	2.2%(507)	1.7%(393)

Fig. 1. Major pulmonary complication event rates (unadjusted) in matched cohort of patients undergoing noncardiac inpatient surgery. Patients receiving sugammadex were matched to patients receiving neostigmine across 12 hospitals using exact match criteria of institution, sex, age, comorbidities, obesity, surgical procedure type, and neuromuscular blockade agent. The composite pulmonary complication primary outcome included pneumonia, respiratory failure, and other major complications.

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- The primary outcome:
- A composite of postop pulmonary complications Plausibly related to residual NMB
  - Pneumonia
  - Respiratory failure
  - Other complications: aspiration pneumonitis, pulmonary congestion, iatrogenic pulmonary emblism, infarction, pneumothorax
- Unclear clinical significance or relationship to NMB were not included
  - atelectasis, pulmonary edema, etc.

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Table 2. Intraoperative Characteristics of Patients Receiving Sugammadex and Neostigmine in Matched Analytic Cohort

	Neostigmine n = 22,856	Sugammadex n = 22,856	Absolute Standardized Difference
Neuromuscular blockade agent, No. (%)			
Vecuronium only	5,054 (22.1)	5,035 (22.0)	0.01
Rocuronium only	17,553 (76.8)	17,553 (76.8)	
Vecuronium and rocuronium	249 (1.1)	268 (1.2)	
Last train-of-four documented within 30 min of extubation, No. (%)			0.32
Not documented	9695 (42.4)	6641 (29.1)	
0 or 1 twitches	377 (1.6)	939 (4.1)	
2 twitches	503 (2.2)	991 (4.3)	
3 or 4 twitches	12281 (53.7)	14285 (62.5)	
Time from last neuromuscular blockade dose to reversal (15-min interval) [interquartile range]	4.4 [2.9, 6.7]	4 [2.7, 6.0]	0.14
Time from reversal to extubation (5-min interval) [interquartile range]	3 [1.8, 4.6]	2.4 [1.4, 3.8]	0.06
Time from last neuromuscular blockade to extubation (15-min interval) [interquartile range]	5.6 [3.9, 8.1]	5 [3.5, 7.3]	0.15
Intraoperative neuromuscular blockade administered (ED95/kg · h) [interquartile range]	1.2 [0.9, 1.6]	1.4 [1.1,1.8]	0.20

Anesth Analg 2020

Neostigmine Versus Sugammadex for Reversal of Neuromuscular Blockade and Effects on Reintubation for Respiratory Failure or Newly Initiated Noninvasive Ventilation: An Interrupted Time Series Design

Martin Krause, MD,* Shannon K. McWilliams, MA,† Kenneth J. Bullard, BS,*
Lena M. Mayes, MD,* Leslie C. Jameson, MD,* Susan K. Mikulich-Gilbertson, PhD,†‡
Ana Fernandez-Bustamante, MD, PhD,* and Karsten Bartels, MD, PhD*§

- Interrupted time series method
  - Presugammadex, transition, postsugammadex (Aug 2015~May 2017)
- 7,316 patients
- Reduction of composite respiratory outcomes
  - Reintubation for respiratory failure & new noninvasive ventilation
- 6.1% vs 4.2%, OR 0.667 (95% CI, 0.536-0.830)

Anesthesiol 2021

ANESTHESIOLOGY

Postoperative Pulmonary Complications' Association with Sugammadex *versus* Neostigmine: A Retrospective Registry Analysis

Gen Li, M.Stat., M.Chem.,
Robert E. Freundlich, M.D., M.S., M.S.C.I.,
Rajnish K. Gupta, M.D., Christina J. Hayhurst, M.D.,
Chi H. Le, B.S., Barbara J. Martin, R.N., M.B.A.,
Matthew S. Shotwell, Ph.D.,
Jonathan P. Wanderer, M.D., M.Phil., F.A.S.A., F.A.M.I.A.

Anesthesiology 2021; 134:862–73

- Retrospective, observational, cohort study
- Jan 2010~Jul 2019, switch from neostigmine to sugammadex
- 10,491 patients (7,800 neostigmine, 2,691 sugammadex)
- No difference in PPC (5.9% vs 4.2%)
  1. Pneumonia:3.2% vs 2.1%
  2. Prolonged mechanical ventilation: 1.1% vs 1.1%
  3. Unplanned intubation: 1.6% vs 1.0%
- the global rank from 0 to 6

Anesthesiol 2021

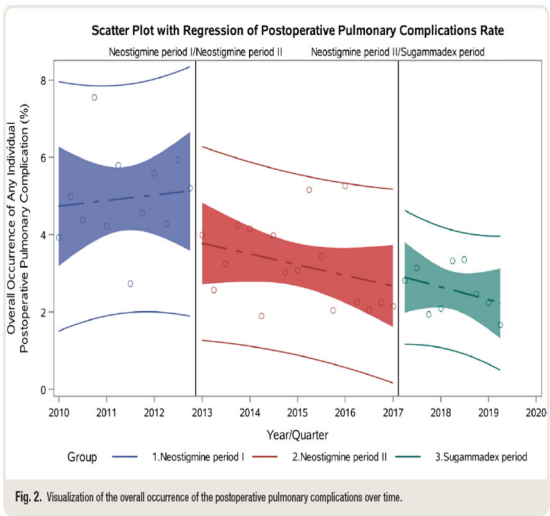


Fig. 2. Visualization of the overall occurrence of the postoperative pulmonary complications over time.

GUIDELINES

Eur J Anesthesiol 2014

Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions

A statement from the ESA-ESICM joint taskforce on perioperative outcome measures

- Review 11,474 articles > finally included 33 articles
- Definitions for 22 individual adverse events with a system of severity grading for each
- 4 composite outcome measures
  - Major adverse cardiac events
  - Postpoperative Pulmonary Complications (PPC)
  - Postoperative morbidity survey
  - Quality of recovery

Eur J Anesthesiol 2014

Table A2.2.2 Postoperative pulmonary complications

Complication	Definition
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count $> 12 \times 10^9 l^{-1}$
Respiratory failure	Postoperative $PaO_2 < 8$ kPa (60 mmHg) on room air, a PaO_2:FiO_2 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

Review

BJA 2017

Postoperative pulmonary complications

A. Miskovic and A. B. Lumb*

Department of Anaesthesia, St James's University Hospital, Leeds LS9 7TF, UK

- Incidence: <1 to 23%
- ↑ Mortality: both short and long term
- ↑ Morbidity: Length of hospital stay
- ↑ Health care costs

BJA 2017

Risk factors

Patient factors	Procedure factors	Laboratory testing
Non-modifiable	**Non-modifiable**	Urea >7.5 mmol litre^{-1} [1 10 25]
Age[6-7 10 13 14 18 20 24 25 27 33 36]	Type of surgery[6-7 10-13 15-18 23 25 27 29]	Increased creatinine[33]
Male sex[12 19 33]	• upper abdominal	Abnormal liver function tests[15]
ASA ≥II[6 11-14 16 19 27 33]	• AAA	Low preoperative oxygen saturation[4 6 29]
Functional dependence (frailty)[10-13 25 27 34 36]	• Thoracic	'Positive cough test'[20]
Acute respiratory infection (within 1 month)[4 6]	• Neurosurgery	Abnormal preoperative CXR[9 27]
Impaired cognition[7]	• head and neck	Preoperative anaemia (<100 g litre^{-1})[4 6]
Impaired sensorium[25]	• vascular	Low albumin[5 10 27]
Cerebrovascular accident[25]	Emergency (vs elective)[4-6 10 11 16 18 19 23 25 29 33 36]	Predicted maximal oxygen uptake[32]
Malignancy[7 15]	Duration of procedure[6 12 14 20 22 27 29 32]	FEV_1:FVC <0.7 and FEV_1 <80% of predicted[5]
Weight loss >10% (within 6 months)[15 25]	Re-operation[18 23 36]	
Long-term steroid use[25]	Multiple GA during admission[19]	
Prolonged hospitalization[15]	**Modifiable**	
Modifiable	Mechanical ventilation strategy[3 19 63-71]	
Smoking[27 12 13 15 25 32 33 61]	GA (vs regional)[4 25 27 72]	
COPD[10 12 13 15-19 24 25 27 32 33 36]	Long-acting NMBDs and TOF ratio <0.7 in PACU[73]	
Asthma[20 32]	Residual neuromuscular block	
CHF[15 16 18 27 29 33]	Intermediate-acting NMBDs with surgical time <2 h (not antagonized)[74]	
OSA[62]	Neostigmine[17 75]	
BMI <18.5 or >40 kg m^{-2}[15]	Sugammadex with supraglottic airway[75 76]	
BMI >27 kg m^{-2}[7]	Failure to use peripheral nerve stimulator[21 74]	
Hypertension[15]	Open abdominal surgery (vs laparoscopic)[5 26 77-79]	
Chronic liver disease[29]	Perioperative nasogastric tube[18 20 22 23 25 80]	
Renal failure[19]	Intraoperative blood transfusion[19 25 36]	
Ascites[12]		
Diabetes mellitus[15 17]		
Alcohol[17 25]		
GORD[17]		
Preoperative sepsis[13-15 33]		
Preoperative shock[12]		

Previous Studies

- Intermediate NMBDs, ↑ desaturation in PACU &unplanned reintubation, especially <2h surgery (Br Med J 2012 Grosse-Sundrup M)
- A dose dependent increase in PPC, intermediate NMBDs, lessened by correct management of reversal (Anesthesiol 2015 McLean DJ)
- Neostigmine is independently associated with PPCs (Br Med J 2012 Grosse-Sundrup M)
- Use of peripheral nerve stimulation , ↓ PPCs (Anesthesiol 2014 Sasaki M)
- Sugammadex, laryngospasm & negative pressure pulmonary edema (Eur J Anesthesiol 2016 Komasawa N, Masui 2014 Ikeda-Miyagawa Y)
- Sugammadex, PPCs, conflicting (Minerva Anesthesiol 2016 Martinez-Ubieto J / Anaesth Intensive Care 2012 Cammu GV)
- Sugammadex, PPCs, reduce (Eur J Anaesthesiol 2014 Ledowski T)
- Sugammadex, PPCs, RCT, major abdominal surgery, conflicting (Can J Anaesthesiol 2019 Alday E)

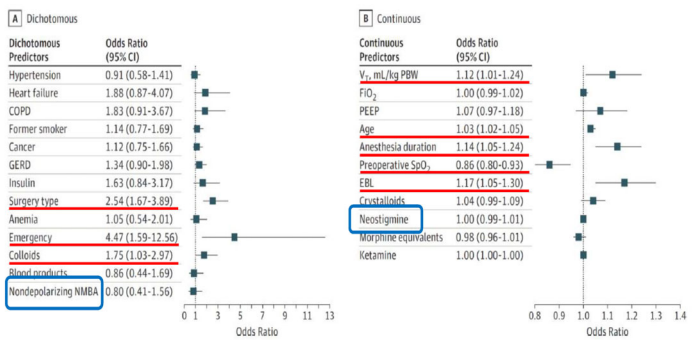
JAMA Surg 2017

Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery:

A Multicenter Study by the Perioperative Research Network Investigators

- A multicenter, prospective, observational study
- 1,202 patients, 7 US hospitals
- ASA class 3, noncardiothoracic surgery, ≥2 hrs
- PPC: 33.4%
  - the need for prolonged oxygen therapy by nasal cannula: 19.6%
  - Atelectasis: 17.1%
- ↑ early postoperative mortality, ICU admission, length of stay

JAMA Surg 2017



Eur J Anaesthesiol 2014

Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade

Sugammadex, neostigmine or no reversal

Thomas Ledowski, Laura Falke, Faye Johnston, Emily Gillies, Matt Greenaway, Ayala De Mel, Wuen S. Tiong and Michael Phillips

BACKGROUND Postoperative residual neuromuscular blockade (RNMB) is associated with significant morbidity.

OBJECTIVE The aim of this retrospective data analysis was to investigate the influence of the method of RNMB reversal on postoperative outcome.

SETTING Tertiary teaching hospital in Western Australia.

PATIENTS With Ethics Committee approval, data from 1444 patients who received at least one dose of a non-depolarising muscle relaxant intraoperatively during 2011 were analysed.

MAIN OUTCOME MEASURES Endpoints included unwanted events in the postanaesthesia care unit (PACU); symptoms of pulmonary complications within 7 postoperative days (0 to 100 outcome score based on 'temperature >38°C', 'leucocyte count $>11 \times 10^9$ l^{-1}', 'physical examination consistent with pneumonia' and 'shortness of breath'); PACU turnover time; and length of hospital stay.

RESULTS Data from 1444 patients (722 sugammadex, 212 neostigmine and 510 no-reversal) were analysed. The incidence of postoperative nausea and vomiting (PONV) in PACU was higher in neostigmine-reversed than sugammadex-reversed patients (21.5 vs. 13.6%; $P<0.05$). No differences were found regarding other PACU incidents, length of PACU stay or hospital stay. Pulmonary outcome deteriorated significantly (outcome score increased) with age and American Society of Anesthesiologists (ASA) physical status. This was observed particularly in ASA 3/4 patients more than 60 years of age in neostigmine-reversed or non-reversed patients, but almost no detrimental effect of age on pulmonary outcome was found in the sugammadex group ($P<0.05$).

CONCLUSION RNMB reversal with sugammadex was associated with the lowest rate of PONV and may reduce the risk of pulmonary complications in elderly ASA 3/4 patients.

TRIAL REGISTRATION Australian New Zealand Clinical Trials Registry: ACTRN12612000087853.

Published online 20 November 2013

J Clin Med 2020

Effects of Sugammadex on Post-Operative Pulmonary Complications in Laparoscopic Gastrectomy: A Retrospective Cohort Study

Jiwon Han [1], Jung-Hee Ryu [1,2], Bon-Wook Koo [1], Sun Woo Nam [1], Sang-Il Cho [1] and Ah-Young Oh [1,2,*]

- A propensity score matching
- 3,802 evaluated, 1,232 analyzed
- Primary outcome: pulmonary complications (EPCO guideline)
- Secondary outcomes: 90-d re-op, ICU admission, 30-d readmission, length of hospital stay, 90-d mortality

J Clin Med 2020

Table 3. Postoperative pulmonary complication rate in the propensity-matched cohort.

	Sugammadex (n = 616)	Neostigmine (n = 616)	p Value
Total	286 (46.4%)	304 (49.4%)	0.305
Respiratory infection	12 (1.9%)	6 (1.0%)	0.154
Respiratory failure	3 (0.5%)	3 (0.5%)	1
Pleural effusion	111 (18.0%)	144 (23.4%)	0.02 [1]
Atelectasis	223 (36.2%)	219 (35.6%)	0.812
Pneumothorax	3 (0.5%)	4 (0.6%)	0.705
Aspiration pneumonitis	0 (0.0%)	1 (0.2%)	0.317
Others	1 (0.2%)	3 (0.5%)	0.317

Presented as number (%). [1] $p < 0.05$.

Table 4. Secondary outcomes in the propensity-matched cohort.

	Sugammadex (n = 616)	Neostigmine (n = 616)	p Value
Re-operation within 90days	17 (2.1%)	13 (2.1%)	1
Postoperative ICU admission	44 (7.1%)	48 (7.8%)	0.665
Re-admission or emergency room visit within 30 days	58 (9.4%)	69 (11.2%)	0.303
Length of hospital stay	8.72 (4.1)	9.09 (6.6)	0.238
Death within 90 days	1 (0.2%)	0 (0.0%)	0.317

Presented as number (%) or mean (standard deviation). ICU, Intensive Care Unit.

Jt Comm J Qual Saf 2020

A Comprehensive Estimation of the Costs of 30-Day Postoperative Complications Using Actual Costs from Multiple, Diverse Hospitals

Ryan P. Merkow, MD, MS; Ying Shan, MS; Aakash R. Gupta, MPH; Anthony D. Yang, MD, MS; Pradeep Sama, MBA; Mark Schumacher, MS; David Cooke, MD; Cynthia Barnard, PhD; Karl Y. Bilimoria, MD, MS

- Retrospective
- 6,387 patients from 4 US hospitals
- A cost analysis of 30-d postop complications using the National Surgical Quality Improvement Program
- The top 2 complications
  - Prolonged ventilation: $48,168 (95%CI, 21,861-74,476)
  - Unplanned intubation: $26,718 (95%CI, 15,374-38,062)

Br J Anaesth 2017

Association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission after abdominal surgery

T. Thevathasan[1,†], S. L. Shih[2,†], K. C. Safavi[1], D. L. Berger[3], S. M. Burns[1], S. D. Grabitz[1], R. S. Glidden[4], R. D. Zafonte[2], M. Eikermann[4,5,*] and J. C. Schneider[2]

- 13,122 patients, Multivariable regression
- Intraop NMBA, dose dependently related to higher risk of
  - 30-d readmission (OR 1.89, 95% CI 1.26-2.84)
  - hospital length of stay (OR 1.20, 95% CI 1.11-1.29)
  - hospital cost (OR 1.18, 95% CI 1.13-1.24)
- Neostigmine dose, ↑ 30-d readmission (OR 1.04, 95%CI 1.0-1.08)

Br J Anaesth 2018

Monitoring rather than dose matters when using non-depolarising neuromuscular blocking agents

A. Y. Oh
Seoul, South Korea

- Deep NMB optimizes surgical conditions
- Reversal of "deep NMB with sugammadex" was more rapid and predictable than "reversal of moderate NMB with neostigmine"
- Residual NMB, is the point
- Monitoring, essential to avoid residual NMB
- Proper dose of an appropriate antagonist, according to the status of NMB, evaluated by careful monitoring

Br J Anaesth 2019

Retrospective analysis of 30-day unplanned readmission after major abdominal surgery with reversal by sugammadex or neostigmine

Tak Kyu Oh[1], Ah-Young Oh[1,2,*], Jung-Hee Ryu[1,2], Bon-Wook Koo[1], In-Ae Song[1], Sun Woo Nam[1] and Hee-Jung Jee[3]

- 1,479 patients
- Mixed-effect logistic regression analysis
- Sugammadex
  - ↓ 30-d unplanned readmission (OR 0.66, 95% CI 0.46-0.96)
  - ↓ length of hospital stay (OR 0.80, 95% CI 0.77-0.83)
  - ↓ hospital charge (OR 0.76 95% CI 0.67-0.87)

Sugammadex on PPCs ?

2021년
대한신경근연구학회 춘계학술대회
Online Web Seminar

Session B

Focuses on the Current Issues and Trends: Part I

좌장: 삼성메디 이비인후과 이수일, 충남의대 신용섭

Device & Technology Review: EMG vs AMG

정 기 태

조선의대

1. Introduction

Neuromuscular blocking drug (NMBD) which is used not only for endotracheal intubation during the induction of anesthesia but also for the maintenance of anesthesia is inextricably linked to the anesthesiologist. However, the anesthetic procedure using NMBD always has a potential risk of residual neuromuscular block (RNMB) is associated with serious respiratory complications such as airway obstruction, hypoxia, aspiration pneumonia, etc. despite the use of reversal agents in the operating room[1]. Under the risk of RMB, neuromuscular monitoring is a very important guide for the safety of the patient. Although neuromuscular monitoring is an appropriate method for the assessment of the level of neuromuscular blockade (NMB) after the use of NMBD during anesthesia[1], it is paradoxical that many anesthesiologists do not monitor the neuromuscular function actually or make accurate judgments the data obtained from quantitative neuromuscular monitoring even though they know the importance of neuromuscular monitoring[2,3]. In Korea, perioperative neuromuscular monitoring has been included in an Anesthesia Adequacy Assessment conducted since 2018 and it is expected that the awareness of neuromuscular monitoring and its actual use would be increased.

Neuromuscular monitoring devices have been in clinical use since the 1970s[4], and the basic principles have not changed much. However, with the recent development of technology, many neuromuscular monitoring devices with increased convenience and accuracy have been developed. In this review, we will explore the development of neuromuscular monitoring devices and the latest trends.

2. Short history of technical development of neuromuscular monitoring[5]

After Harold Griffiths introduced the use of curare for abdominal surgery in 1942, the use of NMBD became wide in surgery in the 1950s. However, Beecher and Todd reported an increase in mortality after anesthesia in

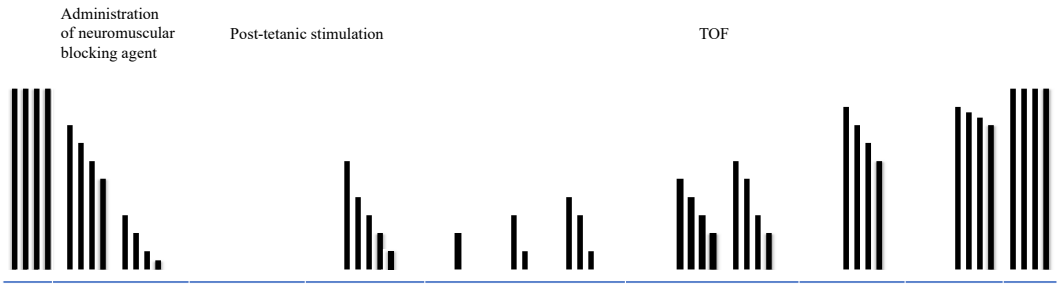
patients using d-tubocurarine in 1954, which led physicians to misunderstand that NMBD is toxic [6]. Dripps et al.[7] objected that the increase in mortality after anesthesia was responsible for the comorbidity of the patients, not NMBD toxicity. Thus, there was consensus about the need for safety in the use of NMBD.

In 1952, Thesleff conducted a study about the muscle tension during the use of succinylcholine using myography which recorded the flexion twitches of ulnar fingers during the stimulation of the ulnar nerve at the elbow[8]. Clinical neuromuscular monitor for anesthesiologists was developed by Christie and Churchill-Davidson in 1958[9]. The monitor called 'St Thomas' Hospital Nerve Stimulator' was aimed to discriminate between residual paralysis and narcotization conveniently by observing the response of the adductor pollicis (AP) muscle after ulnar nerve stimulation at the wrist. They also developed a new nerve stimulator that can apply both twitch and tetanic stimulation in 1965[10].

Although Churchill-Davidson motioned about the method similar to Train-of-four (TOF) in 1965, the TOF ratio was firstly used for the patients with myasthenia gravis in 1968. Roberts and Wilson reported the fade phenomenon during TOF stimulation in patients with myasthenia gravis and suggested the use of the TOF ratio for the assessment of treatment effect[11]. The use of TOF in anesthesia was introduced by Ali et al. in 1970[12]. Their study demonstrated was based the absence of fade after the use of depolarizing NMBD and forecasted the usefulness of TOF monitoring in the assessment of the degree of NMB. They introduced the TOF ratio as an indicator for the degree of NMB and recovery from NMB can be achieved with a TOF ratio above 0.6 which was comparable with the ability to lift the head for five seconds[13,14]. The modern nerve stimulator with a single twitch, TOF, TOF ratio, and post-tetanic count (PTC) was designed and introduced by Viby-Mogensen et al. in 1980[15]. Since then, many neuromuscular monitoring devices have been developed and used until now, and anesthesiologists' interest in neuromuscular monitoring has also increased.

3. Degrees of the neuromuscular blockade[16,17]

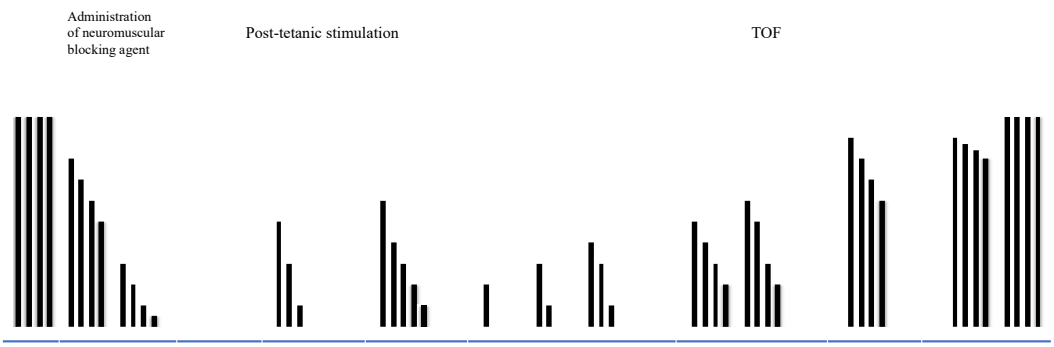
Although there is still definite agreement to define the exact depth of NMB, modified degrees of NMB was suggested in the international consensus conference[18]. After administration of intubation dose of NMBD, a patient will be in the state of intense block quickly and the response of TOF and PTC became disappear (Fig. 1). Deep block, the following phase after intense block, is defined as the phase when the response to tetanic stimulation begins. After achievement of PTC more than 6-8, the recovery to TOF count = 1 is expected soon, which means the phase of moderate block[16]. The moderate block is defined as the phase when the 1 to 3 TOF twitch appears. After the appearance of the fourth twitch of TOF and became possible to calculate the TOF ratio, the recovery phase begins. The recovery phase can be categorized as a light (shallow) block, minimal block (near recovery), and full recovery according to the TOF ratio. Until the light block (TOF ratio 0.1-0.4) fade can be observed during subjective TOF monitoring, while fade disappears during the minimal block (TOF ratio >0.4 to <0.9) and full recovery (TOF ratio >=0.9).



	Intense Block	*Deep Block*	*Moderate Block*	*Recovery*		
Train-of-four (TOF) Count	0	0	1 - 3	4		
Post-tetanic count (PTC)	0	≧1	-	-		
				Light Block	*Minimal Block*	*Full Recovery*
TOF ratio	-	-	-	0.1 - 0.4	>0.4 / <0.90	≧ 0.9 – 1.0
				TOF ratio 0.4: Head lift >5s Both leg lift TOF ratio 0.7 : Handgrip TOF ratio 0.85 : Sustained bite		TOF ratio 0.89 : Ability to cough effectively

Fig. 1. Suggested definitions of degrees of neuromuscular block[16].

Recently, Biro et al[19] has suggested modified degrees of neuromuscular block which separated a broad degree of 'deep block' (ranges from a TOF count = 0 to a PTC ≥1) into the 'profound block' (ranges from a TOF count = 0 to a PTC 1-3) and 'deep block' (PTC ≥4) because of the needs for the clinical application. For example, some surgeries such as laparoscopic, robotic, eye, and airway surgery require profound block (more intense than deep block) to avoid movement. Moreover, those surgeries may take a much shorter time to close the wound than traditional surgical procedures and conventional reversal agents such as neostigmine or pyridostigmine would not be effective for the reversal from NMB in the state of the profound block. Therefore, the detailed classification may be necessary for the selection of reversal agents and avoiding the risk of RNMB.



	Complete Block	*Profound Block*	*Deep Block*	*Moderate Block*	*Shallow Block*	*Minimal Block*	*Acceptable Recovery*
Train-of-four (TOF) Count	0	0	0	1 - 3	4	4	4
Post-tetanic count (PTC)	0	1 - 3	≧ 4	-	-	-	-
TOF ratio	-	-	-	-	< 0.4	0.4 – 0.9	≧ 0.9

Fig. 2. Recently proposed modified degree of neuromuscular block[19].

4. Modes of neuromuscular monitoring

Several modes of neuromuscular monitoring have been introduced for the assessment and monitoring of NMB (Table 1). Mechanomyography (MMG) which measures the mechanical response of the adductor pollicis muscle induced by ulnar nerve stimulation is a gold standard of neuromuscular monitoring because of its precise result and reproducibility[1]. However, it is not used in the clinical situation due to difficulty in the setup. Clinically, acceleromyography (AMG) and electromyography (EMG) are commonly used modes for the quantitative measurement of NMB by the mechanical or electrical response[17]. AMG measures the force by the acceleration movement of muscles such as flexor hallucis brevis, orbicularis oculi, or corrugator supercilia using Newton's Second Law of Motion (force = mass x acceleration). EMG measures the evoked action potential of target muscles (e.g. adductor pollicis, abductor digiti minimi, or first dorsal interosseus muscle) during the muscle contraction which is produced by the stimulation of peripheral nerve (e.g. ulnar nerve) via skin electrodes. Other modes such as kinemyography (KMG) which measures the voltages during the bending of a piezoelectric sensor strip and phonomyography (PMG) which measures the low-frequency sounds evoked by muscle contraction are also used for the assessment of neuromuscular function.

Table 1. Modes of Neuromuscular Monitoring

	MeasuresModes	Sensor	Note
Mechanomyography (MMG)	Force of contraction	Force	Gold standard with precise and reproducible result Difficult to adapt clinically due to difficulty of setup the equipment
Acceleromyography (AMG)	Force by the acceleration movement of muscle	Piezoelectric crystal	Most used Reliable TOF ratio Overestimation
Electromyography (EMG)	Amplitude of action potential of muscle	Electrodes	Best indicator of pure neuromuscular function Affected by electrocautery or temperature
Kinemyography (KMG)	Voltage generated during the movement of muscle	Piezoelectric sensor	Less reproducible than EMG
Phonomyography (PMG)	Sound intensity	High-fidelity microphone	Low clinical use

5. AMG vs. EMG

Still, AMG is the most widely used mode due to its advantages which produces a real-time measurement of objective neuromuscular function at low cost. However, there are several limitations in the clinical uses. AMG requires calibration before the first injection of NMBD to detect supramaximal current for the adjustment of twitch response corresponding to 100%. Moreover, the careful maintenance of the arm posture and measurement environments such as restriction of the position of arm throughout the surgery, free movement of the thumb, and

avoidance of impediment by drapes or positioning are required throughout the measurement of AMG because the acceleration sensor of AMG measures only in one plane of motion. Thus, AMG cannot be applied in the surgery which interferes with the position of the arm that measures the NMB unless using the special protective device. However, a modern AMG device with three-dimensional sensor technology has been introduced to overcome the drawbacks with calibration and postural limitation by assessing the complex motion of the thumb in response to neurostimulation. AMG monitors with the three-dimensional sensor can be applied for surgeries which are tucking arms close to the body. AMG also has a problem called the “reverse fade” effect showing a TOF ratio higher than the ideal baseline value of 1.0. According to the report of Suzuki et al.[20], the TOF ratio value of 1.10 to 1.47 has been recorded. This can lead to the problem such as overestimation of TOF ratio during the recovery from NMB.

EMG measures the action potential and converts them to a mechanical response. It can be the best indicator of pure neuromuscular function because of low interference with other events and stable amplitude despite constant stimulation[1]. EMG measures neuromuscular function by physiological way using electrical signal rather than the force of muscle contraction, which provides more precise results than AMG. The data of neuromuscular function obtained from EMG is most similar to that from MMG[21]. Moreover, unlike AMG, it does not require a special setup or care for position and does not have the ‘reverse fade’ effect. Although EMG has a possibility of incorrect measurement by interference from electrical stimulation such as electrocautery, modern EMG has an automatic function of pausing and resuming the measurement by detecting the electrical interference. Another minor disadvantage of EMG is higher costs in comparison to AMG because of the use of a unique electrode in EMG devices.

The overestimation of the TOF ratio by AMG can be problematic for the goal of RNMB avoidance as it leads to the misconception that recovery from NMB is achieved with a TOF ratio value of 0.9 or higher, even though the normalized value is less than 0.9. According to the previous reports, the values of the TOF ratio obtained from AMG were 10–20% higher than those from MMG or EMG[20,22,23]. Kopman et al.[24] reported the difference of TOF ratio between EMG and AMG when the TOF value of AMG had recovered to approximately 0.7 and 0.9 were 0.069-0.125 and 0.055-0.096, respectively (Fig. 3.). Although, the application of an elastic preload to the thumb decreased the variability of baseline values of TOF, the difference of TOF ratio between EMG and AMG became larger during the recovery. They concluded that TOF values of AMG overestimate the degree of recovery from NMB in comparison to the values of EMG and TOF values < 0.90 obtained from AMG are inaccurate and indicates incomplete recovery from NMB. Furthermore, “normalization” of each measured value of the TOF ratio is difficult and takes more time to interpret. Therefore, a simple method of reducing the TOF ratio value by about 10% can be used, or a method aiming at 1.0 instead of 0.9 as a target value for the recovery from NMB in AMG, but this is an inaccurate measurement[25].

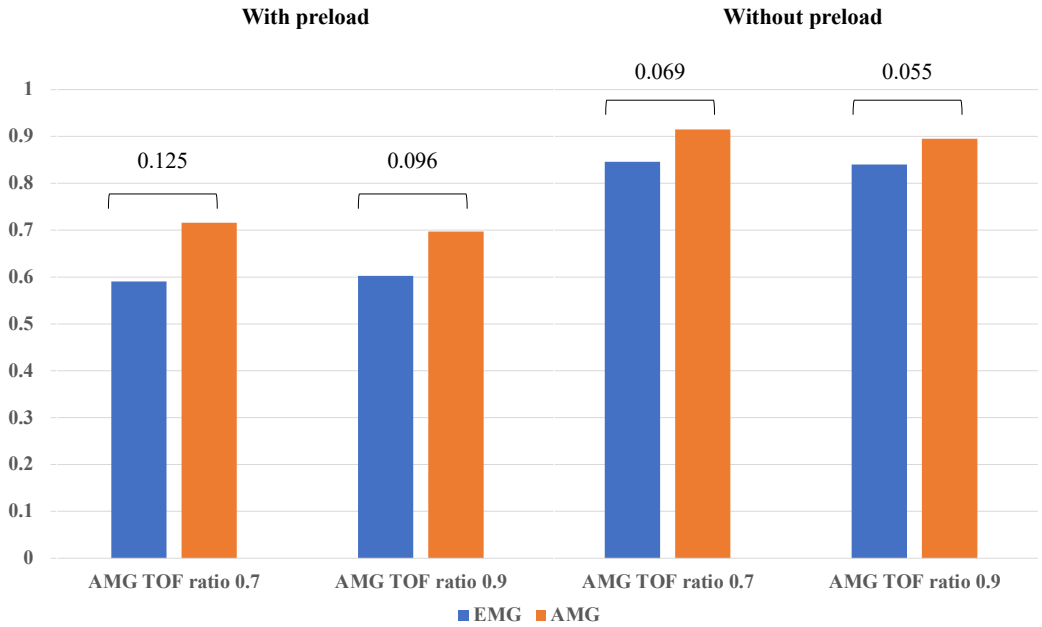


Fig. 3. The difference of TOF ratio between EMG and AMG during recovery from NMB[24]. The value of the TOF ratio of EMG at both TOF ratios of AMG of 0.70 and 0.90 shows smaller values. TOF, Train-of-four; EMG, electromyography; AMG, acceleromyography.

6. Modern technical development of neuromuscular monitoring devices

With the recent development of technology, neuromuscular monitoring devices close to the ideal are being released. An ideal neuromuscular monitoring device requires functions such as large monitors for the trends display and annotation of the events, short TOF intervals (about 20 seconds), a warning system with a user setting thresholds limits, and automatic PTC mode[16]. Recently introduced neuromuscular monitoring devices such as the TOFscan (IdMed, Marseille, France), TetraGraph (Senzime BV, Uppsala, Sweden), and TwitchView (Blink Device Company, Seattle, USA) can implement most of those functions (Table 2).

Especially, the automatic function called automatic PTC or automatic TOF-PTC mode is very useful for the anesthesiologist during the induction and maintenance of anesthesia (Fig. 4.)[16]. After starting the neuromuscular monitoring with automatic mode and administration of NMBD, the device would measure TOF in short intervals (20-30 seconds interval) repeatedly if the TOF count appears. When the TOF count becomes 0, the PTC mode starts for the assessment of deep or profound block with about 3-5 minutes interval to avoid inaccurate measurement by post-tetanic potentiation, repeatedly. The measurement of PTC is automatically repeated until the TOF count becomes 1, then the PTC sequence would be finished and reverted to the TOF mode with short intervals automatically. Among the new neuromuscular monitors available in Korea, TOFscan and TwitchView provide the automatic PTC mode.

Table 2. Characteristics of Up-to-date Neuromuscular Monitoring Devices available in Korea

Mode	TOFscan®	Tetragraph®	Twitch View®
Type	AMG	EMG	EMG
Pulse	Monophasic / 200 μs	Monophasic / 200, 300 μs	Monophasic / 100, 200, 300 μs
TOF	40 mA (20-60 mA)	Automatic (10-60 mA)	Automatic (0-80 mA)
Automatic TOF	15s, 30s, 1m, 2m, 5m, 15m	20s, 1m, 5m, 15m, 60m	10s, 2m, 5m, 15m, 60m
PTC	Lockout about 2m 30s	+	Lockout about 5m
Automatic PTC	+	-	+
DBS	3.3, 3.2	-	-
ST	0.1, 1 Hz	1 Hz	+
TET	50 Hz	-	+
Battery	2,000 mA Li-Ion	8 hrs	8 hrs
Sensor	Reusable / Disposable	Disposable	Disposable
Simulator	-	+	-

AMG, acceleromyography; EMG, electromyography; TOF, Train-of-four; PTC, post-tetanic count; DBS, double burst suppression; ST, Single twitch; TET, tetanic stimulation

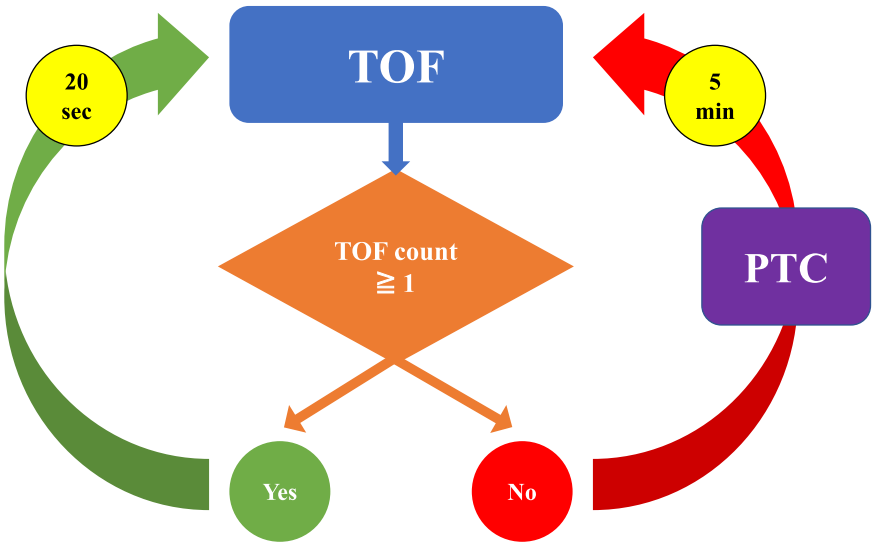


Fig. 4. The schematic algorithm of automatic PTC mode. The measurement of TOF with 20-30 seconds interval repeats until the disappearance of TOF count and the PTC mode starts with about 3-5 minutes interval automatically for the assessment of deep or profound block. When the TOF count reappears, PTC mode terminated automatically and reverted to the TOF mode. TOF, Train-of-four; PTC, post-tetanic count.

Some neuromuscular monitors have not yet been released in Korea. StimPod NMS450 (Xavant Technology Ltd., South Africa) is an interesting device that can use both AMG with triaxial accelerometer and EMG modes. However, the values of the TOF count of AMG were smaller about 39% than that of EMG, which represents the underestimation of TOF count in the AMG with the StimPod, in contrast[26]. TOF-cuff (RGB Medical, Madrid, Spain) has a unique mechanism using compressomyography technique that measures TOF responses by changes in pressure peaks during the muscle contraction induced by stimulation of the brachial plexus[16]. TOF-cuff has an advantage with convenience because it uses a modified blood pressure cuff on the arm for the neuromuscular monitoring, but has limitations of underestimation in the measurement of TOF ratios and inaccuracy for the prevention of RNMB in comparison to the EMG or AMG[27]. Recent reports showed delayed recovery to a normalized TOF ratio more than 0.9 (about 25 min longer) with EMG or AMG compared with the TOF-Cuff[28].

7. Conclusion

Many experts have emphasized the importance of objective quantitative neuromuscular monitoring and the consensus on the imperatives of neuromuscular monitoring during the use of NMBD has been achieved in several guidelines[16,18,29-32]. However still, a large number of patients about 40-60% leave the operating room without an acceptable recovery from NMB, and they are exposed to the potential risk of complications associated with RNMB[31,33,34]. Especially, qualitative peripheral nerve stimulation in the decision of recovery from NMB has risks creating RNMB[31]. Furthermore, the importance of quantitative neuromuscular monitoring has been highlighted as the advent of sugammadex which requires the determination of dosage based on the degree of NMB[32]. Also, with the recent increase in the number of surgeries requiring deep or profound NMB which is almost impossible to guarantee full recovery with the use of conventional reverse agents, the need for neuromuscular monitoring is increasing. Thus, objective quantitative neuromuscular monitoring became mandatory for the management of anesthetized patients after the use of NMBD in recent years.

Modern neuromuscular monitors with a state-of-the-art system make it easier and more accurate than ever to evaluate neuromuscular functions during anesthesia. Recently released EMG-based devices are in the limelight because they are not only easy to use but also show accurate values of TOF similar to MMG[25]. However, AMG devices with modern 3D technology overcome the previous limitations and, if used properly, also provide ease of use and acceptable results. Anesthesiologists should build up knowledge of neuromuscular mechanism and monitoring including how to use the latest device for proper neuromuscular monitoring and patient safety.

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Management of Neuromuscular Blockade during Neurophysiologic Monitoring

임 채 성

충남의대

서론

수술 중 신경생리감시는 다양한 유발전위, 근전도, 뇌파, 뇌 혈류 등의 감시를 통해 수술 중 신경 손상 가능성을 조기 예측하기 위해 그 사용이 증가하고 있다. 수술 전에는 기관 삽관을 위해, 수술 중에도 더 나은 수술 시야의 확보를 위해 신경근 차단제를 사용하기도 한다. 하지만, 신경생리감시가 신경근 차단 정도에 따라 영향을 받을 수 있어 이에 대한 이해와 술 전 논의가 필요하다.

본론

SSEP (somatosensory evoked potentials)와 BAEP (brainstem auditory evoked potentials)는 신경근 차단제의 영향을 받지 않아 사용하는데 부담이 없지만, MEP (motor evoked potentials)와 EMG (electromyogram)는 신경근 차단제의 영향을 많이 받는다. 하지만 그림1에서 볼 수 있듯이 T1의 10-20% 차단이나 TOF의 2/4 출현 정도의 부분신경근차단 (partial neuromuscular block, pNMB)에서는 MEP와 EMG의 감시가 충분히 가능하다. 이를 위해서는 신경근 차단 전에 기준선을 설정해야 하고, 적절한 부분신경근차단 정도를 엄격하게 유지하기 위해서는 정확한 신경근 감시와 함께 신경근 차단제를 지속 주입하는 것이 바람직하다. 부분신경근차단으로 인해 감소되는 MEP의 근육 반응을 증대시키기 위해 MEP 자극검사 전에 tetanic stimulation을 사용하는 것에 대한 연구들이 발표되고 있다.

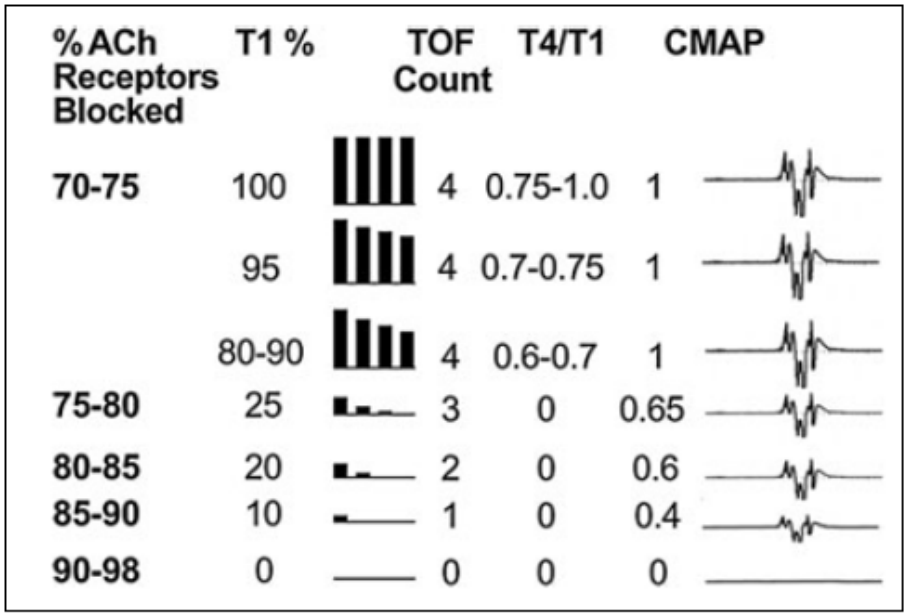

Fig. 1 Relationship of receptors blocked, single twitch response (T1), Train of four and MEP amplitude. Shown in the left column is the approximate percentage of acetylcholine receptors (AChR) blocked by neuromuscular blocking agents. To the right is the approximate height (%) of the T1 response at these levels compared to baseline. Next is a depiction of the train of four (TOF) response, the count of the 4 possible responses that are present, and the ratio of the fourth response to the first (T4/T1). Finally, the approximate peak amplitude of the compound muscle action potential (CMAP) of the MEP (참고문헌1에서 인용).

결론

수술 중 신경생리감시에서 부분신경근차단을 적용함으로써 얻을 수 있는 장점은 다음과 같다. (1) facilitates surgical exposure, (2) eliminates the need for the surgeon to interrupt the procedure periodically to allow MEP testing, (3) reduces the risk of unexpected movement (especially in patients tolerant to opioid anesthetics), and (4) reduces the excessive EMG noise which may improve the signal to noise ratio and reduce acquisition time for subcortical SSEP or epidural D wave recordings.

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Hot Topics in Neuromuscular Research Area : Bibliometric Analysis of Last 5 year's Top publications

이 상 석

인제의대 상계백병원

BIBLIOMETRICS?

Bibliometrics(계량서지학)는 라틴/그리스어로 서적(book)을 의미하는 'Biblio-'와 측정(measurement)을 의미하는 'Metric'의 합성어이며, 과학문헌들에 대한 정량적 분석과 문헌 간의 네트워크를 분석하는 학문 분야이다. 스위스 식물학자인 알폰스 캉돌(Alphonse P. Candolle, 1806-1893)은 그의 저서 "Histoire de science et des savants depuis deux sciecles (1885)"에서 국제 학회에 소속된 과학자들의 국가별 분포를 이용하여 과학적 탁월성을 나타내는 핵심지표를 정확하게 수학적인 방법으로 연구한 첫번째 시도로 알려져 있다. 1969년, Alan Pritchard에 의해서 비로소 'bibliometrics'라는 용어가 처음 사용되었으며, 그는 정의로서 '기록된 정보를 통계적으로 유의미하게 표현하는 방식'이라고 해설하였다.

개인이나 집단의 학술성과는 여러 가지 방법으로 평가할 수 있는데, 발표한 논문 수나 그 논문들이 받은 인용빈도 등을 계량하는 정량평가가 객관적인 방법으로 인정받고 있다. 계량서지학적 방법을 적용하면 학술지별, 기관별, 연구자별, 논문 별 연구 성과의 객관적인 정량평가가 가능하다. 또한, 계량서지학적 분석은 사례연구 분석, 상호검토(peer review), 경제적 수익률 분석, 조사 및 협의 등과 같이, 보건과학에서 연구의 영향을 평가하는데 활용되고 있다. 계량서지학적 방법은 다른 연구평가 방법보다 중요한 이점을 제공한다. 이 방법은 공동연구에 대한 유용한 정량적 지표와, 범학문적 연구에 대한 측정지표를 제공한다. 분석 도구가 세부적일수록 양질의 더 나아가 우수한 종합지표를 생성할 수 있다. 계량서지학적 분석은 최근 몇 년간 개발된 다양한 복합지표를 사용한다. 계량서지학적 방법이 강력한 분석 도구가 되려면, 각 측정지표의 강점과 취약점 및 사용 배경을 명확히 이해해야 한다. 궁극적으로, 계량서지학적 방법은 독립적으로 사용될 때보다는 다른 방법들과 결합되어 사용되면 더욱 효과적이다. 예를 들어, 상호검토 결정을 보완하기 위해 계량서지학적 분석을 같이 사용하면 효과적이다. 특히, 분석할 자료가 방대하고 복잡한 대규모 상호검토를 실행할 경우 정량적 검토가 유용할 수 있다.

Bibliometric의 주된 분야는 'productive count'와 'literature usage count'를 포함한다. 전자는 출판물에 기여한 국가, 저자, 저널, 출판연도 및 학술단체의 수를 집계하는 것이며, 후자는 인용분석을 사용하여 문헌의 쓰임새를

추적하는 것이다. 이러한 기본 기능을 바탕으로 bibliometrics는 다음과 같은 활용이 가능하다; 1) To study research trends and growth of knowledge, 2) To identify past, present publishing trends as well as forecast future publishing trends, 3) To identify core periodicals in different disciplines, 4) To identify authorship trends in documents on various subjects, 5) To study productivity of institutions/individuals and disciplines.

THE PROCEDURE OF BIBLIOMETRIC ANALYSIS

Bibliometric 분석은 6개의 단계를 거치게 된다. 첫번째 단계는 자료추출을 위한 database의 선택과정이다. 분석을 위한 데이터는 Web of Science (Clarivate Analytics, Philadelphia, PA, USA; seehttps://clarivate.com/products/web-of-science) Core Cellection중에서 Science Citation Index Expanded (SCI-EXPANDED) bibliographic database에서 추출되었다. Bibliographic 분석을 위해서 여러가지 formal literature database가 사용될 수 있는데, 대표적인 것이 Web of Science (WoS)와 Scopus이다. Bibliographic 분석을 위한 자료의 완전성을 고려할 때 WoS의 자료가 더 적합한 것으로 알려져 있다. 이 연제를 위하여 WoS 자료를 사용하였다.

	WoS	Scopus
Strength	Advanced citation searching and analysis features	Advanced citation searching and analysis features
	Citation data available from 1900	Better coverage of Social Science titles
	Broad coverage of high impact journals	Includes conference proceedings
Weakness	Conference papers, theses, books and book chapters are excluded	Books, book chapters and theses excluded
	Limited coverage of non-English publications	Citation data from papers published since 1996 only

두번째 단계는 Keyword설정이다. 문헌 제목과 초록 혹은 키워드목록에 “neuromuscular blockade” or “neuromuscular agents” or “neuromuscular revers*”를 포함하는 모든 문헌을 검색하였다. 세번째 단계는 Subject설정으로서 연구분야와 동떨어진 문헌을 배제하기 위하여 주제의 범위를 WoS category중에서 ‘anesthesiology’ 혹은 ‘critical care’에 한정하였다. 네번째 단계는 검색의 시간범위를 한정하는 것인데, 연구 및 인용 경향에 대한 전반적인 정보를 분석하기 위해서 5 년간의 자료를 분석할 필요가 있었기에 timespan은 2016에서 2021년 검색일(6월 5일)까지의 출판물을 대상으로 한정했다. 다섯번 째는 문헌의 종류를 선정하는 것이며, ‘Articles’ 혹은 ‘Proceedings Papers’로 한정하였고, 마지막으로 문헌에 사용된 언어를 ‘English’로 제한하였다.

MAIN RESULTS OF BIBLIOMETRIC ANALYSIS

General information and annual publication output

Table 1 은 WoS collection에서 추출된 신경근 관련 연구들의 기본 정보를 담고 있다. 총 378편의 문헌을 대상으로 하였으며, 이들은 모두 ‘article’ or ‘early access article’ or ‘proceedings paper’속성을 가진 문헌만 대상으로

하였다. 이 문헌들에 사용된 키워드의 총 수는 993 Keywords Plus 및 725 Author's Keywords였다. 전체 저자 수는 2,057명이며, 단독 저자 문헌은 6개에 불과하였다. Collaboration index는 5.33으로서 낮은 편이었다. 저자 당 문헌비는 0.19이며, 이는 대략 평균적으로 한 문헌에 5명의 저자가 참여하였다는 것을 의미한다.

Table 1. Main Information

Description	**Results**
MAIN INFORMATION ABOUT DATA	
Timespan	2016:2021
Sources (Journals, Books, etc)	24
Documents	391
Average years from publication	2.73
Average citations per documents	8.371
Average citations per year per doc	2.124
References	7554
DOCUMENT TYPES	
article	378
article; early access	9
article; proceedings paper	4
DOCUMENT CONTENTS	
Keywords Plus (ID)	993
Author's Keywords (DE)	725
AUTHORS	
Authors	2057
Author Appearances	2536
Authors of single-authored documents	6
Authors of multi-authored documents	2051
AUTHORS COLLABORATION	
Single-authored documents	6
Documents per Author	0.19
Authors per Document	5.26
Co-Authors per Documents	6.49
Collaboration Index	5.33

신경근 관련 연구의 년간 출판물은 79편 (2016) → 71편 (2017) → 58편 (2018) → 58편 (2019) → 75편 (2020) → 41편 (2021.5) 로서 일정량을 유지하고 있으며, Table 2에는 article 과 년도로 평균한 인용횟수를 보여주고 있다.

Table 2. Annual total citation per year

Year	N	MeanTCperArt	MeanTCperYear	CitableYears
2016	79	14.32911392	2.865822785	5
2017	71	11.02816901	2.757042254	4
2018	58	12.39655172	4.132183908	3
2019	58	5.620689655	2.810344828	2
2020	75	3.586666667	3.586666667	1
2021	41	1.048780488		0

CORE JOURNALS

신경근 관련 연구 출판물을 다루고 있는 핵심 저널을 확인하기 위해서 각 저널 별 출판물을 집계하고 source impact와 Bradford법칙을 적용하였다.

Table 3은 대표적인 성과지표로서 h, m, g-index, total citation (TC), net production (NP), publication starting year (PY_start) 데이터를 근거로 한 저널 랭킹을 나타낸다. 한편, Table 4는 Bradford법칙에 의한 저널 순위를 표시하였다. Bradford법칙에 의해서, 저널 목록은 3개의 영역으로 구분되고, Zone 1은 core source로 간주된다. Zone 1에 해당하는 core journal은 ANESTHESIA AND ANALGESIA, BRITISH JOURNAL OF ANAESTHESIA, BMC ANESTHESIOLOGY, EUROPEAN JOURNAL OF ANAESTHESIOLOGY 순서로 4편이 해당하였다.

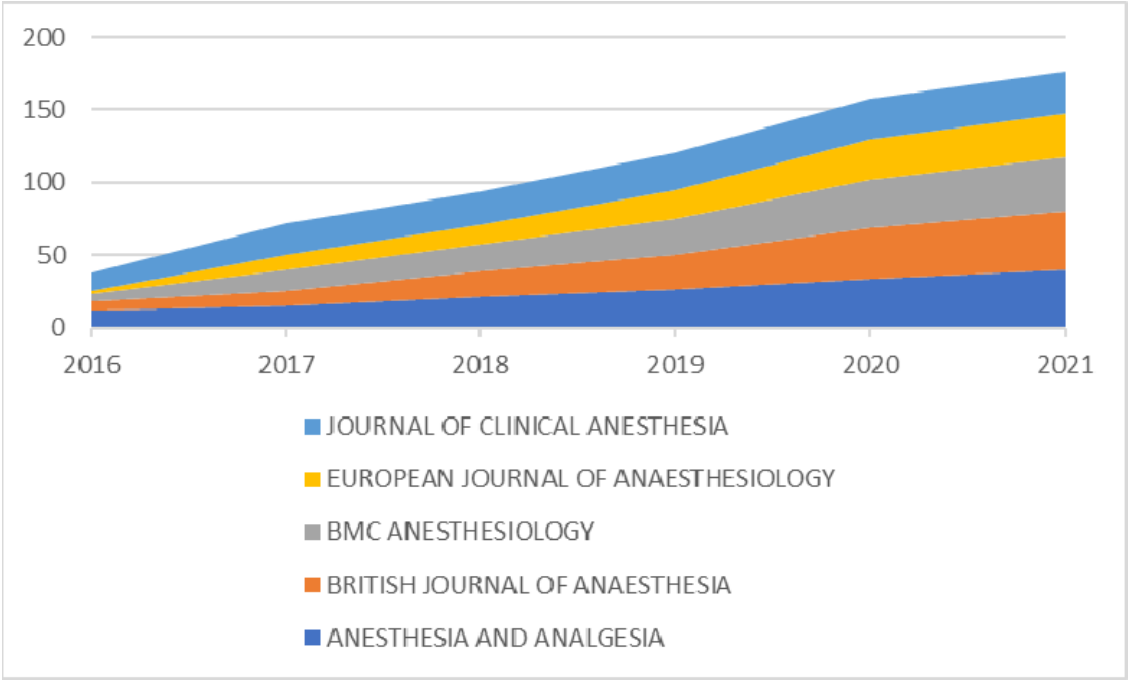
Table 3. Source Impact (Ranks by h-index)

Element	h_index	g_index	m_index	TC	NP	PY_start
BRITISH JOURNAL OF ANAESTHESIA	16	25	2.666666667	673	35	2016
ANESTHESIA AND ANALGESIA	13	21	2.166666667	530	38	2016
ANAESTHESIA	12	23	2	575	26	2016
ANESTHESIOLOGY	10	17	1.666666667	300	22	2016
JOURNAL OF CLINICAL ANESTHESIA	10	13	1.666666667	220	27	2016
EUROPEAN JOURNAL OF ANAESTHESIOLOGY	7	12	1.166666667	172	27	2016
ACTA ANAESTHESIOLOGICA SCANDINAVICA	6	11	1	140	20	2016
BMC ANESTHESIOLOGY	6	7	1	94	21	2016
MINERVA ANESTESIOLOGICA	6	10	1	111	13	2016
CANADIAN JOURNAL OF ANESTHESIA-JOURNAL CANADIEN D ANESTHESIE	5	7	0.833333333	59	13	2016
JOURNAL OF ANESTHESIA	5	7	0.833333333	84	22	2016

Table 4. Journal Ranks by Bradford's Law

SO	Rank	Freq	cumFreq	Zone
ANESTHESIA AND ANALGESIA	1	40	40	Zone 1
BRITISH JOURNAL OF ANAESTHESIA	2	40	80	Zone 1
BMC ANESTHESIOLOGY	3	37	117	Zone 1
EUROPEAN JOURNAL OF ANAESTHESIOLOGY	4	30	147	Zone 1
ANAESTHESIA	5	29	176	Zone 2
JOURNAL OF CLINICAL ANESTHESIA	6	29	205	Zone 2
JOURNAL OF ANESTHESIA	7	28	233	Zone 2
ACTA ANAESTHESIOLOGICA SCANDINAVICA	8	22	255	Zone 2
ANESTHESIOLOGY	9	22	277	Zone 2
JOURNAL OF CLINICAL MONITORING AND COMPUTING	10	22	299	Zone 3
MINERVA ANESTESIOLOGICA	11	14	313	Zone 3
PEDIATRIC ANESTHESIA	12	14	327	Zone 3
CANADIAN JOURNAL OF ANESTHESIA-JOURNAL CANADIEN D ANESTHESIE	13	13	340	Zone 3
REVISTA BRASILEIRA DE ANESTESIOLOGIA	14	10	350	Zone 3
JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	15	9	359	Zone 3
ANAESTHESIA AND INTENSIVE CARE	16	8	367	Zone 3
ANAESTHESIA CRITICAL CARE \& PAIN MEDICINE	17	6	373	Zone 3
INTERNATIONAL JOURNAL OF OBSTETRIC ANESTHESIA	18	6	379	Zone 3
ANAESTHESIST	19	4	383	Zone 3
PERIOPERATIVE MEDICINE	20	3	386	Zone 3
BEST PRACTICE \& RESEARCH-CLINICAL ANAESTHESIOLOGY	21	2	388	Zone 3
ANASTHESIOLOGIE \& INTENSIVMEDIZIN	22	1	389	Zone 3
BRAZILIAN JOURNAL OF ANESTHESIOLOGY	23	1	390	Zone 3
JOURNAL OF NEUROSURGICAL ANESTHESIOLOGY	24	1	391	Zone 3

Fig. 2는 Bradford법칙에 의한 Zone 1에 속하는 Top journal의 출판 dynamics를 표시한다. 이 영역의 저널들은 신경근 관련 연구를 꾸준히 출판하고 있으며 출판량도 일정수준을 계속 유지하고 있다.



CORE JOURNAL ARTICLES

신경근 관련 연구 출판물 중에서 가장 많은 인용횟수를 보인 상위 논문을 Table 7에 제시하였다. 추적기간 동안 가장 높은 인용횟수를 보인 논문은 Checketts 등에 의한 “Recommendations for standards of monitoring during anaesthesia and recovery”이다. Anaesthesia 저널에 2016년에 출판된 이 논문은 주술기 표준 마취 감시에 관한 영국과 아일랜드 마취학회 연합의 가이드라인의 4번째 업데이트 판이다. 이번 edition이 주목을 끌게 된 것은 처음으로 appendix에 neuromuscular monitoring에 관한 구체적인 가이드라인을 실었다는 점이었다.

Harper 등에 의한 perioperative anaphylaxis의 epidemiology와 임상양상을 다룬 문헌이 Second most common cited literature에 해당하였다. 이 문헌은 제6국가 감사 프로젝트의 하나로서 영국내 모든 국민보건서비스(National Health Service; NHS) 지원 병원에서 지난 1년간 보고된 주술기 아나필락시스 보고 266건에 대한 리뷰를 다루고 있다. 신경근 차단제는 주술기 아나필락시스 사례의 40-66%에 해당하는 것으로 알려져 있다. 이 보고서는 Rocuronium이 가장 흔히 보고된 약물이며 그 빈도는 1/17,000 (95% CI: 1/11686 – 25799) 정도라고 한다.

세번째로 많이 인용된 문헌은 Naguib 등에 의한 “Consensus Statement on Perioperative Use of Neuromuscular Monitoring”이며, 신경근 감시에 관한 체계적인 첫번째 공식 가이드라인으로 평가할 수 있다.

네번째 인용순위의 문헌은 Bulka 등에 의한 비탈분극성 신경근 차단제와 길항제가 수술 후 폐렴 발생과의 관계에 관한 연구이다. 신경근 차단제를 사용한 환자는 대조군에 비하여 postop. pneumonia 발생위험이 1.79배가 높으며, 적절한 길항제를 사용하지 않는 경우에는 길항제를 사용한 경우보다 postop. pneumonia발생위험이 2.26배 더 높았다. 비탈분극성 신경근 차단제 사용 후 잔류근이완 문제를 부각하고 실제 수술 후 폐렴과 같은 합병증 발생 위험도를 측정하여 신경근 차단제의 적절한 길항의 중요성을 강조한 연구로 평가된다.

Table 7. Most globally cited articles

Paper	DOI	Total Citations	TC per Year	Normalized TC
CHECKETTS MR, 2016, ANAESTHESIA	10.1111/anae.13316	265	44.167	18.4938
HARPER NJN, 2018, BR J ANAESTH	10.1016/j.bja.2018.04.014	125	31.25	10.0834
NAGUIB M, 2018, ANESTH ANALG	10.1213/ANE.0000000000002670	84	21	6.7761
BULKA CM, 2016, ANESTHESIOLOGY	10.1097/ALN.0000000000001279	68	11.333	4.7456
MEMTSOUDIS SG, 2018, ANESTH ANALG	10.1213/ANE.0000000000003434	46	11.5	3.7107
TACQUARD C, 2017, ACTA ANAESTHESIOL SCAND	10.1111/aas.12855	45	9	4.0805
SAJAYAN A, 2016, BR J ANAESTH	10.1093/bja/aew017	42	7	2.9311
MADSEN MV, 2016, EUR J ANAESTH	10.1097/EJA.0000000000000360	42	7	2.9311
SCOLARO RJ, 2017, ANAESTH INTENSIVE CARE	10.1177/0310057X1704500504	38	7.6	3.4457
THEVATHASAN T, 2017, BR J ANAESTH	10.1093/bja/aex240	35	7	3.1737

MAIN AUTHORS, AFFILIATION, INSTITUTIONS AND COUNTRIES

Table 5에는 가장 생산성이 높은 저자들의 순위가 게시되어 있다. 각 논문에는 참여하는 저자들의 숫자가 다르기 때문에 단순히 논문의 숫자만으로 평가(Author appearance on the article)하는 것은 bias가 있으므로 각 논문의 공동저자들이 모두 평균적인 역할을 하였다는 가정하에 총 저자수로 normalized한 결과가 'Aticles Franctionalized'이다. 대부분 미국 저자들이 순위에 포함되고 있는데 TOP 20내에 한국 저자가 두 명이 포함되어 있다는 점은 주목할 만하다.

Table 5. Most Relevant Authors (ranked by articles fractionalized)

Authors	Articles	Articles Fractionalized
EIKERMANN M	15	1.81
MASUI K	5	1.50
HUNTER JM	4	1.41
GATKE MR	6	1.20
OH AY	7	1.14
SUZUKI T	6	1.04
YAMAKAGE M	4	1.03
DE BOER HD	4	1.00
BURBRIDGE MA	1	1.00
KOLLENGODE R	1	1.00
MATHER LE	1	1.00
PATEL S	1	1.00
SCHMITT HJ	1	1.00
ERRANDO CL	5	0.97
IWASAKI H	5	0.90
TAKAGI S	5	0.87
TAKAZAWA T	5	0.80
FUCHS-BUDER T	4	0.80
KIM HJ	4	0.78
HOULE TT	6	0.76

책임저자의 국적에 의한 분류는 Table 6에 나열 되어있다. 논문 수에 의한 순위는 미국, 한국, 일본, 영국, 호주 순서이며, 조사기간내에 국내저자들의 높은 생산지수가 인상적이다. 여러 국가 간의 협업에 의한 생산물로 국제화지수를 나타내는 MCP ratio는 전반적으로 높지 않은데, 비교적 높은 생산지수와 연동해서 보면, 미국(0.327), 호주(0.35), 스페인(0.308), 벨기에(0.333), 브라질(0.444)이 국제화 수준이 평균 수준이며 한국(0.025), 일본(0.0)은 국제화지수가 매우 낮다.

Table 6. Most Relevant Countries by corresponding author

Country	Articles	Freq	SCP	MCP	MCP_Ratio
USA	98	0.25064	66	32	0.327
KOREA	40	0.1023	39	1	0.025
JAPAN	37	0.09463	37	0	0
UNITED KINGDOM	24	0.06138	19	5	0.208
AUSTRALIA	20	0.05115	13	7	0.35
FRANCE	19	0.04859	14	5	0.263
GERMANY	17	0.04348	13	4	0.235
SPAIN	13	0.03325	9	4	0.308
DENMARK	12	0.03069	10	2	0.167
TURKEY	12	0.03069	12	0	0
ITALY	10	0.02558	8	2	0.2
BELGIUM	9	0.02302	6	3	0.333
BRAZIL	9	0.02302	5	4	0.444
CHINA	9	0.02302	9	0	0
CANADA	8	0.02046	7	1	0.125
NETHERLANDS	7	0.0179	5	2	0.286
EGYPT	6	0.01535	4	2	0.333
HUNGARY	5	0.01279	3	2	0.4
SWITZERLAND	5	0.01279	3	2	0.4
CZECH REPUBLIC	4	0.01023	4	0	0

MOST RELEVANT WORDS

Table 7에는 전체 문헌을 통해서 가장 빈번히 등장하는 단어들이 추출 source에 따라 순서대로 나열 되어있다. 자동 컴퓨터 알고리즘에 의해 생성된 Keywords Plus는 논문의 레퍼런스의 제목에 자주 나타나는 단어 또는 구(phrase)이며, 이것은 저자들이 설정한 키워드 혹은 논문의 제목에 반드시 출현하지는 않을 수 있다. 유진 가필드(1925-2007)에 의하면 Keyword Plus는 논문의 내용을 더 함축하여 표현할 수 있는 대표단어라고 주장하였다. 저자들이 직접 설정하는 Author's Keywords는 저자가 논문의 내용을 가장 잘 표현한다고 생각하는 용어 목록으로 구성된다. 반면, 초록과 제목에 사용된 용어들은 주제나 리서치 스트림을 생성할 가능성이 적은 보다 일반적(general)이다.

Table 7. Most Relevant Words

Keywords Plus		Author's Keyword		Title		Abstract	
Words	Occurrences	Words	Occurrences	Words	Occurrences	Words	Occurrences
anesthesia	77	sugammadex	67	neuromuscular	173	patients	1122
reversal	58	rocuronium	56	sugammadex	98	neuromuscular	875
rocuronium	55	neuromuscular blockade	48	study	97	sugammadex	658
sugammadex	44	neostigmine	31	blockade	84	rocuronium	491
recovery	43	neuromuscular block	27	rocuronium	75	time	455
management	41	anesthesia	24	trial	70	study	383
neostigmine	35	anaphylaxis	21	patients	61	surgery	382
risk	33	neuromuscular	20	reversal	61	blockade	363
surgery	32	neuromuscular blocking agents	19	block	53	recovery	355
vecuronium	30	neuromuscular monitoring	16	controlled	53	anesthesia	332
general-anesthesia	29	anaesthesia	12	surgery	52	min	330
blockade	27	monitoring	12	postoperative	50	neostigmine	330
blocking-agents	27	complications	9	randomized	50	tof	326
propofol	26	hypersensitivity	9	anesthesia	43	results	323
neuromuscular blockade	24	reversal	9	neostigmine	43	reversal	321
multicenter	20	airway management	8	versus	39	postoperative	318
atracurium	19	neuromuscular blocking	8	effect	36	nmb	279
pharmacokinetics	19	blocking agents	7	randomised	36	block	274
neuromuscular block	17	electromyography	7	induced	35	compared	259
sevoflurane	16	intubation	7	recovery	34	dose	259

CONCLUSION AND PROGNOSIS

신경근 관련 연구의 productivity와 trends를 알아보기 위하여 bibliometric 분석법을 사용하였다. 신경근 관련 연구는 미국이 가장 높은 생산력을 보이고 우수한 저자와 출판물이 많은 편이지만, 국내 저자들의 생산성도 매우 높은 편에 속한다. 전체 생산성과에 비하여 낮은 국제화지수는 국내연구의 단점으로 지적할 수 있다. Multi-center/country co-work이 지속적으로 요구된다. 신경근 관련 연구는 상대적으로 전체 생산량에 기여하는 저자들의 숫자가 적은 편이며, 연구의 범위도 좁은 편이다. 연구의 경향과 흐름을 분석하는 다양한 방법을 도입함으로써 연구분야의 다양화를 시도할 필요가 있을 것으로 분석된다.

Bibliometric 분석법의 제한점으로 지적되고 있는 것은 bibliometric analysis에는 비공식(informal) 출판물 및 커뮤니케이션이 포함되지 않기 때문에, 과학적 발전을 온전히 담을 수 없어 이를 제대로 예측하기 어렵다는 한계가 있다. 또한, 분석 연구에 사용되는 참고 문헌이 항상 표준화된 것은 아니므로, 이로 인해 인용 빈도에 따라 저자의 순위를 매기는 동안 문제가 발생할 수 있다는 점이다.

Bibliometric 분석법은 주관을 배제한 비교적 객관적으로 문헌에 대한 정량적인 평가와 성과측정을 제공하는 장점이 있으며, 정책의 도입, 신의료기술의 검토, 펀딩 연구 선정 등에 폭넓게 사용되고 있는 방법으로서, 연구자들이 임상연구를 기획하고 준비하는 단계에서 다양하게 활용할 가능성이 있을 것으로 생각된다.

2021년
대한신경근연구학회 춘계학술대회
Online Web Seminar

Session C

Focuses on the Current Issues and Trends: Part II

좌장: 을지의대 양홍석

Perioperative Administration of Drugs and Its Neuromuscular Consequences

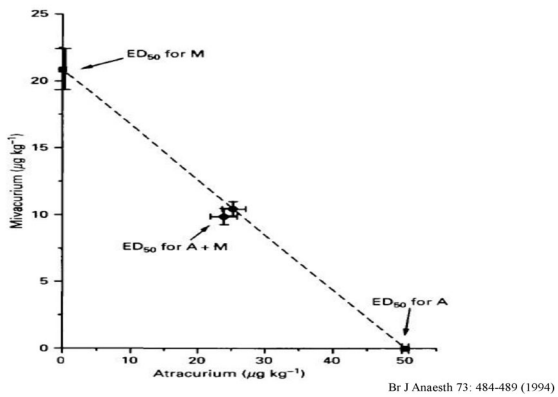
최 재 문

울산의대

Nondepolarizing NMBDs

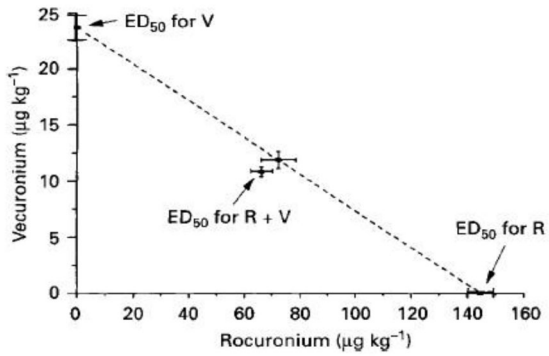
- Aminosteroid
  - Vecuronium
  - Rocuronium
  - Pancuronium
  - Pipecuronium
- Benzylisoquinolinium
  - Mivacurium
  - Atracurium
  - Cisatracurium
  - Doxacurium

Atracurium and Mivacurium



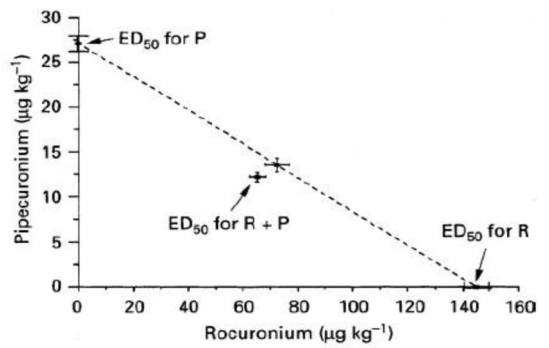
Br J Anaesth 73: 484-489 (1994)

Vecuronium and Rocuronium



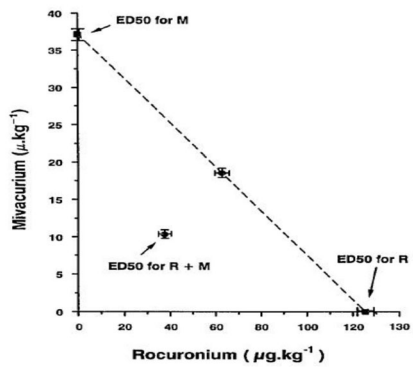
Br J Anaesth 75: 37-42 (1995)

Pipecuronium and Rocuronium



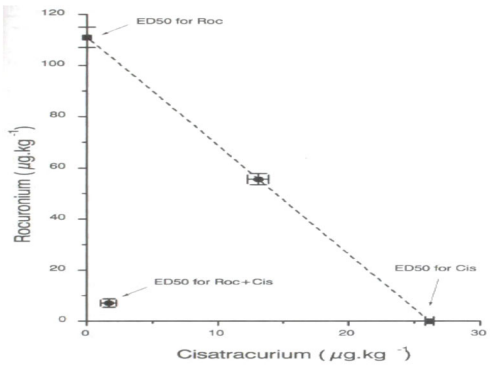
Br J Anaesth 75: 37-42 (1995)

Mivacurium and Rocuronium



Anesthesiology 81: 388-395 (1994)

Cisatracurium and Rocuronium



Anesthesiology 89: 1116-1124 (1998)

Potentiation

- Priming
- Volatile anesthetics
- Antibiotics
- Hypothermia
- Lithium
- Magnesium sulfate
- Ephedrine
- Nicardipine
- Dexmedetomidine

Priming – Rocuronium

Group	Priming dose (mg kg^{-1})	Priming interval (min)	Intubating dose (mg kg^{-1})	Onset time (s)	Clinical duration of action (min)
1	0.06	2	0.54	79.5 ± 22.4	37.9 ± 10.1
2	0.10	2	0.50	70.3 ± 21.1	39.1 ± 9.8
3	0.06	3	0.54	63.2 ± 18.6†	38.7 ± 9.4
4	0.10	3	0.50	48.4 ± 12.8†	45.2 ± 9.7‡
5	0	0	0.60	87.9 ± 17.8*	36.3 ± 8.0

Eur J Anaesthesiol 19: 517-521 (2002)

Priming – Rocuronium

	Bolus group	*Priming group*
Laryngeal adductor muscles		
Lag time (sec)	28.6 ± 11.2	24.6 ± 9.2
Onset 90% (sec)	67.9 ± 24.4#	41.1 ± 7.1*#
Onset (sec)	74.0 ± 23.8#	44.7 ± 7.4*#
Peak effect %	93 ± 11	94 ± 9
Adductor pollicis muscles		
Lag time (sec)	24.6 ± 12.7	23.9 ± 10.4
Onset 90% (sec)	115.8 ± 40	88.5 ± 21.1*
Onset (sec)	139.2 ± 51.5	105.4 ± 29.9*
Peak effect %	94 ± 9	95 ± 9

Can J Anesth 52: 50-54 (2005)

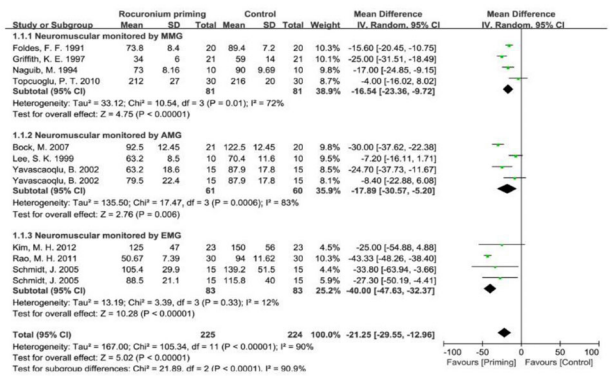
Priming – Rocuronium

	Control (n = 23)	Prime (n = 23)	Magnesium (n = 23)	Magnesium and prime (n = 23)
Onset; s	150 (56)*	125 (47)*	94 (25)**	56 (16)
Duration; min	33 (12)	39 (18)	42 (12)	43 (10)

*p < 0.001 vs. magnesium and prime group; **p < 0.01 vs. magnesium and prime group.

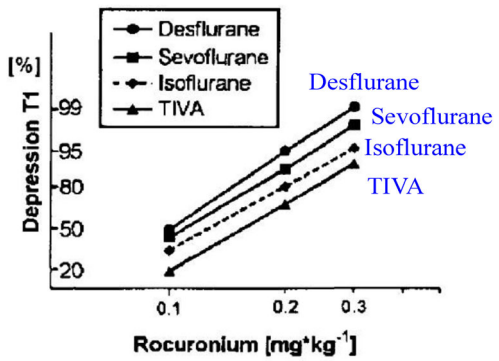
Anaesthesia 67: 748-754 (2012)

Priming – Rocuronium Onset Time



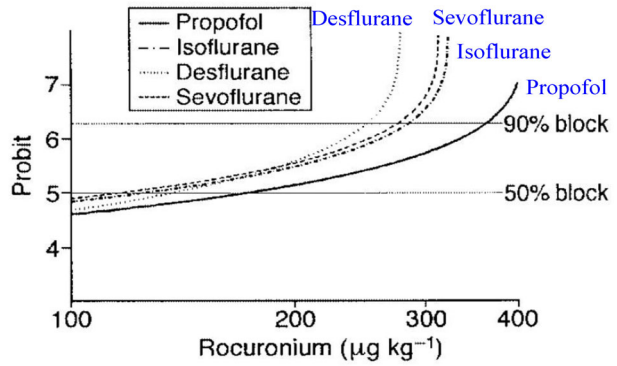
PLOS ONE 9: e114231 (2014)

Volatile Anesthetics



Can J Anaesth 45: 526-532 (1998)

Dose-Response Curves for Rocuronium



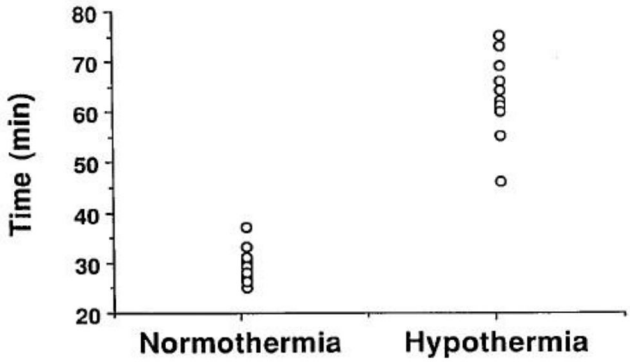
Br J Anaesth 84: 43-47 (2000)

Antibiotics

Neuromuscular blocking agent	Neuromuscular blocking agent alone	Neuromuscular blocking agent preceded by		
		Neomycin (200 µg/ml)	Streptomycin (400 µg/ml)	Polymyxin B (25 µg/ml)
		µg/ml		
d-Tc	0.48 ± 0.02 (12)	0.14 ± 0.01 (4)	0.15 ± 0.01 (9)	0.13 ± 0.01 (4)
Pancuronium	2.16 ± 0.02 (11)	1.18 ± 0.03 (8)	0.53 ± 0.01 (4)	0.33 ± 0.01 (4)
SCh	7.28 ± 0.06 (12)	2.71 ± 0.13 (4)	1.36 ± 0.03 (4)	0.45 ± 0.04 (6)

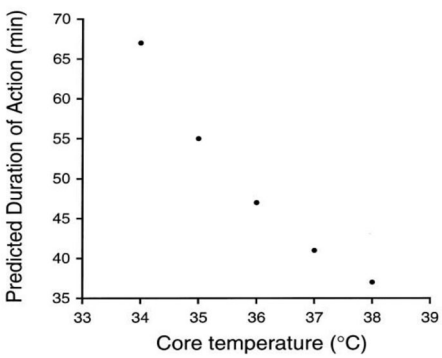
Anesth Analg 58: 107-115 (1979)

Hypothermia – Vecuronium



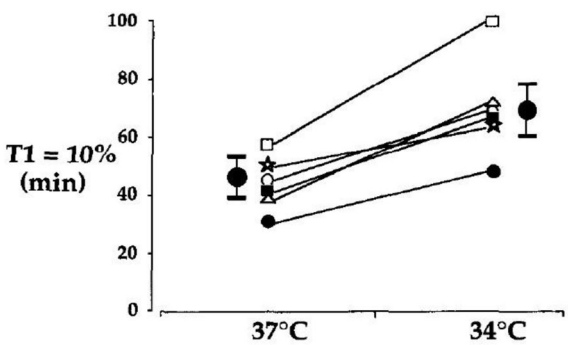
Anesthesiology 74: 815-819 (1991)

Hypothermia – Vecuronium



Anesthesiology 92: 84-93 (2000)

Hypothermia – Atracurium



Anesth Analg 80: 1007-1014 (1995)

Lithium

	Time (Min) Return to 50 Per Cent Control		Time (Min) Return to 100 Per Cent Control	
	Before	After	Before	After
Succinylcholine 0.03 mg/kg	6.3 (4.1–8.5)	10.1 (9–11.2)	8.6 (4.2–14.4)	15 (7.5–26)
0.1 mg/kg	14.1 (11.7–17)	23.9 (20.3–29.5)	19.8 (14.7–26.6)	59.9 (25.1–120)
0.3 mg/kg	16.6 (16–17.2)	31.4 (28.4–34.5)	20.3 (20–21.5)	36.6 (33.2–40)
Pancuronium 0.01 mg/kg	9.9 (8.7–10.2)	20.2 (18.1–22.7)	16.5 (14.2–17.4)	26.7 (22.1–28)
0.02 mg/kg	18.2 (16.1–21.1)	41.7 (38.3–43.8)	26.4 (24.4–28.2)	60.5 (57–62.3)
0.04 mg/kg	39.9 (36.1–42)	68.4 (64–71.5)	58.4 (54.9–61.2)	95.6 (91.2–98.5)

Anesthesiology 46: 122-126 (1977)

Magnesium – Vecuronium

	$MgSO_4$–vecuronium	Vecuronium
n	30	30
r	0.954	0.967
ED_{50} (μg kg^{-1})	21.3* (20.7–22.3)	26.9 (25.8–28.3)
ED_{90} (μg kg^{-1})	34.2* (32.1–36.5)	45.7 (43.3–49.9)
Slope	4.6	4.1
Y-intercept	−6.2	−5.9

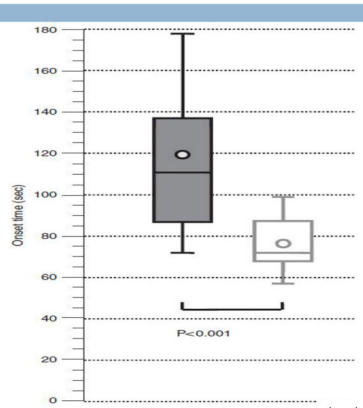
Br J Anaesthesia 74: 405–409 (1995)

Magnesium – Vecuronium

	$MgSO_4$–vecuronium	Vecuronium
Onset (s)	147.3 (22.2)*	297.2 (122)
CD (min)	43.3 (9)*	25.2 (5.1)
RI (min)	20.1 (6.6)*	10.6 (3.4)
D75 (min)	63.4 (9.9)*	35.8 (6.9)

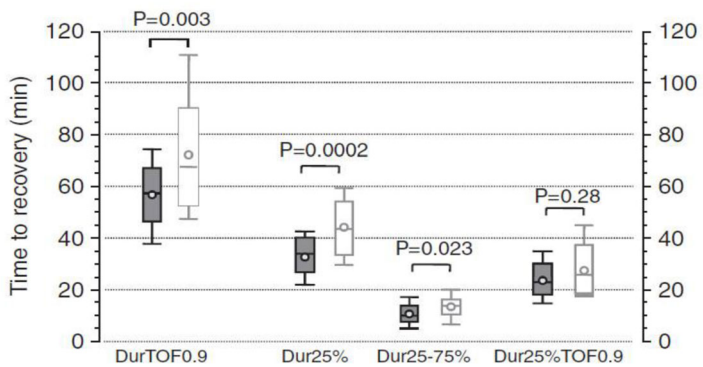
Br J Anaesthesia 74: 405–409 (1995)

Magnesium – Rocuronium



Acta Anaesthesiol Scand 54: 299–306 (2010)

Magnesium – Rocuronium



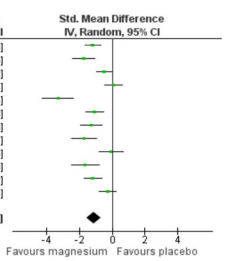
Acta Anaesthesiol Scand 54: 299–306 (2010)

Magnesium – Onset time

Onset time

Study or Subgroup	Magnesium sulphate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Czarnetzki 2010	77	18	37	120	48	38	9.0%	-1.17 [-1.66, -0.68]
Fuch-Buder 1999	147.5	36.32	24	227.5	53.56	24	8.2%	-1.72 [-2.39, -1.05]
Ghodraty 2012	198.7	57.97	59	226	56	29	9.2%	-0.47 [-0.92, -0.02]
Gupta 2006	182	38	25	179	28	25	8.7%	0.09 [-0.47, 0.64]
Khafagy 2007	158	24.14	30	227.4	10.9	15	6.9%	-3.28 [-4.22, -2.34]
Khafagy 2012	70.8	9.6	30	82.6	11.9	30	8.8%	-1.08 [-1.62, -0.53]
Kim 2012	94	25	23	150	56	23	8.3%	-1.27 [-1.91, -0.63]
Kim 2015	111	27	20	184	53	20	7.9%	-1.70 [-2.43, -0.97]
Kussman 1997	105	36	15	107	30	15	8.0%	-0.06 [-0.77, 0.66]
Lampl 1993	137.3	21	15	228.7	74	15	7.4%	-1.63 [-2.48, -0.79]
Pelin 2007	168	36	30	212	38	30	8.7%	-1.17 [-1.72, -0.62]
Usmani 2007	190	17	30	194	12	30	8.9%	-0.27 [-0.78, 0.24]
Total (95% CI)			**338**			**294**	**100.0%**	**-1.09 [-1.53, -0.66]**

Heterogeneity: Tau² = 0.49; Chi² = 68.33, df = 11 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.92 (P < 0.00001)



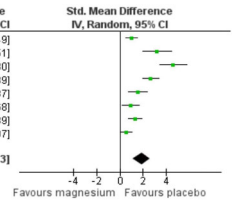
J Clin Anesthesia 34: 524–534 (2016)

Magnesium – Clinical duration

Clinical duration

Study or Subgroup	Magnesium sulphate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Czarnetzki 2010	44.7	14	35	33.2	8.1	37	13.8%	1.00 [0.51, 1.49]
Fuch-Buder 1999	44	7	12	26	3	12	10.3%	3.23 [1.95, 4.51]
Khafagy 2007	45.55	4.27	30	26	3.9	15	10.8%	4.62 [3.45, 5.80]
Khafagy 2012	51.1	4.4	30	34.9	7.2	30	12.9%	2.68 [1.97, 3.39]
Kussman 1997	56.5	13.2	15	35.6	13.2	15	12.4%	1.54 [0.71, 2.37]
Lampl 1993	34.6	9.2	15	26.3	8.3	15	12.7%	0.92 [0.16, 1.68]
Pelin 2007	63.3	12.1	30	48.7	9.5	30	13.5%	1.32 [0.76, 1.89]
Usmani 2007	33	3	30	31	4	30	13.7%	0.56 [0.04, 1.07]
Total (95% CI)			**197**			**184**	**100.0%**	**1.88 [1.13, 2.63]**

Heterogeneity: Tau² = 1.01; Chi² = 63.62, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 4.89 (P < 0.00001)



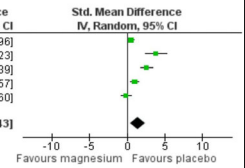
J Clin Anesthesia 34: 524–534 (2016)

Magnesium – Recovery index

Recovery index

Study or Subgroup	Magnesium sulphate Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Czarnetzki 2010	14	6	35	11.2	5.2	37	22.0%	0.49 [0.02, 0.96]
Fuch-Buder 1999	25	5	12	10	2	12	15.8%	3.80 [2.38, 5.23]
Khafagy 2007	22.75	3.34	30	15.3	1.4	15	19.9%	2.56 [1.73, 3.39]
Khafagy 2012	16.8	4.2	30	13	3	30	21.6%	1.03 [0.49, 1.57]
Lampl 1993	14.9	4.9	15	15.4	3.5	15	20.7%	-0.11 [-0.83, 0.60]
Total (95% CI)			**122**			**109**	**100.0%**	**1.42 [0.41, 2.43]**

Heterogeneity: Tau² = 1.15; Chi² = 42.05, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.76 (P = 0.006)

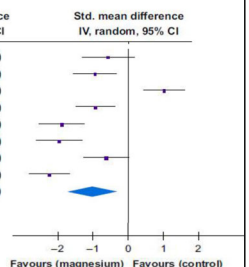


J Clin Anesthesia 34: 524–534 (2016)

Magnesium – Vecuronium

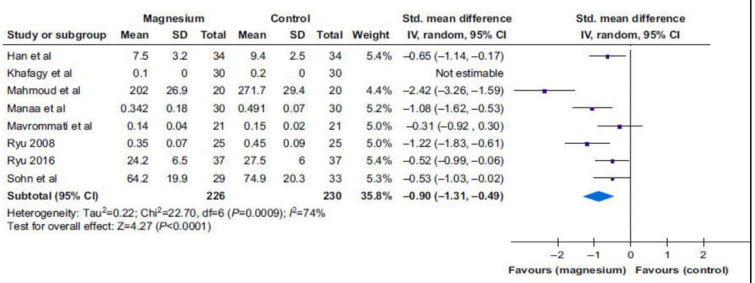
Study or subgroup	Magnesium Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Aravindan et al	1.12	0.28	15	1.3	0.33	15	4.7%	−0.57 (−1.30, 0.16)
Bhatia et al	6.52	1.1	25	7.74	1.43	25	5.1%	−0.94 (−1.53, −0.35)
Choi et al	0.18	0.03	27	0.15	0.03	27	5.2%	0.99 (0.42, 1.55)
Elshamouby et al	131.9	7.3	30	139.6	9	30	5.2%	−0.93 (−1.46, −0.39)
Ko et al	0.08	0.01	29	0.11	0.02	29	5.0%	−1.87 (−2.50, −1.25)
Reena et al	1.26	0.48	29	2.3	0.57	30	5.0%	−1.94 (−2.57, −1.32)
Tramer et al	0.13	0.02	21	0.15	0.04	21	5.0%	−0.62 (−1.24, 0.00)
Walia et al	5.4	0.78	40	7.88	1.36	40	5.2%	−2.22 (−2.78, −1.65)
Subtotal (95% CI)			**216**			**217**	**40.4%**	**−1.01 (−1.75, −0.28)**

Heterogeneity: Tau²=1.03; Chi²=84.10, df=7 (P<0.00001); I²=92%
Test for overall effect: Z=2.69 (P=0.007)



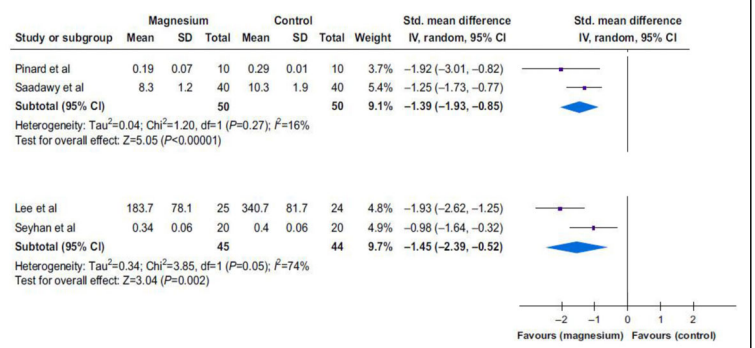
Br J Anaesthesia 126: 608–621 (2021)

Magnesium – Rocuronium



Br J Anaesthesia 126: 608–621 (2021)

Magnesium – Cisatracurium – Atracurium



Br J Anaesthesia 126: 608–621 (2021)

Ephedrine – Rocuronium

	Group I (n = 30)	Group II (n = 30)
Age (yr)	39 ± 6	36 ± 8
Weight (kg)	62 ± 10	63 ± 10
Height (cm)	161 ± 9	163 ± 8
Sex (Female/Male)	23/7	21/9
ASA (I/II)	28/2	27/3
Onset time of rocuronium (s)	72 ± 19	98 ± 31

Anesth Analg 85: 437–440 (1997)

Ephedrine and Esmolol

	Placebo	Ephedrine	Esmolol
Age (yr)	39 ± 9	37 ± 8	38 ± 7
Sex (male/female)	9/11	11/9	11/9
Weight (kg)	74 ± 15	82 ± 13	75 ± 16
Height (cm)	164 ± 12	168 ± 12	168 ± 10
Rocuronium onset time (s)	93 ± 6	64 ± 6.7*	118 ± 11*

Anesth Analg 90: 1217–1219 (2000)

Ephedrine and Esmolol

	Ephedrine (n = 11)	Esmolol (n = 11)	Placebo (n = 11)
Age (years)	34.6 ± 9.8	37.8 ± 13.5	34.9 ± 10.3
Gender			
Female	5 (45%)	6 (55%)	5 (45%)
Male	6 (55%)	5 (45%)	6 (55%)
Weight (kg)	82.3 ± 12.3	81.5 ± 18.7	71.5 ± 8.5
Onset time of rocuronium(s)	52 ± 17*	114 ± 11*	87 ± 7

Acta Anaesthesiol Scandinavica 47: 1067–1072 (2003)

Cardiac Output

Time	Ephedrine	Esmolol	Placebo
Baseline	6.9 ± 1.3	8.1 ± 2.5	8.2 ± 2.3
3	9.1 ± 1.5*	5.5 ± 1.2*	8 ± 2.3
6	8.9 ± 1.4*	5.7 ± 0.8*	8.4 ± 2.3
9	8.9 ± 1.4*	6.5 ± 0.9	8.5 ± 2.4
12	8.8 ± 1.4*	6.6 ± 1.1	8.2 ± 2.5
15	8.9 ± 1.5*	7 ± 1.3	8.3 ± 2.4

Acta Anaesthesiol Scandinavica 47: 1067–1072 (2003)

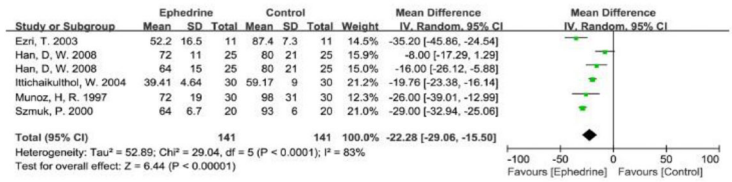
Ephedrine – Vecuronium

Intubation conditions	Placebo	E30	E70	E110
Excellent	8	15	27*	27*
Good	7	10	1	2
Poor	14	5	2	1
Impossible	1	0	0	0

Variable	Placebo	E30	E70	E110
Neuromuscular block (%)	53.8 ± 15.4	59.0 ± 23.2	68.2 ± 21.4*	71.7 ± 23.7*
Onset time (min)	3.5 ± 0.6	3.1 ± 0.5	2.7 ± 0.6*	2.6 ± 0.7*

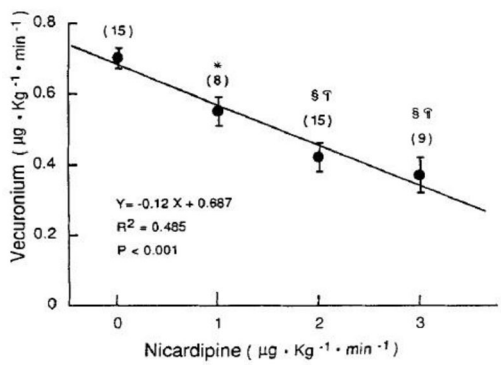
Anesth Analg 96: 1042–1046 (2003)

Ephedrine – Rocuronium Onset Time



PLOS ONE 9: e114231 (2014)

Nicardipine – Vecuronium



Anesth Analg 79: 1159–1164 (1994)

Nicardipine – Rocuronium

	C group ($n = 28$)	N group ($n = 27$)	E group ($n = 27$)
Intubation conditions			
Excellent/good	10/18 (36/64)	23/4 (85/15)	2/22 (7/82)
Acceptable (excellent + good)	28 (100)	27 (100)	24(89)
Poor	0 (0)	0 (0)	3 (11)*,†
Intubation score	8.3 (0.6)	8.9 (0.4)*,‡	7.6 (0.9)*,†
Onset of rocuronium (S)	112.1 (29)	80.6 (19)*,‡	136.7 (29)*,†
BIS			
Before induction	91 (2)	92 (3)	90 (3)
Just after intubation	51 (3)	49 (5)	51 (2)
C&L grade I/II	4/24 (14/86)	5/22 (18/82)	5/22 (18/82)
Additional esmolol	26 (93)‡	22 (82)	17 (63)
Additional nicardipine	3 (11)†,‡	0 (0)	0 (0)

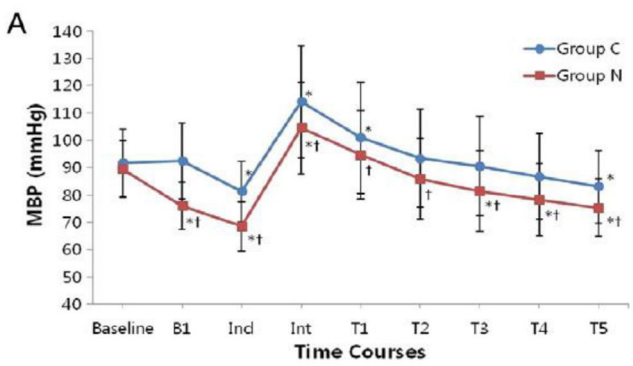
J Anesth 29: 403–408 (2015)

Nicardipine – Rocuronium

	Group C (n = 39)	Group N (n = 39)
Age (y)	42.0 ± 11.1	39.5 ± 9.5
Gender (male/female)	16/23	17/22
Weight (kg)	60.3 ± 8.9	62.3 ± 12.4
Height (cm)	162.6 ± 8.3	163.4 ± 8.6
Grade of intubations *		
Excellent	9 (23.1)	13 (33.3)
Good	20 (51.3)	24 (61.5)
Poor	10 (25.6)	2 (5.1)
Intubating conditions *		
Clinically acceptable	29 (74.4)	37 (94.9)
Clinically unacceptable	10 (25.6)	2 (5.1)
Onset time (s)	204.0 ± 107.2	141.2 ± 59.0 *

J Clinical Anesth 32: 112–118 (2016)

Nicardipine – Rocuronium



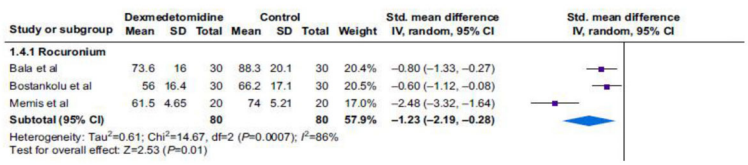
J Clinical Anesth 32: 112–118 (2016)

Dexmedetomidine – Vecuronium

Characteristics	Group D (*n*=40)	Group M (*n*=40)	Group N (*n*=40)
Age (years)	40.70±0.83	38.15±11.25	37.30±14.81
Sex (M:F)	12:28	20:20	17:23
Weight (kg)	69.75±8.48	67.45±9.05	71.25±8.86
ASA (I:II)	29:11	27:13	28:12
Duration of surgery (min)	103.25±29.47	102.50±24.04	103.75±25.78
Vecuronium total dose (mg)	6.64 ± 1.20 **	5.40 ± 0.78**	7.88 ± 1.36

J Anaesthesiol Clin Pharmacol 34: 335–340 (2018)

Dexmedetomidine – Rocuronium



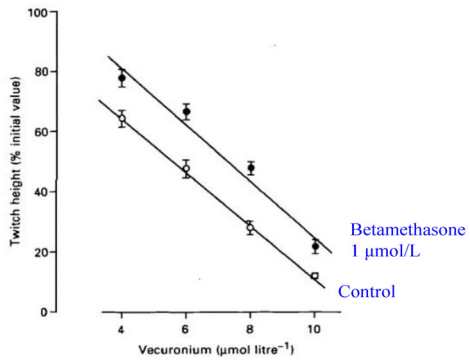
Br J Anaesthesia 126: 608–621 (2021)

Depotentiation

Steroid

Anticonvulsants

Betamethasone – Vecuronium



British Journal of Anaesthesia 67: 447-451 (1991)

Dexamethasone

	ROC	VEC	ATR
Saline			
$LogIC_{50}$	0.786 ± 0.0384	0.246 ± 0.0108§	0.690 ± 0.0356§#
Slope	-4.88 ± 0.698	-2.80 ± 0.396§	-3.98 ± 0.532§#
IC_{50}	6.14 ± 0.604	1.76 ± 0.182	4.90 ± 0.504
Dex			
$LogIC_{50}$	0.920 ± 0.0618¶	0.542 ± 0.0211¶	1.06 ± 0.0409¶
Slope	-5.57 ± 0.569	-2.89 ± 0.405	-3.97 ± 0.373
IC_{50}	8.39 ± 1.14	3.49 ± 0.568	11.5 ± 1.18
IC_{50} ratio	1.27 ± 0.0970	1.93 ± 0.170§	2.38 ± 0.105§#

Genetics and Molecular Research 13: 5892-5900 (2014)

Prednisolone – Atracurium

	Onset time (s), median (range)	Duration TOFR 0.7 (min), mean (SD)	Duration TOFR 0.9 (min), mean (SD)
Group A: chronic inflammatory bowel disease with long-term prednisolone medication (n=27)	280 (180–480)	36.1 (7.9)	40.9 (9.0)
Group B: chronic inflammatory bowel disease; no cortisone medication (n=24)	260 (180–360)	47.9 (7.6)#	53.4 (9.2)#
Group C: control group (n=24)	270 (160–460)	44.5 (9.1)	50.8 (10.5)

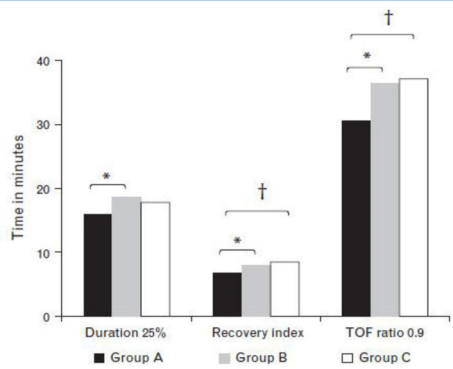
British Journal of Anaesthesia 100: 798–802 (2008)

Prednisolone – Rocuronium

	Duration (min) median (range)	Duration TOF ratio 0.9 (min) median (range)
Group A ($n = 20$)*	12.6 (0–20.7)	25.7 (23.0–34.3)
Group B ($n = 20$)*	16.7 (0–25.3)†	34.7‡ (32.7–44.2)
Group C ($n = 20$)*	16.9 (0–29.3)†	36.5‡ (31.7–42.3)

Acta Anaesthesiol Scand 53: 443–448 (2009)

Dexamethasone – Rocuronium



Eur J Anaesthesiol 31: 417–422 (2014)

Tamoxifen

Correspondence

Antiestrogenic drugs and atracurium – a possible interaction?

To the Editor:
We read with interest the case report of Bizzarri-Schmid and Desai describing a case of prolonged neuromuscular blockade with atracurium.[1] We have had a similar experience which we think is worth reporting.

from a brief period of hypotension following induction, the cardiovascular system remained stable throughout surgery.

It took 86 minutes for the first twitch of the TOF to reappear after the initial dose of atracurium. The expected time for return is 36.9 ± 8.6 minutes.[2] No further doses of atracurium were given. Surgery lasted for 140 minutes and the TOF ratio at this stage was 0.33. The residual neuromuscular block was reversed with neostigmine 2.85 mg and atropine 1.4 mg. Reversal was rapid and after 85 seconds the TOF ratio had reached 0.7. The patient

Can Anaesth Soc J 33: 682 (1986)

Anticonvulsants – Rocuronium

	Control group	Anticonvulsan group
n	27	14
Onset (s)		
Mean (SD)	63 (12)	62 (13)
Median (range)	60 (44–90)	62 (38–85)
T1 25% (min)		
Mean (SD)	38 (15)[a]	25 (6)**[b]
Median (range)	37 (18–88)	25 (16–37)
TOF 0.7 (min)		
Mean (SD)	58 (22)[c]	35 (9)**[b]
Median (range)	57 (30–122)	35 (24–52)
RI (min)		
Mean (SD)	15 (9)[d]	9 (3)[b]
Median (range)	12 (4–46)	9 (4–13)

Br J Anaesthesiol 78: 90-91 (1997)

Carbamazepine – Rocuronium

	Carbamazepine Group (n = 11) (min)	Control Group (n = 11) (min)
Lag time	0.9 ± 0.2 (n.s.)	0.9 ± 0.3
Onset time	2.8 ± 1.2 (n.s.)	2.6 ± 1.0
10% recovery	19.8 ± 6.9*	29.2 ± 13.5
25% recovery	25.7 ± 7.6*	36.1 ± 13.1
50% recovery	30.4 ± 8.2*	43.5 ± 15.6
75% recovery	36.5 ± 10.6*	57.0 ± 23.8
Recovery index (RI)	10.9 ± 4.6*	20.8 ± 12.5

Anesthesiology 90: 109-112 (1999)

Phenytoin – Rocuronium

	Phenytoin (minutes)	Control (minutes)	Significance
Lag time	0.6 ± 0.2	0.6 ± 0.1	n.s.
Onset time	2.3 ± 0.9	1.9 ± 0.5	n.s.
10% recovery	20.5 ± 5.8	27.2 ± 5.5	P < .001
25% recovery	23.8 ± 5.5	31.1 ± 5.6	P < .001
75% recovery	30.6 ± 6.7	39.3 ± 6.2	P < .001
90% recovery	32.5 ± 7.3	41.2 ± 6.1	P < .001
Recovery index (RI)	6.7 ± 2.3	8.3 ± 1.7	P < .05

J Neurosurg Anesthesiol 13: 79-82 (2001)

Other Drugs

- Lidocaine
- Phenylephrine
- Midazolam
- Dantrolene
- Sugammadex

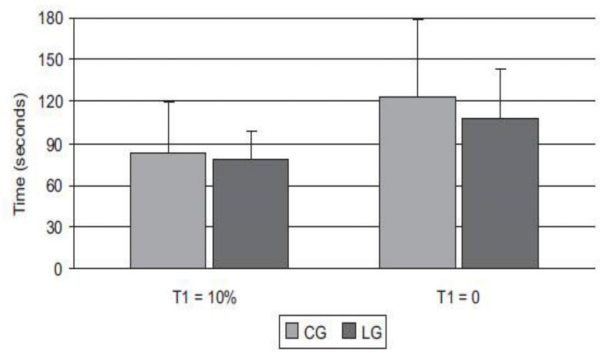
Lidocaine – Rocuronium

Intubation scores.

Group	Excellent	Good	Poor	Impossible
Su (n = 25)	23 (92%)	2 (8%)	0	0
R60* (n = 25)	12 (48%)	12 (48%)	1 (4%)	0
RL60 (n = 25)	20 (80%)	5 (20%)	0	0

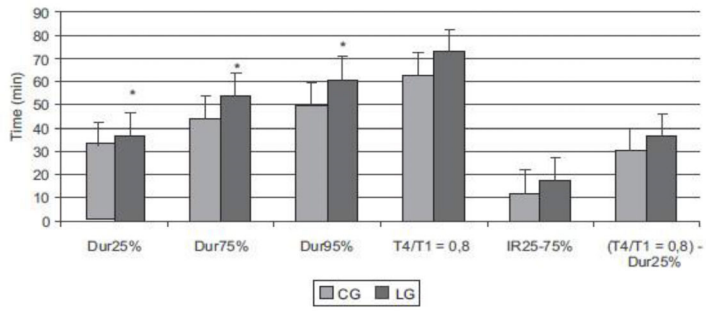
Acta Anaesthesiol Scand 47: 583–587 (2003)

Lidocaine – Rocuronium



Revista Brasileira de Anestesiologia 55: 371-380 (2005)

Lidocaine – Rocuronium



Revista Brasileira de Anestesiologia 55: 371-380 (2005)

Lidocaine – Rocuronium

	Placebo	Lidocaine	*P*
Onset			
Onset time (s)	*n* = 26 119.5 (44.9)	*n* = 26 113.9 (35.3)	0.618
Recovery			
DurTOF0.9 (min)	*n* = 25 54.3 (16.9)	*n* = 26 58.2 (15.1)	0.394
Dur25% (min)	*n* = 25 30.6 (8.01)	*n* = 26 33.3 (7.2)	0.210
Dur25–75% (min)	*n* = 24 10.6 (4.12)	*n* = 26 11.6 (5.01)	0.458
Dur25%TOF0.9 (min)	*n* = 25 23.2 (9.2)	*n* = 26 24.8 (9.3)	0.541

Acta Anaesthesiol Scand 56: 474–481 (2012)

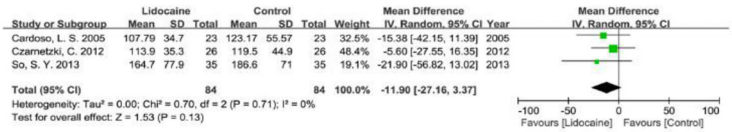
Lidocaine – Rocuronium

	Group C (n = 35)	Group L (n = 35)
Onset time of rocuronium (s)	186.6 ± 71.0	164.7 ± 77.9

	Intubating conditions			
	Excellent	Good	Poor	Inadequate
Group C (n = 35)	27 (77.1%)	7 (20.0 %)	1 (2.9%)	0 (0%)
Group L (n = 35)	29 (82.9%)	6 (17.1%)	0 (0%)	0 (0%)

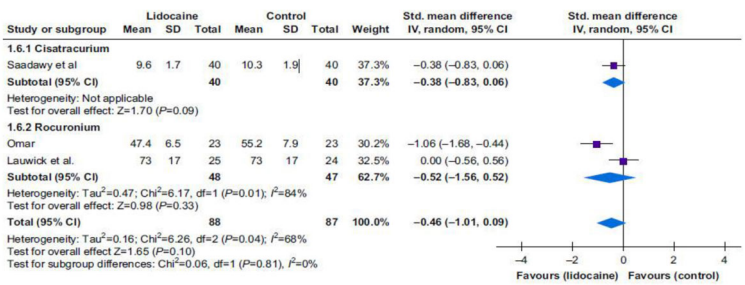
Korean J Anesthesiol 64: 29–33 (2013)

Lidocaine – Rocuronium Onset Time



PLOS ONE 9: e114231 (2014)

Lidocaine – Consumption



Br J Anaesthesia 126: 608–621 (2021)

Phenylephrine – Rocuronium

	S group (n = 34)	P group (n = 30)
Onset (sec)	72 ± 14	84 ± 18*
Duration (min)	43 ± 9	41 ± 3

Korean J Anesthesiol 59: 244–248 (2010)

Midazolam – Rocuronium

	Onset of action (s)	T_1 25% (min)	T_1 75% (min)	Recovery index (min)	TOF 25% (min)	TOF 50% (min)
Control (n = 11)	98.2 ± 35.7	36.2 ± 7.1	50.7 ± 9.0	14.5 ± 3.1	46.7 ± 9.8	58.3 ± 12.3
Midazolam (n = 11)	103.6 ± 37.6	36.5 ± 10.7	51.0 ± 16.6	14.5 ± 6.3	45.4 ± 11.5	54.5 ± 15.2

J International Med Res 30: 318–321 (2002)

Dantrolene – Vecuronium

Case Reports › Masui. 1993 Oct;42(10):1508-10.

[Neuromuscular effects of vecuronium in patients receiving long-term administration of dantrolene]

Abstract

We report two patients who received anesthesia using vecuronium (VCB) subsequent to long-term treatment with orally administered dantrolene. The present data suggest that these doses used of dantrolene do not prolong the duration of neuromuscular blockade induced by VCB. An 8 year old boy was given general anesthesia after medication with 20 mg.day-1 of dantrolene orally for two years. Anesthesia was induced with thiamylal and maintained with nitrous oxide in oxygen and halothane. The neuromuscular blocking effect of vecuronium was evaluated using mechanomyogram (Myograph 2000, Biometer). The potency of VCB was in the normal range and the duration and recovery time were not prolonged. A 49 year old male had been treated with 50 mg.day-1 of orally administered dantrolene for several years prior to the operation. Anesthesia was induced with thiamylal and maintained with nitrous oxide in oxygen and isoflurane. The neuromuscular blocking effect of VCB was monitored by the same method as described above. Again, there was no apparent prolongation of neuromuscular blocking action of VCB. Evidently, VCB may be used in the clinic under standard conditions of neuromuscular monitoring in patients under previous long-term treatment with dantrolene.

Masui 42: 1508-1510 (1993)

Dantrolene – Rocuronium

The effect of long-term oral dantrolene on the neuromuscular action of rocuronium

-a case report-

Jinwoo Jeon, Sejin Song, Mun-Cheol Kim, Kye-Min Kim, and Sangseok Lee

Department of Anesthesiology and Pain Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Oral dantrolene causes a dose-dependent depression of skeletal muscle contractility. A 52-year-old man treated with oral dantrolene for spasticity after spinal cord injury was scheduled to undergo irrigation and drainage of a thigh abscess under general anesthesia. He had taken 50 mg oral dantrolene per day for 3 years. Under standard neuromuscular monitoring, anesthesia was performed with propofol, rocuronium, and sevoflurane. A bolus dose of ED_{95} (0.3 mg/kg) of rocuronium could not depress T1 up to 95%. An additional dose of rocuronium depressed T1 completely and decreased the train-of-four (TOF) count to zero. There was no apparent prolongation of the neuromuscular blocking action of rocuronium. The TOF ratio was recovered to more than 0.9 within 40 minutes after the last dose of rocuronium. A small dose of oral dantrolene does not prolong the duration of action and recovery of rocuronium. (Korean J Anesthesiol 2014; 66: 153-156)

Kor J Anesthesiol 66: 153-156 (2014)

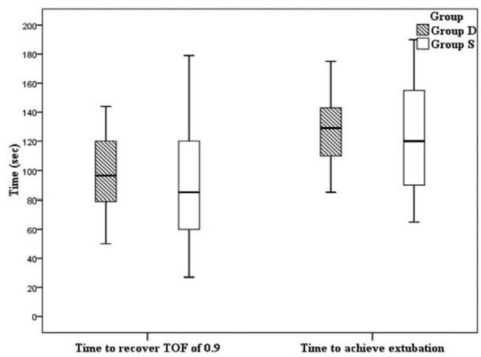
Sugammadex – Dexamethasone

Table 3. TIme to Recovery

	Time to recovery (s)	*P* value[c]
Control	154 ± 54	
Dexamethasone after induction	134 ± 55	0.6266
Dexamethasone before reversal	131 ± 68	0.5368

Anesth Analg 122: 1826-1830 (2016)

Sugammadex – Dexamethasone



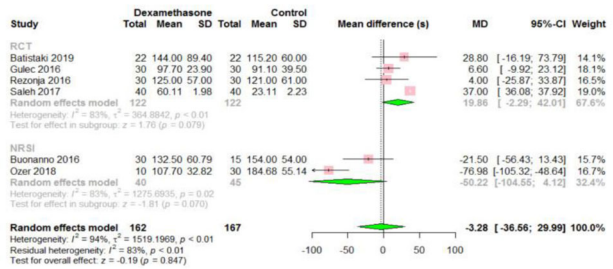
Anesth Analg 122: 1147-1152 (2016)

Sugammadex – Dexamethasone

Patient baseline characteristic[a]	Control group (*n* = 31)	Dexamethasone group (*n* = 31)	*P*
Age [years (interquartile range)]	62 (52–68)	63 (52–71)	0.826
Gender: male [n (%)]	16 (51.6)	16 (51.6)	1.000
Body weight [kg (interquartile range)]	75 (70–88)	74 (63–85)	0.301
American Society of Anesthesiologists physical status (interquartile range)	2 (2–3)	2 (2–3)	0.836
Surgery duration (intubation-extubation time) [h (±standard deviation)]	2.42 (±0.83)	2.35 (±0.54)	0.790
Rocuronium dose per hour [mg/h (±standard deviation)]	41.83 (±12.21)	42.01 (±16.79)	0.525
Sugammadex dose [mg/kg (±standard deviation)]	2.62 (±0.48)	2.81 (±0.58)	0.291
Depth of NMB[b] before sugammadex administration [TOF[c] (interquartile range)]	0 (0–2)	0 (0–1)	0.070

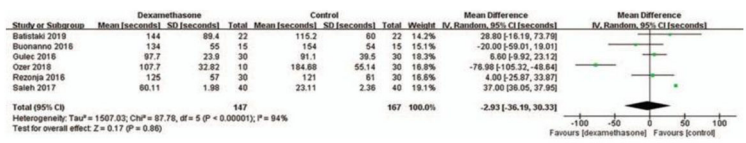
BMC Anesthesiol 16: 101 (2016)

Sugammadex – Dexamethasone



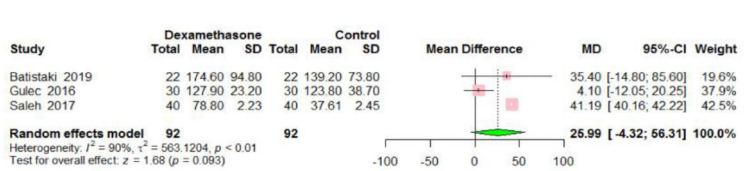
J Clin Medicine 9: 1240 (2020)

Sugammadex – Dexamethasone



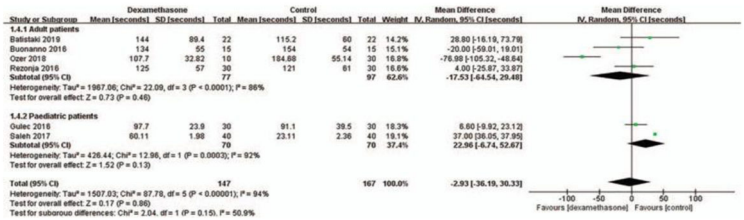
Medicine 100: e23992 (2021)

Sugammadex – Dexamethasone



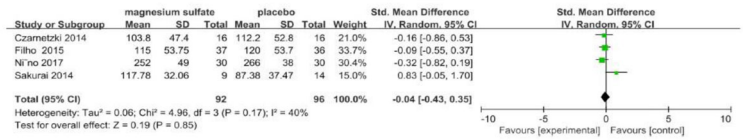
J Clin Medicine 9: 1240 (2020)

Sugammadex – Dexamethasone



Medicine 100: e23992 (2021)

Sugammadex – Magnesium



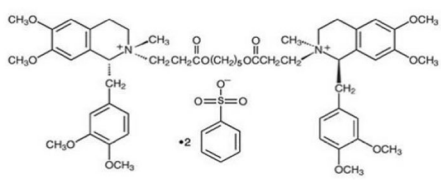
J Clin Anesthesia 60: 78-79 (2020)

Farewell to Nimbex: What is the Alternatives?

김 규 남

한양의대

Cisatracurium: Nimbex



- One of the three cis-cis isomers comprising the ten isomers of the atracurium.
- Combining the name “atracurium” with “cis”
- For the desirable properties without the histamine release.

Stenlake JB et al. Eur J Med Chem 1984

Cisatracurium: Nimbex

- D A Hill and G L Turner first synthesized cisatracurium in 1989.
- Clinical development of cisatracurium was completed in a short period from 1992 to 1994.
- Approval for human use by the FDA in 1995.

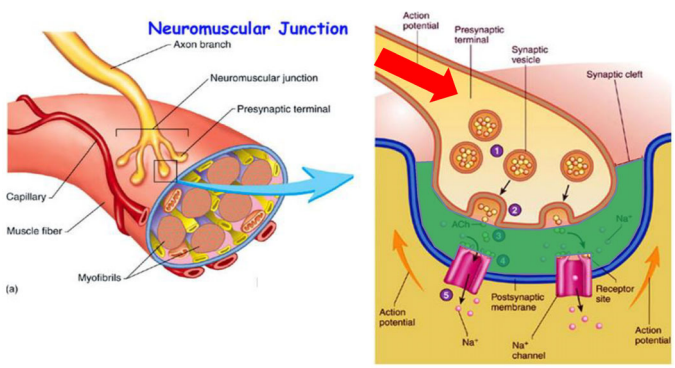
- Nimbex : excellent Neuromuscular blocker + “i”

Stenlake JB et al. Eur J Med Chem 1984

Mechanism of Action

- Cisatracurium binds competitively to nicotinic acetylcholine (cholinergic) receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in blockade of neuromuscular transmission.
- Because it is not degraded in the neuromuscular junction, the depolarized membrane remains depolarized and causing muscle paralysis.
- Antagonized by acetylcholinesterase inhibitors such as neostigmine.

Mechanism of Action



Cisatracurium: Nimbex

- Pharmacodynamic dose response of NIMBEX during opioid/N_2O/O_2 Anesthesia in adult

NIMBEX Dose	Time to 90% block in minutes	Time to maximum block in minutes	25% recovery in minutes	95% recovery in minutes
0.1 mg/kg (2 x ED_{95})	3.3 (1.0-8.7)	5.0 (1.2-17.2)	42 (22-93)	64 (25-93)
0.2 mg/kg (4 x ED_{95})	2.4 (1.5-4.5)	2.9 (1.9-5.2)	65 (43-103)	81 (83-114)
0.25 mg/kg (5 x ED_{95})	1.6 (0.8-3.3)	2.0 (1.2-3.7)	78 (66-86)	91 (76-109)
0.4 mg/kg (8 x ED_{95})	1.5 (1.3-1.8)	1.9 (1.4-2.3)	91 (59-107)	121 (110-134)

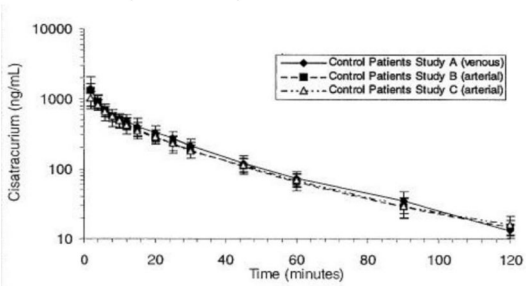
Cisatracurium: Nimbex

- NIMBEX profiles for onset and duration

	Time to Onset[a] (sec)	Time to 90% Block (min)	Time to Maximum Block (min)	Clinical Duration[b] (min)
ADULTS 0.15 mg/kg[c,d] 0.20 mg/kg[c]	120[d,e] 90[d,e]	2.6 (range: 1.0-4.4) 2.4 (range: 1.5-4.5)	3.5 (range: 1.6-6.8) 2.9 (range: 1.9-5.2)	55 (range: 44-74) 65 (range: 43-103)
PEDIATRIC PATIENTS (2-12 yrs) 0.10 mg/kg[c] 0.15 mg/kg[f]		 1.7 (range: 1.3-2.7) 2.1 (range: 1.3-2.8)	 2.8 (range: 1.8-6.7) 3.0 (range: 1.5-8.0)	 28 (range: 21-38) 36 (range: 29-46)
INFANTS[g] (1-23 mos) 0.15 mg/kg[f]		1.5 (range: 0.7-3.2)	2.0 (range: 1.3-4.3)	43 (range: 34-58)

Cisatracurium: Nimbex

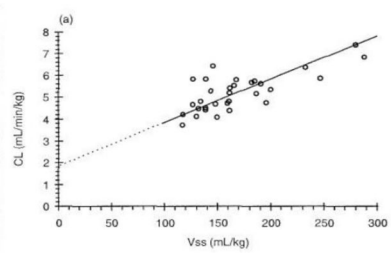
- Plasma concentration-time data following IV bolus administration
  : two-compartment open model



Kisor DF et al. Anesth Analg 1996

Cisatracurium: Nimbex

- Metabolized by Hofmann elimination
  : laudanosine and a monoquaternary acrylate metabolite
- Hofmann elimination accounts for 77% of the total clearance.
- 16% of total : Renal elimination



Kisor DF et al. Anesth Analg 1996

Cisatracurium: Nimbex

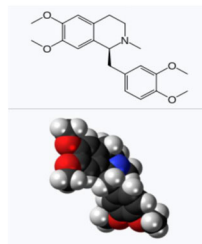
- Hofmann elimination dependent on temperature and pH
  (ex, cardiopulmonary bypass and therapeutic hypothermia)
  : need a lower dose of cisatraurium

→ There is little risk to the use of cisatracurium in patients with liver or renal disease.

Kisor DF et al. Anesth Analg 1996
Cammu G BJA 2000

Cisatracurium: Nimbex

- Laudanosine
  : CNS stimulating properties
  : Crosses the blood-brain barrier
  → cause excitement and seizure



- Cisatracurium is four-five times as potent as atracurium.
  → less laudanosine is produced.
  → the clinical relevance of this effects is negligible.

Fordale V et al. EJA 2002

Classification of Nondepolarizing NMBs

	Clinical duration		
	Long-acting (>50min)	Intermediate-acting (20-50min)	Short-acting (10-20min)
Steroidal compounds	Pancurinium	Vecuronium Rocuronium	
Benzylisoquinolinium compounds	d-Tubocurarine	Atracurium Cisatracurium	Mivacurium

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Clinical Research

Current use of neuromuscular blocking agents and antagonists in Korea: a 2018 survey

Jin Sun Kim[1], Jung Woo Han[1], Jae Ho Lee[1], Jae Moon Choi[2], Ha Jung Kim[2], Tae-Yun Sung[3], Yong Beom Kim[4], Yong Seop Shin[5], and Hong Seuk Yang[6]

Question	Result
Position	
Resident trainees	38 (21.8)
Board-certified anesthesiologists	136 (78.2)
Affiliation	
University hospital	135 (77.6)
Nonteaching hospital	39 (22.4)

Current use of NMBA in Korea

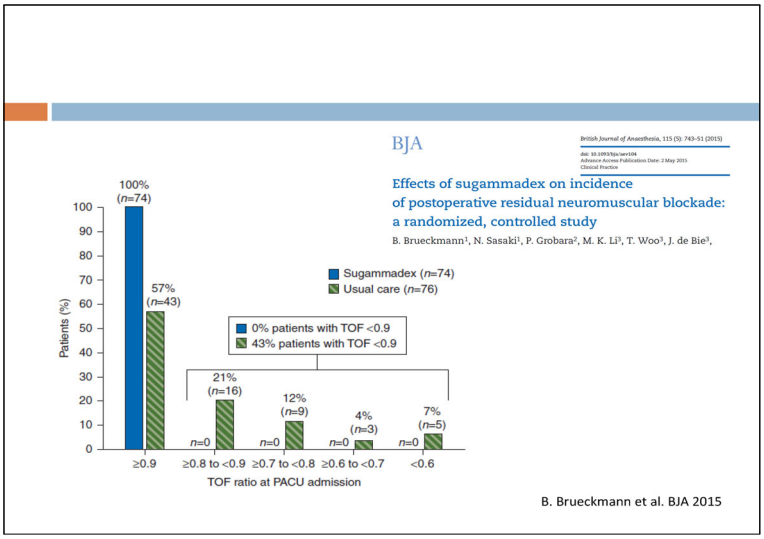
- Usage Status of Neuromuscular Blocking Agents

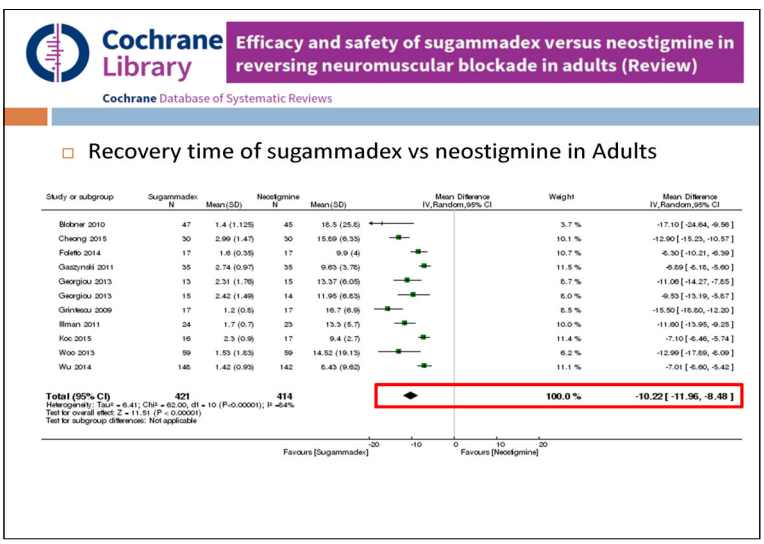
Question	Result
Choose NMBAs that are mainly used for endotracheal intubation (multiple selection is possible)	
Succinylcholine	17 (9.8)
Rocuronium	167 (96.0)
Vecuronium	14 (8.0)
Atracurium	2 (1.1)
Cisatracurium	44 (25.3)
Choose NMBA that is mainly used for maintenance of anesthesia	
Succinylcholine	0 (0)
Rocuronium	145 (83.3)
Vecuronium	15 (8.6)
Atracurium	1 (0.6)
Cisatracurium	13 (7.5)

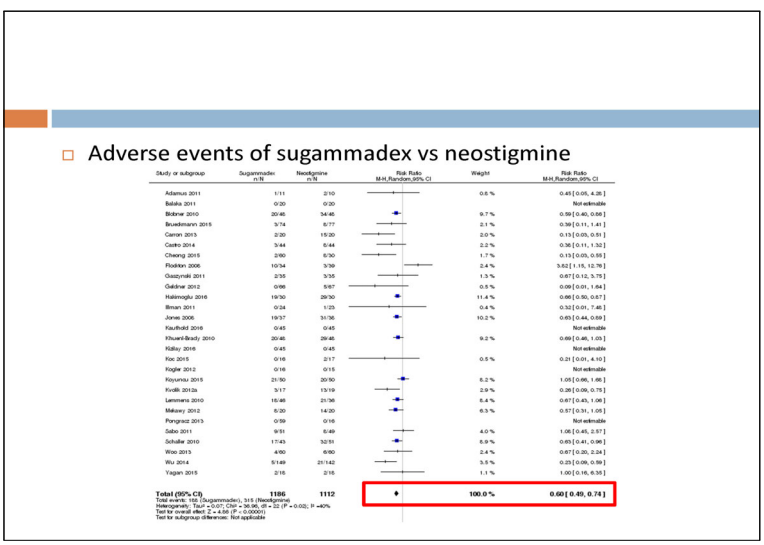
Current use of NMBA in Korea

- Usage Status of Reversal Agents of Neuromuscular Blocking

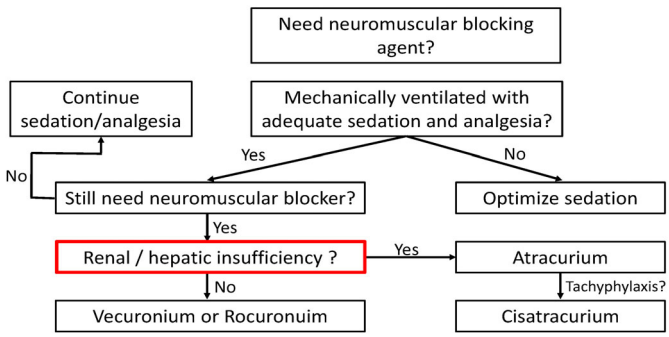
Question	Result
Choosereversal agents of neuromuscular blockade that were prepared in your hospital (multiple selection is possible)	
Neostigmine	79 (45.4)
Pyridostigmine	153 (87.9)
Edrophonium	0 (0)
Sugammadex	155 (89.1)


BJA
British Journal of Anaesthesia, 115 (5): 743–51 (2015)
Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study
B. Brueckmann[1], N. Sasaki[1], P. Grobara[2], M. K. Li[3], T. Woo[3], J. de Bie[3],
100% (n=74)
57% (n=43)
Sugammadex (n=74)
Usual care (n=76)
0% patients with TOF <0.9
43% patients with TOF <0.9
21% (n=16)
12% (n=9)
4% (n=3)
7% (n=5)
n=0
Patients (%)
≥0.9
≥0.8 to <0.9
≥0.7 to <0.8
≥0.6 to <0.7
<0.6
TOF ratio at PACU admission
B. Brueckmann et al. BJA 2015


Cochrane Library
Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults (Review)
Cochrane Database of Systematic Reviews
Recovery time of sugammadex vs neostigmine in Adults
Study or subgroup
Sugammadex N
Mean(SD)
Neostigmine N
Mean(SD)
Mean Difference IV,Random,95% CI
Weight
Mean Difference IV,Random,95% CI
Blobner 2010 47 1.4 (1.125) 45 18.5 (25.6) 3.7 % -17.10 [-24.64, -9.56]
Cheong 2015 30 2.99 (1.47) 30 15.69 (6.33) 10.1 % -12.90 [-15.23, -10.57]
Foletto 2014 17 1.6 (0.35) 17 9.9 (4) 10.7 % -8.30 [-10.21, -6.39]
Gaszynski 2011 35 2.74 (0.97) 35 9.63 (3.76) 11.5 % -6.89 [-8.16, -5.60]
Georgiou 2013 13 2.31 (1.76) 15 13.37 (6.05) 6.7 % -11.06 [-14.27, -7.85]
Georgiou 2013 15 2.42 (1.49) 14 11.95 (6.83) 8.0 % -9.53 [-13.19, -5.87]
Grinteseu 2009 17 1.2 (0.6) 17 16.7 (6.9) 8.5 % -15.50 [-18.60, -12.20]
Ilman 2011 24 1.7 (0.7) 23 13.3 (5.7) 10.0 % -11.60 [-13.95, -9.25]
Koc 2015 16 2.3 (0.9) 17 9.4 (2.7) 11.4 % -7.10 [-8.46, -5.74]
Woo 2013 59 1.53 (1.83) 59 14.52 (19.13) 6.2 % -12.99 [-17.89, -8.09]
Wu 2014 146 1.42 (0.93) 142 8.43 (9.62) 11.1 % -7.01 [-8.60, -5.42]
Total (95% CI) 421 414 100.0 % -10.22 [-11.96, -8.48]
Heterogeneity: Tau² = 6.41; Chi² = 62.00, df = 10 (P<0.00001); I² =84%
Test for overall effect: Z = 11.51 (P < 0.00001)
Test for subgroup differences: Not applicable
-20
-10
0
10
20
Favours [Sugammadex]
Favours [Neostigmine]


Adverse events of sugammadex vs neostigmine
Study or subgroup
Sugammadex n/N
Neostigmine n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Total (95% CI) 1186 1112 100.0 % 0.60 [0.49, 0.74]

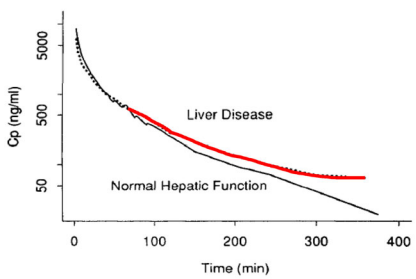
Cisatracurium ?



University of Wisconsin Hospitals Clinical Practice Guideline 2017

Patients with end-stage liver failure

- Plasma concentration (Cp) versus time data



T Magorian et al. A&A 1995

Patients with end-stage liver failure

- Values for the Pharmacokinetic variables

	Typical value	Standard error	Interindividual variability[a]
Cl (mL/min)	217	21.8	0.75–1.34
Cl_{rapid} (mL/min)	645	77.4	Not estimated, see text
Cl_{slow} (mL/min)	121	13.1	Not estimated, see text
V_1 (L)			
Normal liver function	5.96	1.01	0.46–2.16
Liver disease	7.87	1.33	0.46–2.16
V_2 (L)			
Normal liver function	3.57	0.56	0.61–1.64
Liver disease	5.30	0.83	0.61–1.64
V_3 (L)			
Normal liver function	6.88	1.34	0.61–1.64
Liver disease	10.20	1.99	0.61–1.64

Clearance (Cl), Volume of the Central (V1), Second (V2), and Third (V3)

T Magorian et al. A&A 1995

Patients with end-stage liver failure

- Values for the Derived Pharmacokinetic variables

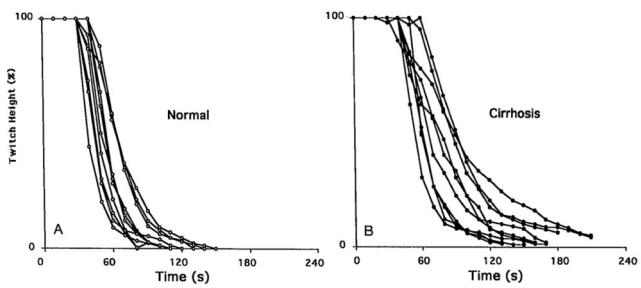
Variable	Typical value
Vss (L)	
Normal liver function	16.4
Liver disease	23.4
$t_{1/2\alpha}$ (min)	
Normal liver function	2.2
Liver disease	3.1
$t_{1/2\alpha}$ (min)	
Normal liver function	17.0
Liver disease	24.2
$t_{1/2\beta}$ (min)	
Normal liver function	76.4
Liver disease	111.5

Volume of distribution at steady state (Vss), elimination half-life (t1/2β)

T Magorian et al. A%A 1995

Patients with end-stage liver failure

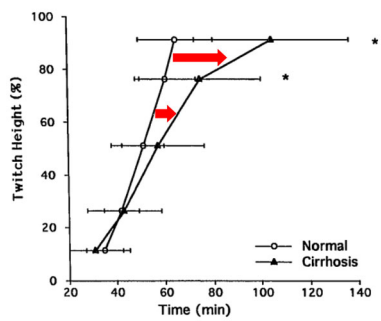
- Onset curves showing twitch height versus time



M Khalil et al. Anesth. 1994

Patients with end-stage liver failure

- Recovery from NMB in twitch height versus time



M Khalil et al. Anesth. 1994

Patients with end-stage liver failure

- Neuromuscular data and post-anesthesia care unit duration of stay

Variable	Group 1 Sugammadex normal liver (N.=14)	Group 2 Neostigmine normal liver (N.=14)	Group 3 Sugammadex liver cirrhosis (N.=13)	Group 4 Neostigmine liver cirrhosis (N.=14)
Duration of intubating dose of rocuronium (min)	36.0 (5.9)	35.9 (4.7)	42.8 (4.5)*	41.5 (5.7)*
Duration of the first top-up dose of rocuronium (min)	15.4 (4.3)	16.4 (4.4)	28.2 (4.9)*	33.8 (15.0)*
Duration of the last top-up dose of rocuronium (min)	34.1 (4.0)‡	40.2 (7.2)‡	47.5 (5.9)*‡	50.0 (8.9)*‡
Total dose of rocuronium (mg)	179.3 (26.8)	172.9 (43.1)	133.0 (33.0)*	125.4 (17.7)*
Time to train of ratio recovery to 0.9 (min)	2.6 (1.0)†	15.7 (3.6)	3.1 (1.0) †	14.5 (3.6)
Time to train of ratio recovery to 1.0 (min)	3.54 (1.1)†	18.6 (4.3)	4.4 (1.3)†	17.1 (3.2)
Duration of stay in PACU (min)	22.8 (2.4)†	43.2 (5.0)	23.0 (2.3)†	43.9 (7.4)

*Significant difference between normal patients and patients with liver cirrhosis (P<0.001); †significant difference between sugammadex and neostigmine (P<0.001); ‡significant difference between the first and last top-up doses of rocuronium (P<0.001).

Mohamed ABDULATIF et al. Minerva Ane 2018

Patients with end-stage renal failure

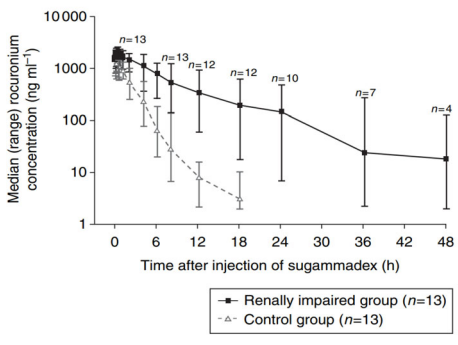
- PK variables for sugammadex and rocuronium

	Renal failure	Control
Sugammadex kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	27 500 (114)	1730 (34.8)*
Range (μg min ml^{-1})	6480–147 000	1060–3330
CL (ml min^{-1})	5.5 (108)	95.2 (22.1)*
Range (ml min^{-1})	1.15–18.1	58.3–138
V_{ss} (litre)	16.0 (35.5)	13.8 (20.5)
Range (litre)	9.3–31.8	10.0–19.7
$t_{1/2,\beta}$ (h)	35.7 (121)	2.3 (44.4)*
Range (h)	10.7–282	1.6–7.5
MRT (h)	48.2 (132)	2.4 (25.5)*
Range (h)	13.2–399	1.8–4.0
Rocuronium kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	1080 (53.8)	296 (37.4)*
Range (μg min ml^{-1})	412–2370	143–538
CL (ml min^{-1})	41.8 (46.9)	167 (30.8)*
Range (ml min^{-1})	23.2–88.8	108–314
V_{ss} (litre)	22.1 (29.9)	19.1 (28.3)
Range (litre)	14.0–41.6	12.2–30.7
$t_{1/2,\beta}$(h)	7.5 (39.9)	3.0 (67.5)*
Range (h)	3.4–13.3	1.2–8.2
MRT (h)	8.8 (52.7)	1.9 (29.2)*
Range (h)	3.7–19.7	1.2–3.3

Staals LM et al. BJA 2010

Patients with end-stage renal failure

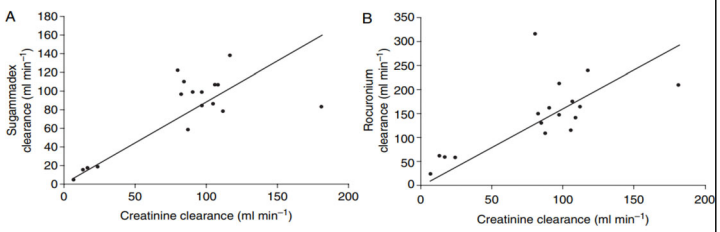
- Rocuronium plasma concentration vs time plots



Staals LM et al. BJA 2010

Patients with end-stage renal failure

- Regression plots of total plasma clearance of sugammadex and rocuronium



Staals LM et al. BJA 2010

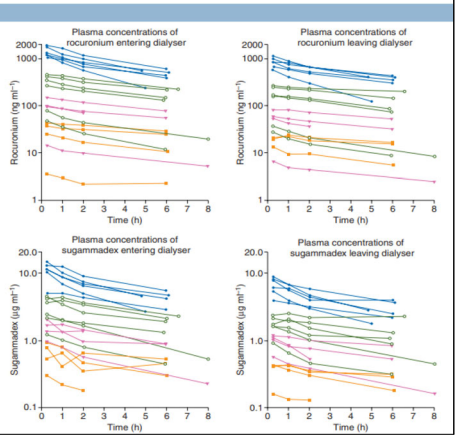
Patients with end-stage renal failure

- Large differences in the PKs of rocuronium and sugammadex were observed in severe to end-stage renal failure.
- Total plasma CL of sugammadex and rocuronium was much lower in renal patients.
- Reversal of the NMB induced by rocuronium 0.6 mg/kg with sugammadex 2.0 mg/kg was rapid and effective in both patient groups.
  - T2 to recovery of the TOF ratio to 0.9
    - Renal patients : 2.0 min (0.72)
    - Healthy control : 0.65 min (0.63)
- No patient showed signs of recurarization.

Staals LM et al. BJA 2010 BJA 2008

Patients with end-stage renal failure

Overlay plots of concentrations in plasma



Patients with end-stage renal failure

- Pharmacokinetic variables for sugammadex and rocuronium

	First dialysis	Second dialysis	Third dialysis	Fourth dialysis
Blood flow rate (ml min^{-1})				
n	5	6	4	4
Median	207	207	207	211
Range	200–210	202–210	204–211	199–218
Sugammadex				
Reduction ratio				
n	5	6	4	4
Mean (SD)	0.69 (0.11)	0.57 (0.15)	0.52 (0.23)	0.53 (0.14)
Range	0.51–0.80	0.32–0.76	0.22–0.78	0.38–0.67
Rocuronium				
Reduction ratio				
n	5	6	4	4
Mean (SD)	0.75 (0.08)	0.63 (0.14)	0.52 (0.05)	0.46 (0.12)
Range	0.65–0.85	0.45–0.80	0.49–0.59	0.38–0.63

G. Cammu et al. BJA 2012

Patients with end-stage renal failure

- The median time of sugammadex to the recovery
  - the T4/T1 ratio to 0.7 : 2.7 min (range 2.0–7.6 min)
  - the T4/T1 ratio to 0.8 : 3.2 min (range 2.7–8.1 min)
  - the T4/T1 ratio to 0.9 : 4.2 min (range 3.4–9.8 min)
- Sugammadex and the sugammadex–rocuronium complex were effectively removed from the body by haemodialysis using a high-flux dialysis method.

G. Cammu et al. BJA 2012

Atracurium

- Non-depolarizing NMBA of the benzylisoquinolinium class
- ED 95 under N_2O/O_2 : 0.23 mg/kg
- Dose for intubation : 0.5-0.6 mg/kg
- Metabolized by Hofmann elimination and nonspecific ester hydrolysis

  : laudanosine and a monoquaternary acrylate metabolite.

  → There is little risk to the use of cisatracurium in patients with liver or renal disease.

G. Cammu et al. BJA 2012

Side Effects of Atracurium

Histamine release

- Cutaneous flushing (face, neck and arms, commonly)
- Cardiovascular effects
  - Decrease in arterial pressure
  - Increase in heart rate
- Respiratory effects
  - Increased airway resistance and bronchospasm

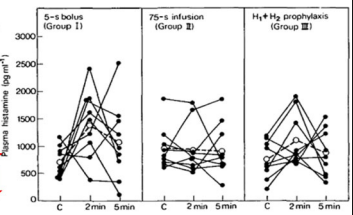
M. Naguib et al. BJA 1995 Ortalli GL et al. Minerva Ane 1993 Siler JN et al. Anesthesiology 1985

Side Effects of Atracurium

- **Prevention of histamine release**
  1. Slower injection rate (75 seconds)
  2. Combination of anti-histamine pretreatment (H_1 + H_2)

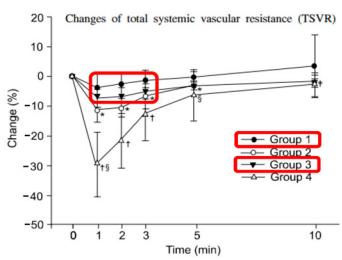
Effect of atracurium 0.6 mg kg^{-1} on plasma histamine concentration
**P<0.05 (one way analysis of variance)*

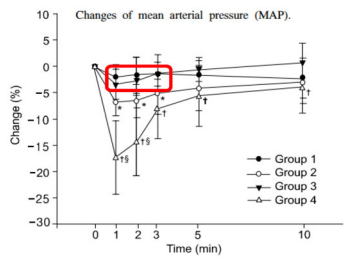
	Plasma histamine (pg ml^{-1})	
	Control	+2 min
Group I 5-s bolus	715.3±93.6	1415.1±203.5*
Group II 75-s slow injection	954.1±131.7	949.9±154.1
Group III H_1 + H_2 prophylaxis	751.1±113.3	1107.0±160.4



R.P.F Scott et al. BJA 1985

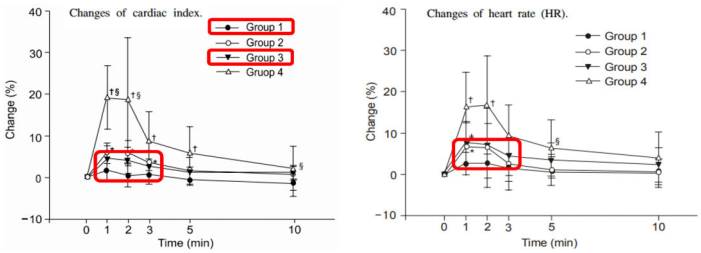
Side Effects of Atracurium





Y. K. Choi et al. KJA 2007

Side Effects of Atracurium



Y. K. Choi et al. KJA 2007

Summary

Atracurium

- Non-depolarizing NMBA of the benzylisoquinolinium class
- Metabolized by Hofmann elimination and nonspecific ester hydrolysis
  : laudanosine and a monoquaternary acrylate metabolite
- There is little risk in patients with liver or renal disease.
- Histamine release
- Prevention of histamine release
  1. Slower injection rate (75 seconds)
  2. Combination of anti-histamine pretreatment (H1 + H2)

Summary

Rocuronium in hepatic impairment

- Rocuronium is eliminated primarily by the liver (>70%) with a small fraction (10-25%) eliminated in the urine.
- The volume of the central compartment and volume of distribution at steady state was increased.
- The prolonged onset of rocuronium was observed.
- The plasma clearance did not alter.
- The longer elimination half-life might result in a longer duration of action.
- Sugammadex rapidly antagonize moderate neuromuscular block and associated with 80% reduction in the time compared to neostigmine.

Summary

Rocuronium in renal impairment

- Plasma clearance of rocuronium was reduced.
- The elimination half-life was longer.
- Volume of distribution remained unchanged or slightly increased.
- Plasma clearance of sugammadex was reduced.
- Reversal of the NMB with sugammadex was rapid and effective.
- There was no signs of recurarization.
- Sugammadex and the sugammadex–rocuronium complex were effectively removed by haemodialysis using a high-flux dialysis method.

2021년
대한신경근연구학회 춘계학술대회
Online Web Seminar

Session D

Beyond Sugammadex:
Still Remained Questions

좌장: 원광대 산본병원 김교상, 순천향의대 이정석

Safety & Efficacy of Sugammadex for Reversal of Neuromuscular Blockade in Pediatric Patients

전진영

가톨릭의대

Several clinical studies have shown that sugammadex is a safe, effective agent for the rapid reversal of aminosteroidal neuromuscular blockade and an alternative to cholinesterase inhibitors used in the reversal of neuromuscular blockade for any depth of muscle relaxation[1]. Since the pharmacokinetic and pharmacodynamic profiles of neuromuscular blockade are affected by different age[2], they may be not the same due to the larger volume of distribution and the presence of immature neuromuscular receptors between pediatric and adult patients[3].

The latest researches and recent studies will be discussed in this presentation.

A meta-analysis by Liu et al.[4] reported that compared to neostigmine or a placebo, sugammadex may reverse rocuronium-induced neuromuscular blockade more rapidly with comparable incidence of adverse events in pediatric patients. This study evaluated the efficacy and safety of sugammadex for reversing neuromuscular blockade in pediatric patients. Randomized clinical trials(RCTs) were included if they compared sugammadex with neostigmine or placebo in pediatric patients undergoing surgery involving the use of rocuronium or vecuronium by searching MEDLINE and other three Databases. Compared with neostigmine or placebo, sugammadex may reverse rocuronium-induced neuromuscular blockade in pediatric patients rapidly and safely.

As mentioned at the beginning, sugammadex has not been approved for use in children in the United States. In Europe, it is only approved for the lower doses for children above 2 years of age. As a result, the literature in pediatrics is limited [5]. One of the original prospective studies looking at sugammadex use in children showed similar efficacy to adults but with very small numbers.

Plaud et al. [6] showed the median time to return of the TOF ratio to 0.9 was 0.6 (n=1), 1.2 (n=4), 1.1 (n=6), and 1.2 (n=5) min in infants, children, adolescents, and adults, respectively. Two pediatric patients showed prolonged return to full recovery of TOF with 4.4 and 5.2 min, and no adverse effects were noted in the study. From 2011 to 2016, there were nine additional studies in children that looked at the time interval from

administration of reversal agents to train-of four ratio T4/T1 of 0.9. Combined the studies looked at a total of 517 patients from 2 to 18 years old. A systematic review of all 10 studies showed that sugammadex was significantly more effective than the control in reducing the time from administration of reversal agents to TOF ratio greater than 0.9 in pediatric patients[4]. Compared with neostigmine, sugammadex was able to reduce the incidence of bradycardia but no significant differences were found for the incidence of other adverse events between the two groups, such as nausea and vomiting, diarrhea, or bronchospasm. Of note, the studies did contain a considerable amount of heterogeneity including lacking a standard definition for bradycardia. One of the first studies to look at patients less than 2 years old, Alonso et al.[7] described a cohort of 23 neonates who received 4 mg/kg of sugammadex. Eight-one days old patients had a median return of TOF 0.9−1.3 min (range: 0.6–3.0 min), and the 15 1−7-day-old patients had a mean return of TOF 0.9−1.2 min (range: 0.4–2.2 min). More recently, Gaver et al.[8] performed a retrospective analysis of 968 patients from birth to 18 years old who received sugammadex and matched neostigmine controls. The cohort included 18 neonates and 137 1-year olds. The sugammadex group had fewer instances of bradycardia ($P<0.001$), and no other adverse events as hypotension, bronchospasm, anaphylaxis or PONV were different between the two groups [8]. The number of minutes between administration of reversal agent to time out of the operating room was significantly shorter in the sugammadex group[8]. Three minutes of operating room time may not be clinically significant but the study suggests that sugammadex is effective in the pediatric population, and there were no safety concerns raised in the cohort. A similar retrospective case series by Franz et al.[9] looked at 331 patients less than 2 years old who received sugammadex versus 1141 patients in the same age cohort during the same timeframe who received neostigmine. The average time in minutes between the end of surgery and out of operating room was similar for neostigmine versus sugammadex [9]. Again, no adverse events were reported, and patients younger than a week old were included in the study. Simonini et al.[10] retrospectively looked at 423 pediatric patients to compare postoperative adverse effects between patients who received sugammadex 2 versus 4mg/kg. The study did not observe any difference with factors like delirium, laryngospasm, bradycardia, or nausea within 30 minutes postextubation. Much like the other studies, it was underpowered to make definitive conclusions, but it also did not identify any specific safety issues in children. Matsui et al.[11] looked at 72 patients between 2 and 24 months old and randomized them to 1, 2, or 4 mg/kg doses of sugammadex, and the time to TOF 0.9 was compared after receiving rocuronium. The 2 and 4 mg/kg groups had similar outcomes but the 1 mg/kg groups took significantly longer with three failed reversals. This study suggests that the effective dose is similar to adults.

Although the literature in pediatrics is improving, most of the available studies in pediatrics are underpowered, retrospective, and measure too many different variables to draw reliable, collective conclusions[12]. Many are not randomized, and they tend to group disparate age cohorts together.

Pediatrics covers a wide range of developmental stages. All available evidence suggests that sugammadex is likely well tolerated and effective and can be dosed similarly to adults in patients who are 2 years old and greater. The primary concerns in pediatrics would be increasing rates of hypersensitivity or bradycardia, and there is currently no indication of those issues [13]. Bradycardia in particular will always be a concern in the youngest patient, but the alternatives as neostigmine or succinylcholine also carry similar concerns.

It is particularly scarce in the less than 2-year-old. Especifically, in neonates train-of-four monitoring can be technically difficult and there are anecdotal issues that the typical 2 mg/kg dosing may not always be effective. However, whenever sugammadex fails to achieve adequate reversal, the best approach is typically to give more until achieving the desired effect.

Conclusively again, sugammadex may reverse rocuronium-induced neuromuscular blockade in pediatric patients rapidly and safely. However, vigilance has been heightened if it may use in pediatric patients. More studies with larger numbers and prospective randomization cohorts will help to fill out clinical practice in the near future.

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Adequate dose of sugammadex beyond the guideline

김 주 덕

고신의대

- Adequate dose of sugammadex
- Adequate dose of sugammadex beyond guideline
  - **Patients with end-stage renal disease**
  - Pediatrics patients
  - Morbid patients

Adequete dose

브리디온 ™주(슈가마덱스나트륨)

BRIDION®

▫ 원료약품 및 그 분량

이 약 1mL 중,

유효성분 : 슈가마덱스나트륨 (별규) ---------- 108.8 mg

(슈가마덱스로서 ---------- 100 mg)

기타첨가제 : 수산화나트륨, 염산 35%

용제: 주사용수

▫ 성상

무색 내지 연한 황색을 띠는 투명한 용액이 담긴 무색투명한 바이알

▫ 효능·효과

로쿠로늄 또는 베쿠로늄에 의해 유도된 신경근 차단의 역전

용법, 용량

성인:

4) 신장애 환자

- 경증 내지 중등증의 신장애 환자 (Creatinine clearance 30 - 80 ml/min)에 대한 용량조절은 필요하지 않다.
- 중증의 신장애 환자(Creatinine clearance < 30 ml/min) 또는 투석이 필요한 환자에게 이 약의 투여는 권장되지 않는다.

6) 비만 환자:

- 비만 환자에 대한 이 약의 용량은 실제 체중을 기준으로 투여해야 한다.

소아:

- 18세 미만의 소아에 대한 이 약의 투여는 안전성·유효성이 확립되어 있지 않다. (사용경험이 적다)

Sugammadex use in patients with end-stage renal disease

Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function

- Thirty adult patients were studied
  - 15 patients with ESRD [creatinine clearance(CLcr) < 30 ml/min] and 15 controls (CLcr > 80 ml/min)
- A single dose of rocuronium 0.6 mg/kg
- At reappearance of the T2→ sugammadex 2.0 mg/kg
- The time from administration of rocuronium to reappearance of T2
  - 53.8 min in the really impaired group
  - 40.6 min in the control group (P = 0.06)
- Recovery of the TOF ratio to 0.9 was
  - 2.0 (0.72) min in renal patients and 1.65 (0.63) min in controls (NS)

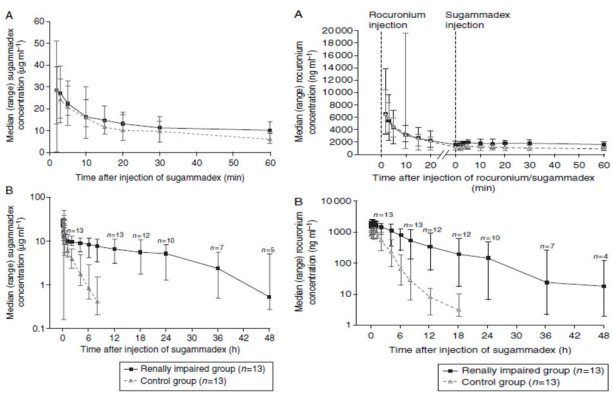
Staals et al. British Journal of Anaesthesia 101 (4): 492–7 (2008)

Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study†

- A single dose of rocuronium 0.6 mg/kg
- At reappearance of the T2→ sugammadex 2.0 mg/kg
- Venous blood samples to assess total rocuronium and sugammadex plasma concentrations
  - directly before administration of sugammadex and at 2, 3, 5, 10, 15, 20, 30, and 60 min
  - 2, 4, 6, 8, 12, 18, and 24 h after administration of sugammadex
  - In patients with renal failure, 36 and 48 h after sugammadex administration

Staals et al. British Journal of Anaesthesia 104 (1): 31–9 (2010)

Sugammadex and rocuronium plasma concentrations



Staals et al. British Journal of Anaesthesia 104: 31–9 (2010)

Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study†

- PK variables for sugammadex 2.0 mg/kg and rocuronium 0.6 /mg
- Large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls were observed.

	Renal failure	Control
Sugammadex kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	27 500 (114)	1730 (34.8)*
Range (μg min ml^{-1})	6480–147 000	1060–3330
CL (ml min^{-1})	5.5 (108)	95.2 (22.1)*
Range (ml min^{-1})	1.15–18.1	58.3–138
V_{ss} (litre)	16.0 (35.5)	13.8 (20.5)
Range (litre)	9.3–31.8	10.0–19.7
$t_{1/2,\beta}$ (h)	35.7 (121)	2.3 (44.4)*
Range (h)	10.7–282	1.6–7.5
MRT (h)	48.2 (132)	2.4 (25.5)*
Range (h)	13.2–399	1.8–4.0
Rocuronium kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	1080 (53.8)	296 (37.4)*
Range (μg min ml^{-1})	412–2370	143–538
CL (ml min^{-1})	41.8 (46.9)	167 (30.8)*
Range (ml min^{-1})	23.2–88.8	108–314
V_{ss} (litre)	22.1 (29.9)	19.1 (28.3)
Range (litre)	14.0–41.6	12.2–30.7
$t_{1/2,\beta}$(h)	7.5 (39.9)	3.0 (67.5)*
Range (h)	3.4–13.3	1.2–8.2
MRT (h)	8.8 (52.7)	1.9 (29.2)*
Range (h)	3.7–19.7	1.2–3.3

Staals et al. British Journal of Anaesthesia 104 (1): 31–9 (2010)

Dialysability of sugammadex and its complex with rocuronium

- In patients undergoing low-flux haemodialysis (n=7)
  - no significant reductions in sugammadex plasma
  - The median (range) reduction ratio (RR)

  → sugammadex 0.93 (0.87–1.20) and rocuronium 0.65 (0.57–0.90)

Staals et al. British Journal of Anaesthesia 104 (1): 31–9 (2010)

Dialysability of sugammadex and its complex with rocuronium

- Six patients in the ICU with acute severe renal impairment
- Rocuronium 0.6 mg/kg, followed 15 min later by sugammadex 4.0 mg/kg.
- Dialysis (using a high-flux dialysis method) clearance in plasma and dialysate,
  - reduction ratio, the extent of the plasma concentration reduction at the end of a dialysis episode when compared with before dialysis
- During the first dialysis episode
  - RRs indicated mean reductions of 69% and 75% in the plasma concentrations of sugammadex and rocuronium, respectively.
- Reductions were around 50% during sequential dialysis episodes.

G. Cammu et al. British Journal of Anaesthesia 109 (3): 382–90 (2012)

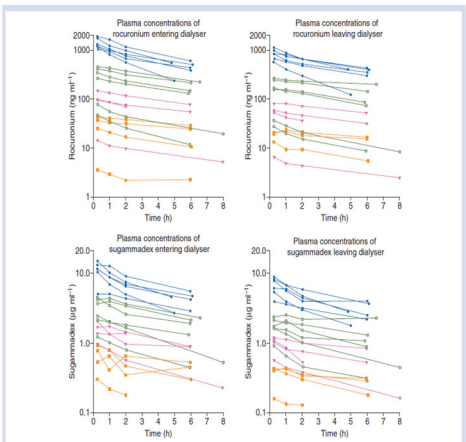


Fig 1 Overlay plots of concentrations in plasma entering the dialyser and leaving the dialyser vs time for the sequential dialysis episodes. Each single line represents the measurements of one patient. Solid circles: first dialysis episode; open circles: second dialysis episode; solid triangles: third dialysis episode; and solid squares: fourth dialysis episode. Concentrations pertain to total sugammadex and total rocuronium. Time 0, start of dialysis.

G. Cammu et al. British Journal of Anaesthesia 109 (3): 382–90 (2012)

Sugammadex & sugammadex-rocuronium complex

- exclusively excreted unchanged via the kidneys
- excretion is prolonged in patients with renal failure

- Concerns regarding
  - the prolonged presence of sugammadex-rocuronium complexes and the paucity of safety data in these patients have led to the recommendation that sugammadex should not be used in patients with a glomerular filtration rate of less than 30 mL/min.

EXPERT OPINION ON DRUG SAFETY 2019: 18; 883–891
Staals et al. British Journal of Anaesthesia 104: 31–9 (2010)

Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease

- Forty patients undergoing kidney transplant:
  - 20 with renal failure [creatinine clearance (ClCr) <30 ml/min] and 20 control patients (ClCr >90 ml/ min).
- Profound neuromuscular block (posttetanic count, 1-3) was maintained during surgery.
- Sugammadex 4 mg/kg was administered on completion of skin closure.
- MAIN OUTCOME MEASURES
  - The efficacy of sugammadex was evaluated by the time taken for the TOF ratio to recover to 0.9.
  - The safety of sugammadex was assessed by monitoring for recurrence of neuromuscular block every 15 min for 2 h.

Eur J Anaesthesiol 2015; 32:681–686

Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease

Table 2 Time (min) from sugammadex administration to recovery of train-of-four ratio to 0.7, 0.8 and 0.9

	Renal failure	Control	*N*	*P*
TOF ratio 0.7	3.5 ± 2.1 (0.5 to 8.8)	1.95 ± 0.93 (0.8 to 4.1)	40	0.004
TOF ratio 0.8	4.3 ± 2.5 (0.5 to 9.4)	2.3 ± 1.1 (0.8 to 5.3)	40	0.003
TOF ratio 0.9	5.6 ± 3.6 (0.5 to 15.3)	2.7 ± 1.3 (1.0 to 6.4)	39[a]	0.003

Data reported as mean ± standard deviation (range). TOF, train-of-four. [a]One patient was excluded from the renal failure group due to an equipment failure that compromised the assessment of neuromuscular function after the TOF ratio had recovered to 0.8.

- No adverse events or evidence of recurrence of neuromuscular block were observed.
- CONCLUSION
  - In patients with renal failure, sugammadex (4mg/kg) effectively and safely reversed profound rocuronium induced neuromuscular block, but the recovery was slower than healthy patients.

Eur J Anaesthesiol 2015; 32:681–686

Reversal of deep neuromuscular blockade in patients with severe renal impairment

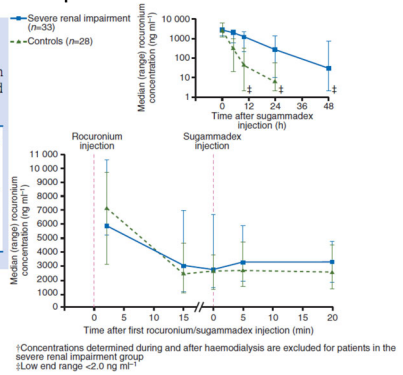
- Patients aged ≥18 years scheduled to undergo a surgical procedure using rocuronium for neuromuscular relaxation
- Patients with severe renal impairment (CL_{CR} <30 ml/min, n =35) vs normal renal function (CL_{CR} ≥80 ml/min, n=32).
- Sugammadex 4 mg kg−1 was administered at 1–2 post-tetanic counts for reversal of rocuronium NMB.
  - Primary efficacy variable was time from sugammadex to recovery to train-of-four (T4/T1) ratio 0.9.
  - Equivalence between groups was demonstrated if two-sided 95% CI for difference in recovery times was within −1 to +1 min interval.

Panhuizen IF, Gold SJ, et al. British Journal of Anaesthesia 114 (5): 777–784 (2015)

Reversal of deep neuromuscular blockade in patients with severe renal impairment

Table 2 Median (95% CI) time (min) from the start of administration of sugammadex to recovery of the TOF ratio to 0.7, 0.8 and 0.9 (ITT group, n=67)[a]. [a]Data for the four patients with prolonged recovery times (3 renal and one control) are included in the efficacy analysis

	Renal group CL_{CR} <30 ml min^{-1} (n=35)	Control group CL_{CR} ≥80 ml min^{-1} (n=32)	P-Value
TOF 0.7	2.3 (1.7–3.3)	1.2 (1.1–1.8)	<0.0001
TOF 0.8	2.5 (2.0–3.8)	1.5 (1.3–2.1)	<0.0001
TOF 0.9	3.1 (2.4–4.6)	1.9 (1.6–2.8)	0.0002



†Concentrations determined during and after haemodialysis are excluded for patients in the severe renal impairment group
‡Low end range <2.0 ng ml⁻¹

Panhuizen IF, Gold SJ, et al. British Journal of Anaesthesia 114 (5): 777–784 (2015)

Reversal of deep neuromuscular blockade in patients with severe renal impairment

- Rocuronium, encapsulated by Sugammadex, was detectable in plasma at day 7 in 6 patients.
- Sugammadex clearance is reduced in renal impairment.
- Conclusions:
  - Sugammadex 4 mg/kg provided rapid reversal of deep rocuronium-induced NMB in renal and control patients.
  - However, considering the prolonged sugammadex-rocuronium complex exposure in patients with severe renal impairment, current safety experience is insufficient to support recommended use of sugammadex in this population.

Panhuizen IF, Gold SJ, et al. British Journal of Anaesthesia 114 (5): 777–784 (2015)

CLINICAL VIGNETTE

Can J Anesth/J Can Anesth (2020) 67:1789–1797
Anaesthesia 2020, 75, 348-352 doi:10.1111/anae.14914
Journal of Clinical Anesthesia 67 (2020) 109981
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Correspondence

High need for sugammadex for rocuronium reversal with acute renal failure and normal need in the same patient with no renal impairment

2 Associate Professor, 3 Assistant Professor, 8 Professor, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Sugammadex use in patients with end-stage renal disease: a historical cohort study

- Data were collected between 7 March 2016 and 1 August 2019 (Paredes S, et al. Mayo Clinic College of Medicine)
- A historical cohort study of 219 patients with chronic kidney disease stage 5
  - CKD 5 patients with GFR ≤ 15 mL/min, with or without the need for renal replacement therapy (RRT)
- The primary outcome any complication possibly related to SGX
  - Hypersensitivity reactions, Need for reintubation, Hypoxemia, Pneumonia, and residual neuromuscular blockade.
- Secondary outcomes
  - any other complication not included in the primary outcome
  - and/or patient mortality within 30 days after the procedure

Paredes S, et al.Can J Anesth (2020) 67:1789–97

Sugammadex use in patients with end-stage renal disease: a historical cohort study

Sugammadex use in end-stage renal disease

TABLE 2 Complications within 30 days after surgery

Variables	Values
Primary outcome complication at 30 days	18 (8.2%)
Hypersensitivity reactions	0 (0%)
Need for reintubation	9 (4.1%)
Hypoxemia	13 (5.9%)
Pneumonia	3 (1.4%)
Mortality	8 (3.7%)
SGX-related mortality	0 (0%)
Any complication at 30 days	
Yes	50 (22.8%)
No	169 (77.2%)

SGX = sugammadex.

Paredes S, et al. Can J Anesth (2020) 67:1789–97

Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: a two-centre retrospective study

- Retrospective observational study (April 2016 and January 2019)
- Adult surgical patients with end-stage renal disease requiring pre-operative renal replacement therapy
- The primary outcome
  - the incidence of postoperative tracheal re-intubation within 48 h.
- The secondary outcome
  - the incidence of deferred tracheal extubation in the operating theatre.
- 125,653 surgical patients, received sugammadex in 26,650
- End stage renal disease patients,158
  - 48 patients (30%) renal transplant and 110 (70%) underwent non-renal transplantation procedures.
- There were 22 instances (14%) of deferred tracheal extubation due to surgical and/or pre-existing medical conditions.

Adams et al. Anaesthesia 2020, 75, 348–352

Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: a two-centre retrospective study

- Out of the 136 patients who had the tracheal tube removed at the end of the procedure,
- 3 patients trachea re-intubated within 48 h:
  - 2 patients developed pulmonary oedema resulting from volume overload
  - 1 patient had worsening sepsis.

Table 2 Doses and timing of rocuronium and sugammadex and train of four recordings for patients with end-stage renal failure who required postoperative tracheal re-intubation.

	Total rocuronium dose; mg	Last dose of rocuronium; mg	Time from final rocuronium dose until sugammadex; min	TOF before sugammadex	Sugammadex dose; mg.kg^{-1}	TOF after sugammadex
Patient 1	140	10	68	4	4.0	Not available
Patient 2	310	10	78	4	3.3	4
Patient 3	40	10	79	4	3.0	Sustained tetanus

Adams et al. Anaesthesia 2020, 75, 348–352

Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: a two-centre retrospective study

- No incidence of recurrence of neuromuscular blockade was observed.
- 24 (18%) patients were found to have incomplete neuromuscular blockade reversal with neostigmine but administration of sugammadex led to successful tracheal extubation.
- In conclusion,
  - sugammadex appears to be safe and effective in adult patients with end-stage renal disease receiving pre-operative renal replacement therapy

Adams et al. Anaesthesia 2020, 75, 348–352

JPPT | Case Report

Sugammadex for Reversal of Neuromuscular Blockade in a Patient With Renal Failure

Kayla Pfaff, BA; Dmitry Tumin, PhD; and Joseph D. Tobias, MD

- 19-year-old, 82.2-kg female with end-stage chronic kidney disease presented for an emergent revision of a ventriculoperitoneal shunt.
- Past medical history included
  - myelomeningocele, hydrocephalus, neurogenic bowel and bladder, lower extremity paralysis, end-stage renal disease with a glomerular filtrate rate less than 15 mL/min, anemia, and secondary hyperparathyroidism.
- She had not received dialysis.

J Pediatr Pharmacol Ther 2019;24(3):238–241

JPPT | Case Report

Sugammadex for Reversal of Neuromuscular Blockade in a Patient With Renal Failure

Kayla Pfaff, BA; Dmitry Tumin, PhD; and Joseph D. Tobias, MD

- Anesthetic induction

  propofol (200 mg), fentanyl (200 mcg), lidocaine (80 mg), and rocuronium (80 mg).
- Anesthesia was maintained with isoflurane in air and oxygen.
- 130 minutes after the administration of rocuronium → no twitches in TOF, 4 posttetanic twitches.
- 150 minutes after the administration of rocuronium → the return of one twitch on the TOF.
- Sugammadex (4 mg/kg) was administered, and within 10 minutes complete reversal of residual neuromuscular blockade, with return of protective airway reflexes, TOF, demonstration of adequate spontaneous ventilation.
- She was discharged to the inpatient ward and discharged home that evening.

J Pediatr Pharmacol Ther 2019;24(3):238–241

Sugammadex in end-stage renal disease: too early for a “free-pass”?

- Sugammadex and Sugammadex-rocuronium complex
  - renally excreted
  - not removed with a standard form of dialysis & removed with a high-flux dialysis
- Recurrence of potential neuromuscular blockade is unlikely
  - association constant (Ka) of sugammadex and rocuronium is relatively high at 17,000-20,400 M^{-1}
  - even such a disassociation could occur, it most likely reassociates immediately
  - in the event dissociation occurs, the concentration of free rocuronium would be very small and unlikely to demonstrate any clinical effect.
  - this free rocuronium would eventually undergo normal biliary excretion.

Sugammadex in end-stage renal disease

Keep in mind!

- Character of end-stage renal disease patients
  - higher risks of perioperative morbidity and mortality due to multiple comorbidities
- Clinical experience of the usage of sugammadex with ESRD patients is scarce
  - no clinical data on long-term disposition of the sugammadex–rocuronium complex
  - more prospective studies are need.
- The action duration of both sugammadex and rocuronium is prolonged.
  - reversal time (TOF ratio > 0.9) may be prolonged
  - quantitative neuromuscular monitoring is mandatory

Hypersensitivity: Still problem? (Hypersensitivity related with NMBD and antagonists)

강 운 석

건국의대

근이완제 사용에 의해 발생할 수 있는 여러가지 부작용 중 가장 심각하고 환자의 생명에 위협이 될 수 있는 것은 hypersensitivity reaction 이다. 과거에 사용하던 근이완제 (succinylcholine, suxamethonium 등) 의 사용이 점차적으로 감소함에 따라 근이완제에 의한 hypersensitivity reaction 은 감소하고 있는 추세이지만 여전히 수술장에서 마취 중 발생할 수 있는 allergic reaction 중 50-70%가 근이완제와 관련이 있는 것으로 추정되고 있다.[1,2] 최근에는 근이완의 역전에 사용되는 sugammadex 및 sugammadex 투여 후 만들어지는 rocuronium-sugammadex complex 에 의한 allergic reaction 도 보고되고 있다. 본 강의를 통해 마취통증의학과 의사가 알아야할 근이완제 및 역전제인 sugammadex 에 의한 anaphylaxis 의 clinical presentation, 그에 따른 diagnosis 및 치료에 대해 여러가지 증례보고와 최신지견들을 통해 알아보고자 한다.

Incidence

NMBA-induced anaphylaxsis

각 나라마다 보고체계가 다르고 경한 증상은 보고에서 누락되는 등의 여러 가지 요소로 인하여 근이완제에 의해 발생하는 allergic reaction 의 보고된 발생빈도는 매우 다양하다. 북유럽에서 2000년대 초반에 보고된 바에 의하면 succinylcholine 과 suxamethonium 을 제외한 근이완제 중 rocuronium 이 allergic reaction 을 유발하는 빈도가 가장 높았으며 rocuronium 에 의한 anaphylaxis 의 incidence 는 1:3,500 ~ 1:44,500 였다.[3]

Sugammadex-induced anaphylaxis

근이완제에 의해 발생하는 allergic reaction 에 비해서 발표된 증례보고의 수가 적고 아직 대규모 조사가 이루어지지 않은 상태이지만 sugammadex 를 가장 많이 사용하고 있는 일본의 경우에 2010년부터 2013년까지의 조사결과에 따르면 1:34,483 의 incidence 를 보이고 있다.

Mechanism

Ig E mediated type 1 hypersensitivity 의한 anaphylaxis reaction 이 대부분이며 전체 allergic reaction 의 약 30% 정도가 약제에 의해 유발된 histamine 과다분비가 주된 원인이 되는 non-immune mediated hypersensitivity reaction 인 것으로 알려져 있다.[1] 그런데 흥미로운 점은 근이완제에 anaphylaxis reaction 을 보인 환자의 약 75% 까지에서 근이완제에 처음 노출된 환자라는 것이 밝혀짐으로써 근이완제에 의해 발생하는 type 1 hypersensitivity reaction 은 전에 이미 노출되었던 알지 못하는 물질에 의한 교차반응이 주된 발생기전으로 추정되게 되었다.[4,5] 교차반응을 유발하게 되는 부분은 근이완제의 구조 중 3차 또는 4차 ammonium ion 부분임이 여러 연구를 통하여 밝혀지게 되었고 이러한 3차 또는 4차 ammonium ion 은 많은 약제 뿐만 아니라 음식, 화장품, 소독제 등의 화학생성물에 현재 사용되고 있다. 따라서 환자 본인도 알 수 없는 시점에서 감작된 상태에서 근이완제에 의한 anaphylaxis 가 발생하게 되는 것으로 추정되고 있다.

Sugammadex 에 의한 anaphylaxis 는 아직 증례보고가 적고 어떤 작용기전에 의해 발생하게 되는지에 대한 연구가 부족한 상태이다. 최근 15건의 sugammadex 사용 후 발생한 hypersensitivity reaction 에 대한 systemic review 를 시행한 결과 모든 환자에서 전에 sugammadex 에 노출된 병력이 없었다.[6] 따라서 이 또한 교차반응이 연관되어있을 것이라고 추정이 되는데 어떠한 물질에 대한 교차반응에 의해서 anaphylaxis 가 유발되는지에 대한 확실한 결론은 내리기 힘들지만 다양한 방면에 사용되고 있고 sugammadex 의 원료인 cyclodextrin 이 교차반응을 유발할 것이라고 추정되고 있다.

Clinical presentation

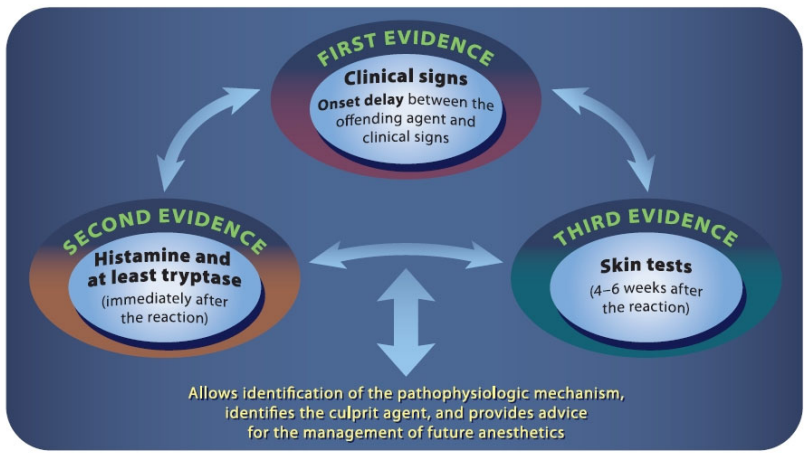
일반적으로 anaphylaxis 는 여러 장기에 동시다발적으로 발생하게 된다. 대부분 urticarial 를 유발하게 되고 (80-90%), 호흡기 (70%), 소화기 (30-45%), 심혈관계 (10-45%), 신경계 (10-15%) 등 여러 장기에서 증상을 나타낸다. 그러나 수술장에서 마취가 된 환자에서는 일반적으로 깨어있는 환자가 호소할 수 있는 주관적 증상, 즉 malaise, pruritus, dizziness, dyspnea 등의 증상을 알 수 가 없고 피부병변의 경우에 수술포 등으로 가려져 있기 때문에 초기에 진단이 어려워질 수도 있다. 초기 진단을 놓치게 되는 경우 치료가 늦어질 수 있고 예후에 영향을 미칠 수 있으므로 환자의 활력징후가 약물 투여 후 급작스럽게 변하는 경우 반드시 피부 등에 다른 증상이 나타나지 않는지 확인하는 것이 필요하다. 임상증상의 severity 는 아래의 표와 같으며 증상의 발현이 빠른 경우 증상이 심한 것이 일반적이다.

Table 1. Clinical Severity Scale of Immediate Hypersensitivity Reactions Adapted from *Ring and Messmer*[6]

Grades	Clinical Signs
I	***Cutaneous-mucous signs:*** erythema, urticaria with or without angioedema
II	***Moderate multivisceral signs:*** cutaneous-mucous signs ± hypotension ± tachycardia ± dyspnea ± gastrointestinal disturbances
III	***Life-threatening mono- or multivisceral signs:*** cardiovascular collapse, tachycardia, or bradycardia ± cardiac dysrythmia ± bronchospasm ± cutaneous-mucous signs ± gastrointestinal disturbances
IV	***Cardiac arrest***

Diagnosis

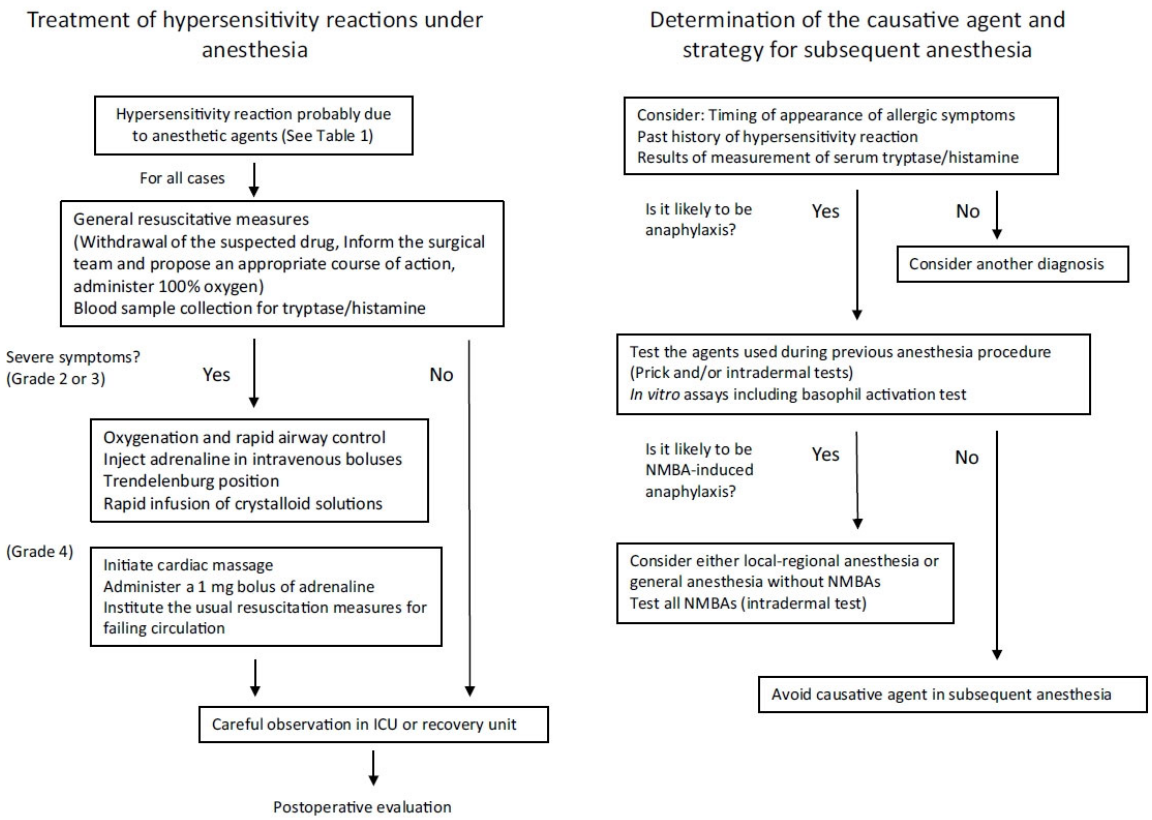
Anaphylaxis 의 진단은 세가지 단계로 이루어지는데 clinical, biological, allergologic process 를 통해서 첫번째로 임상적인 상황을 평가하고 환자의 현재상태를 치료하기 위해서 임상적 진단을 하고 두번째로 anaphylaxis 가 확실한지를 판단하기 위해서 histamine과 tryptase 의 혈중농도를 증상이 발생한 직후 측정하고 세번째로 anaphylaxis 가 맞다면 어떤 물질이 원인이 되었는지를 확인하고 환자에게 앞으로 노출되지 않도록 예방하기 위해서 skin test 를 시행한다.



Treatment

Anaphylaxis 의 증상 발생을 빠르게 인지하는 것이 필수적이다. National anaphylaxis guideline 에 따르면 first line therapy 로 recommendation 되는 유일한 약물은 adrenaline (epinephrine) 이다. 용량과 투여 경로는 환자 증상의 중등도에 따라 결정한다. 일차적 치료는 다음과 같이 시행한다.

① 의심되는 약물을 투여 중단한다.
② 외과의에게 알리고 다른 마취과의사 등에게 도움을 요청한다.
③ Trendelenburg position 을 취한다.
④ Airway 를 확보하고 산소를 투여한다.



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The Future of Neuromuscular Blockade Antagonist

오 석 경

고려의대

Aim of the presentation

- A brief **review** of the literature on **recent advancement** in **neuromuscular blockade antagonists**.

Contents

- The Past
- The Present
- The Future
  (adamgammadex sodium, L-cysteine, calabadion, WP[6])

of Neuromuscular Blockade Antagonist

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The **Past** of
Neuromuscular Blockade Antagonist

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Historical background

- *Chondrodendron tomentosum*

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THE USE OF CURARE IN GENERAL ANESTHESIA

HAROLD R. GRIFFITH, M.D., AND G. ENID JOHNSON, M.D.*
Montreal, Canada

EVERY anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under

Anesthesiology 3:418-420, **1942**

→Introduced the modern concept of "**balanced anesthesia**"
(the combination of hypnotics, relaxants, and opioids)

A STUDY OF THE DEATHS ASSOCIATED WITH ANESTHESIA AND SURGERY*

BASED ON A STUDY OF 599,548 ANESTHESIAS IN TEN INSTITUTIONS 1948–1952, INCLUSIVE

HENRY K. BEECHER, M.D., AND DONALD P. TODD, M.D.

FROM THE ANESTHESIA DEPARTMENT OF THE HARVARD MEDICAL SCHOOL AT THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON

TABLE XXXII. *Frequency of Death Associated with 599,500 Anesthesias.*

Anesthesias Which Included:		Anesthesias Which Did Include:	
No "Curare" (266)*	1 : 2100	"Curare" (118)	1 : 370
No Ether (166)	1 : 2500	Ether (218)	1 : 820
No cyclopropane (299)	1 : 1800	Cyclopropane (85)	1 : 880
No Nitrous Oxide (184)	1 : 2100	Nitrous Oxide (200)	1 : 1100
No Vinyl Ether (355)	1 : 1600	Vinyl Ether (29)	1 : 1300
No Ethylene (353)	1 : 1600	Ethylene (31)	1 : 1700
No Thiopental (223)	1 : 2000	Thiopental (161)	1 : 900
No Spinal (351)	1 : 1500	Spinal (33)	1 : 1800
No Reginal (313)	1 : 1400	Regional (71)	1 : 2300

x 6

TABLE XXV. *"Curare" Deaths*
Primary Cause of Death

	Number Cases	Per Cent
Respiratory Failure (Hypoxia)	74	63
Cardio-vascular Failure (notwithstanding artificial respiration)	44	37
		100%
Role of Anesthesia in Death*		
Toxicity of "Curare" (assumption) (no error apparent)	25	21
Error Technic "Curare's" Use (overdose, respiratory depression or obstruction not corrected)	37	31
Error Choice "Curare" (in severe respiratory impairment, shock, full stomach, where relaxation not needed)	20	17
Error Anesthetic Management (not directly related to "curare")	36	31
		100%

Sectional page 17

Proceedings of the Royal Society of Medicine

Vol. XLI 559

Section of Anæsthetics

President—JOHN CHALLIS

[*April* 2, 1948][1]

d-Tubocurarine Chloride

By T. CECIL GRAY, M.D., D.A.

Dr. T. C. Gray, in reply, thanked Dr. Frankis Evans for his interesting and helpful remarks. He had always considered it important to prevent the undesirable parasympathomimetic effects of prostigmine used as an antidote to tubocurarine by administering with it an adequate dose of atropine. It seemed quite possible that the administration of unbuffered prostigmine might result in depression of the intestinal movements after the initial stimulation.

'Liverpool anaesthetic technique'

- mid-1950s
- neostigmine 5 mg

Prof Thomas Cecil Gray CBE MBChB(Hons) MD FFARCS FRCS FFARCSI(Hon) FRCP(Hon) FANZCA(Hon) DA

11/03/1913 to 05/01/2008

Place of birth: Liverpool, England

Nationality: British

CRN: 502430

Also known as: Cecil

Professor, from 1959

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Anticholinesterase agents

- Limitation
  - ✓Effective at least appearance of 2nd twitch → deep blockade cannot be restored
  - ✓Ceiling effect
  - ✓Muscarinic action
    : bradyarrhythmias, bronchospasm, bronchial secretions, PONV
  - ✓Unpredictable reversal of blockade when used in other comorbidities, hypothermia, use of magnesium sulphate

Bronsert MR et al. *Anesth Analg. 2017*

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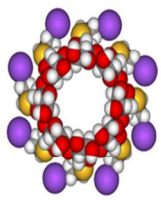
The **Present** of
Neuromuscular Blockade Antagonist

Sugammadex

- Bridion; MSD
- modified **gamma** (γ) cyclo**dex**trins: eight-member **suga**r ring
- lipophilic core + hydrophilic outer end
- the first **selective** relaxant **binding** agent
- **rapidly** and completely **reverse any degree NMB**
- introduced in Europe in September 2008
- rejected 3 times by the U.S. FDA in 2008, 2013, and 2015



Sugammadex

- Limitaion
  - ✓potential **allergic** reactions
  - ✓potential postoperative **bleeding**
  - ✓only selective to **steroid**al NMBAs (rocuronium, vecuronium, pancuronium)
  - → no affinity to benzylisochinquinolinium NMBAs

Ideal NMBAs

- rapid-onset, quick-offset, noncumulative,
- non-depolarizing action,
- independent of end-organ metabolism,
- **reversible by an antagonist**
- **devoid of clinically relevant adverse effects**

Savarese and Kitz 1975; Raghavendra 2002

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The Future of Neuromuscular Blockade Antagonist

1. Adamgammadex sodium

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Adamgammadex sodium

- modified γ –cyclodextrin derivate
- reverse rocuronium-induced NMB
- similar efficacy and **fewer potential side effects than SGX**
- **chemical modification** (the added chiral carbon atoms in the gcyclodextrin) increases the steric hindrance of carboxyl groups, which **reduces the binding-rate with non-targeted molecules.**

Eur J Pharm Sci. 2020 Jan 1;141:105134.

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Preclinical study

- In beagle dogs,
  - ✓concentration-dependent reversal of rocuronium induced NMB
- In zebrafish,
  - ✓lower potential for hypersensitivity and anaphylaxis
  - ✓no risk of bleeding

Chen et al., 2015. Acad. J. Second Mil. Med. Uni. 36, 507–512.;
Qi et al., 2018. Chin. J. Pharmacol. Toxicol. 32, 515–526.

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Clinical study

- approved by the China FDA in 2015 for clinical trial
- 52 healthy volunteers

Number of subjects treated in each dose group.

	Adamgammadex dose group (mg/kg)						
	0.5	2	4	8	16	24	32
No. of subjects receiving active	2	6	6	6	6	6	6
No. of subjects receiving placebo	2	2	2	2	2	2	2
Total subjects	4	8	8	8	8	8	8

- there was no AEs specific to adamgammadex

Eur J Pharm Sci. 2020 Jan 1;141:105134.

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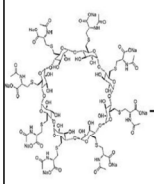

Adamgammadex sodium

Healthy volunteers

32 mg/kg (n = 6)
24 mg/kg (n = 6)
16 mg/kg (n = 6)
8 mg/kg (n = 6)
4 mg/kg (n = 6)
2 mg/kg (n = 6)
0.5 mg/kg (n = 2)
Placebo control

1, No drug-related serious adverse events.
2, Indiscriminate frequency of adverse events with control.
3, A linear pharmacokinetic feature.
4, Primary pathway of excretion is by kidney.

Eur J Pharm Sci. 2020 Jan 1;141:105134.

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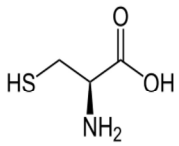
The **Future** of Neuromuscular Blockade Antagonist

2. L-cysteine (reversal of gantacurium/CW002/ CW011)

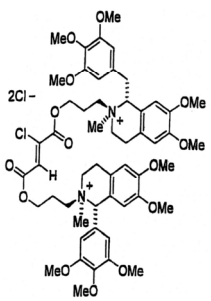
Cysteine

- 2-**Amino**-3-sulfhydrylpropanoic **acid**
  - semi-essential proteinogenic amino acid
  - precursor to the antioxidant glutathione
  - a residue in high-protein foods
- Cysteine exists as **L-** and D-enantiomers → L-Cysteine

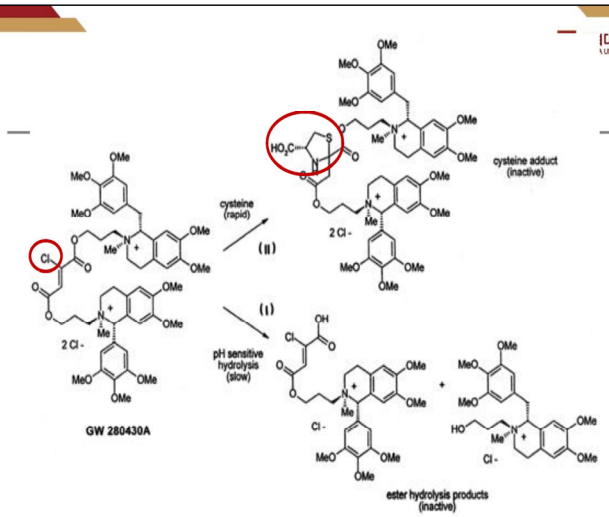


Gantacurium (AV 430A; GW280430A)

- **asymmetric** mixed-onium **chlorofumarates**
- **ultra-short acting non-depolarizing** NMBA
- metabolized by **chemical degradation**
  - **cysteine adduction (fast process)**
  - pH-sensitive hydrolysis (slow process)
    like Hofmann elimination (cisatracurium & atracurium)
- no renal and hepatic involvement in the elimination of gantacurium



Anesthesiology April 2004, Vol. 100, 835–845.



Cysteine adduction

- replacement of **chlorine** by **cysteine**
- **heterocyclic ring** is formed which cannot longer interact with the postjunctional acetylcholine receptor
- **metabolites** of gantacurium showed **no neuromuscular properties**

TABLE 11–7 Clinical characteristics of nondepolarizing muscle relaxants.

Drug	ED_{95} for Adductor Pollicis During Nitrous Oxide/Oxygen/Intravenous Anesthesia (mg/kg)	Intubation Dose (mg/kg)	Onset of Action for Intubating Dose (min)	Duration of Intubating Dose (min)	Maintenance Dosing by Boluses (mg/kg)	Maintenance Dosing by Infusion (μg/kg/min)
Succinylcholine	0.5	1.0	0.5	5–10	0.15	2–15 mg/min
Gantacurium[1]	0.19	0.2	1–2	4–10	N/A	—
Rocuronium	0.3	0.8	1.5	35–75	0.15	9–12
Mivacurium[2]	0.08	0.2	2.5–3.0	15–20	0.05	4–15
Atracurium	0.2	0.5	2.5–3.0	30–45	0.1	5–12
Cisatracurium	0.05	0.2	2.0–3.0	40–75	0.02	1–2
Vecuronium	0.05	0.12	2.0–3.0	45–90	0.01	1–2
Pancuronium	0.07	0.12	2.0–3.0	60–120	0.01	—
Pipecuronium[2]	0.05	0.1	2.0–3.0	80–120	0.01	—
Doxacurium[2]	0.025	0.07	4.0–5.0	90–150	0.05	—

[1]Not commercially available in the United States.
[2]No longer available in the United States.

Clinical Studies of gantacurium

- ED_{95} of gantacurium: 0.19 mg/kg
- the onset of 1× ED_{95} < 3 min
- 4× ED_{95} → onset: 1.5 min, duration of action (TOF > 0.9) : 15 min
- **histamine release** → transient cardiovascular side effects
- dose ratio of ED Hist:ED_{95} for mivacurium is 2.5
- no evidence of histamine release at 2.5× ED_{95}

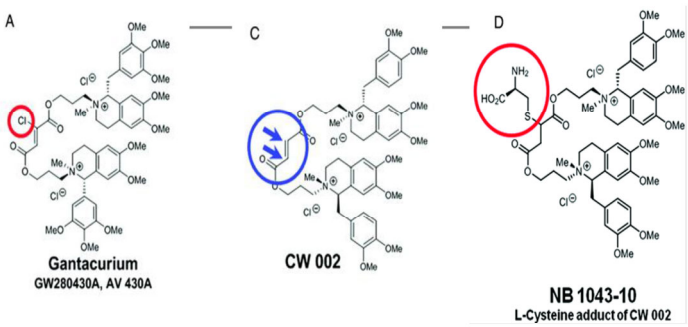
- gantacurium is not available in clinical practice

Reversal of gantacurium-Induced NMB

- Spontaneous recovery is rapid
- Reversed with cholinesterase inhibitors
  - Edrophonium → most suitable as the peak effect < 2 min
    (Neostigmine: peak effect at 7–11 min)
- **cysteine** adduction and alkaline hydrolysis

CW002

- **Gantacurium analogue**
- a new benzoquinolinium fumarate diester
- lacking a chlorine at the fumarate double bond and **being symmetrical**
- designed to **interact** more **slowly** with endogenous **L-cysteine** than gantacurium → **intermediate** duration of action



Anesthesiology July 2010, Vol. 113, 58–73.

Clinical Studies of CW002

- ED_{95} of CW002: 0.077 mg/kg
- onset of 1.8× ED_{95} : 90 s
- recovery to a train-of-four ≥0.90 : 73 min
- minimal cardiopulmonary side effects and no histamine release

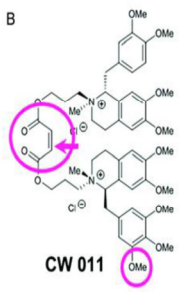
- CW002 is not available for the use in clinical practice

Anesthesiology Dec 2016, Vol. 125, 1136–1143.

CW011

- a non-halogenated olefinic diester analogue of gantacurium (symmetrical maleate)
- slower L-cysteine adduction
- 4–5× ED_{95} (0.025 mg/kg) : 20.8 min, in monkeys
  - half of cisatracurium, 3 times longer than gantacurium

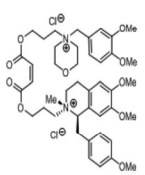
- no studies in humans



CW 1759-50

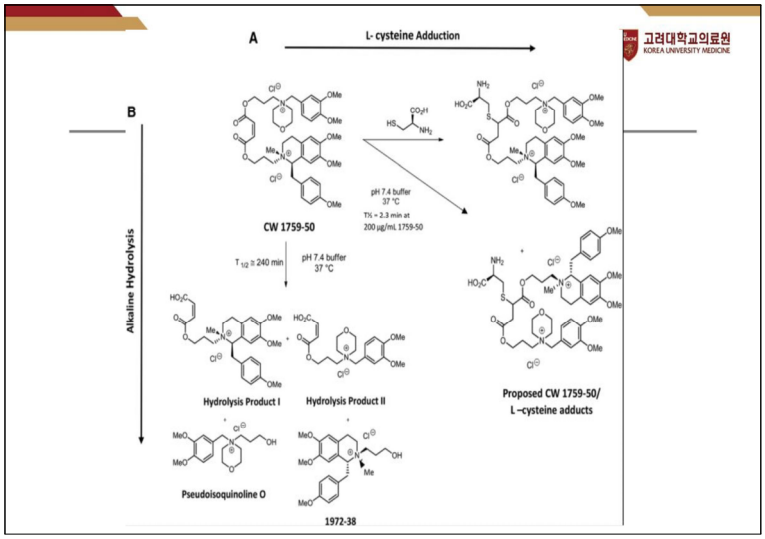
- more potent than gantacurium in rhesus monkey (ED95:0.069 ± 0.02 mg/kg *vs.* 0.081 ± 0.05 mg/kg, $P = 0.006$)
- similar rapid onsets and durations with gantacurium
- reduced circulatory effects

CW 1759-50



- no studies in humans

Anesthesiology November 2018, Vol. 129, 970–988.



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Reversal of CW002 and CW011-Induced NMB

- cholinesterase inhibitors, neostigmine
- cysteine adduction and hydrolysis
- L-Cysteine (10-50 mg/kg) reversal from NMB induced by CW011 $5\times ED_{95}$ within 2–3 min, in monkeys
- **no humans study** on the reversal with **L-cysteine**

Anesthesiology July 2010, Vol. 113, 58–73.

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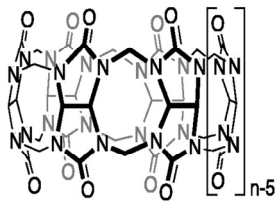
The **Future** of
Neuromuscular Blockade Antagonist

3. Calabadion

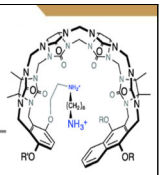
Calabadion

- A new agent to reverse **benzylisoquinoline** and **steroidal** NMBAs as well as anesthetics (local anesthetics, ketamine and etomidate)
- **acyclic**, glycoluril, tetrameric, cucurbituril molecular **containers** (cucurbit[n]urils n = 5, 6, 7, 8, 10)
- C-shape
- calabadion 1: first-generation calabadion

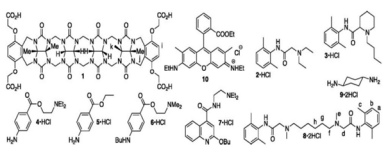


CB[n] (n = 5, 6, 7, 8, 10)

Calabadion 1



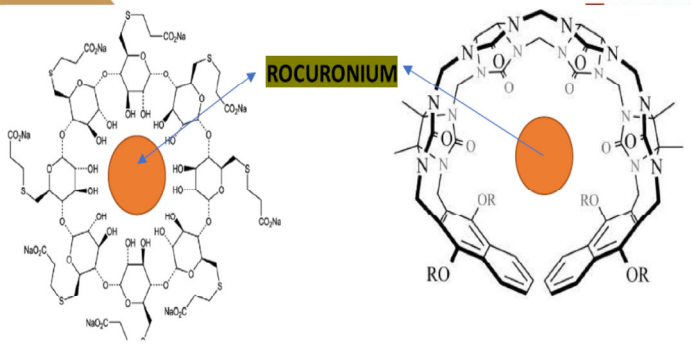
- calabadion-1-rocuronium complex **affinity** is **similar** with sugammadex-rocuronium complex (Ka = 8.4 ± 0.9 × 10^6/M vs. 1.1 ± 0.2 ×10^7/M)
- but, binding-constant for calabadion-1-cisatracurium complex is 10-times lesser
- forms stable host–guest complexes with **local anesthetics** in vitro



Supramol Chem. 24:325–332

Calabadion 2

- calabadion 2 showed a **higher binding affinity** to rocuronium
- 89-fold stronger affinity than calabadion 1 (Ka 3.4 × 109 M^{-1} vs. 3.8 × 107 M^{-1})
- calabadion 2 showed faster recovery than calabadion 1 with lower doses
- eliminated via kidneys, was well tolerated, and had no hemodynamic perturbations
- Reversal of ketamine and etomidate



Shah et al. Ain-Shams Journal of Anesthesiology (2021) 13:15

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The Future of Neuromuscular Blockade Antagonist

4. WP[6]

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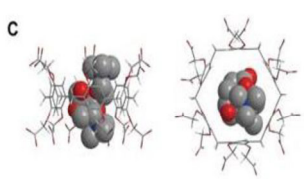
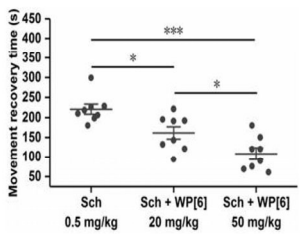
WP[6]

- water-soluble carboxylatopillar[6]arene sodium salt (WP[6])
- high binding affinities towards **succinylcholine** (Sch)
- **antidot**al effects of the host molecules in a lethal Sch poisoning mouse model





Theranostics 2019; 9(11):3107-3121.

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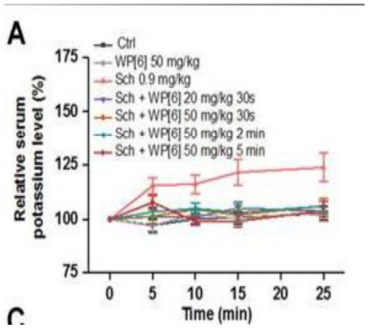
• WP[6] alleviated Sch induced hyperkalemia



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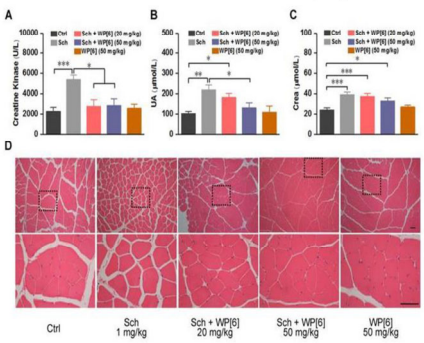
• WP[6] alleviated the Sch induced rhabdomyolysis



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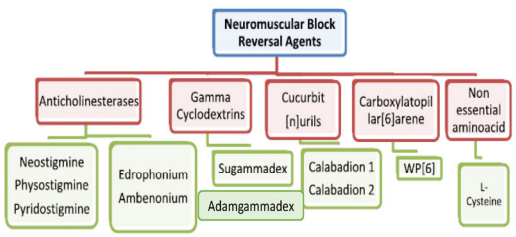
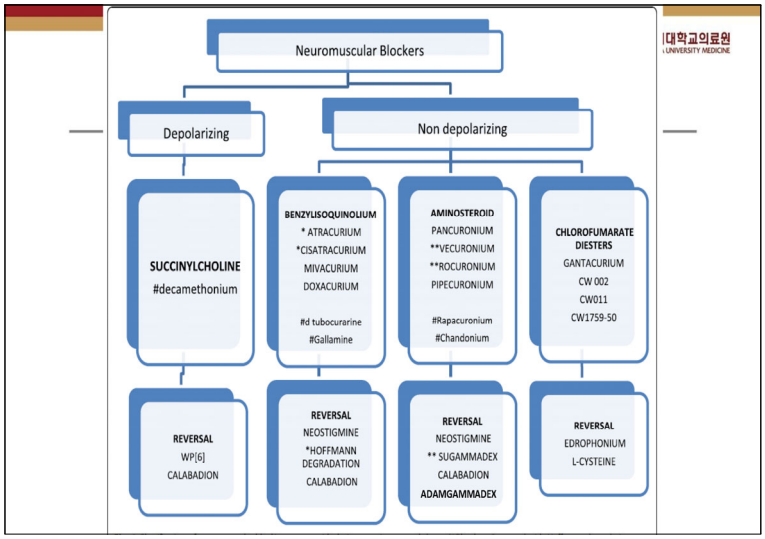
Classification of NMB antagonists



Shah et al. Ain-Shams Journal of Anesthesiology (2021) 13:15



Summary

- A **broad-spectrum reversal agent**, universal for all NMBA, capable of reversing any depth of NMB, is **developed**.
- These presented drugs are **currently not available for clinical use.**
- So far, well established combinations (rocuronium-sugammadex) is the best option.

2021년 대한신경근연구학회 춘계학술대회
Online Web Seminar

인 쇄 | 2021년 6월 23일
발 행 | 2021년 6월 26일

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