

## Postoperative residual curarisation : complication or malpractice ?

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**Summary :** Neuromuscular blocking drugs are often used in anaesthesia ; in some types of surgery, their continuous infusion is indicated to limit the otherwise high incidence of movement. A large amount of postoperative residual curarisation is found after a single bolus, but more especially when continuous infusions are used in healthy patients and even more so in those with organ dysfunction or undergoing special types of surgery. Therefore, one should always optimise the dose requirements over time using neuromuscular transmission monitoring. Such monitoring should also help the clinician to antagonise selectively the neuromuscular block at the end of surgery. One should probably avoid *routine* antagonisation, especially in certain subgroups of patients, until a selective and safe reversal agent has been developed. At present, then, the only objective and reliable guide to facilitating the decision for selective antagonisation is the neuromuscular transmission monitor. Recent data and editorials warning about postoperative residual curarisation after boluses and infusions of neuromuscular blocking drugs have made residual curarisation one of the most feared complications in anaesthesia. There may be a consequent issue of malpractice if neuromuscular transmission monitoring is not used and/or pharmacological antagonisation is not performed.

In 1942 GRIFFITH and JOHNSON administered curare to a patient under general anaesthesia. Their report of the use of curare in 25 patients changed anaesthetic practice throughout the world and heralded the start of the modern era of anaesthesiology (1). Before then, deep inhalational anaesthesia had been the only way to provide adequate muscle relaxation, but was poorly tolerated by debilitated and/or aged patients. The introduction of curare allowed adequate muscle relaxation at a lighter, and therefore better tolerated, level of general anaesthesia. The use of neuromuscular blocking drugs (NMBDs) together with endotracheal intubation (decreasing the risk of aspiration) is the basis of the current concept of balanced anaesthesia : the combination of hypnosis, analgesia and muscle relaxation, resulting in fewer detrimental effects on the respiratory and cardiovascular systems. Inoperability, due to the extremes of age or to advanced pathology, was virtually eliminated by the introduction of NMBDs. It is hard to imagine if

and how, without the NMBDs, open-heart, transplant or intracranial surgery could have developed.

There are, however, potential side-effects related to the use of NMBDs ; they include (2) :

1. *During the induction and maintenance of anaesthesia* : aspiration, difficult or impossible airway management, cardiovascular effects (bradycardia, tachycardia, hypotension, rhythm disturbances), immunological and non-immunological histamine release.
2. *During emergence from anaesthesia and during the stay on recovery* : postoperative residual curarisation (PORC) with possible hypoventilation and hypoxaemia/aspiration.
3. *During and after the long-term administration of non-depolarising NMBDs* : muscle weakness and convulsive effects of compounds or metabolites.

Few deaths are related directly to the use of NMBDs (3). The mortality and morbidity from failed endotracheal intubation is also very low ; death or complications from aspiration during induction are very rare (3, 4). Concerning NMBD-induced cardiovascular effects, it is known that succinylcholine-induced bradycardia and cardiac arrest have a relatively high incidence, particularly in high-risk patients (children, burns, spinal cord and other neuromuscular disorders) (5). NMBDs induce more histamine release than other drugs used in anaesthesia. The overall incidence of anaphylaxis is, however, low (6). Succinylcholine appears to produce the highest incidence of serious immunological histamine release (7). Miscellaneous effects of NMBDs include : fasciculations, myalgia, increased intracranial, intragastric and/or intraocular pressure, masseter muscle spasm, rhabdomyolysis/myoglobinaemia/myoglobinuria, and malignant hyperthermia. Most of these effects are complications of succinylcholine (2). Muscle

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weakness after the prolonged administration of NMBDs in the intensive care unit and the convulsive effects of compounds or metabolites are more often encountered with non-depolarising NMBDs (8, 9).

Whereas intraoperative surgical and anaesthetic conditions are greatly improved by the use of modern NMBDs, anaesthesiologists are still faced with preventing residual curarisation at the end of the procedure, even when reversal agents are used (10). A complete return of neuromuscular function at the conclusion of surgery is highly desirable unless mechanical ventilation is planned: therefore one should determine whether spontaneous recovery has progressed to an extent that allows reversal and then assess the likely effects of reversal agents. The effectiveness of anticholinesterases depends directly on the level of recovery present when they are administered. Preferably, reversal agents should be given only when four twitches of the train-of-four (TOF) are visible. The unwanted side-effects of reversal agents originate from their combination with a vagolytic agent. This combination may lead to several complications: cardiovascular and gastrointestinal effects; muscle weakness (11).

In contrast to most other complications, residual curarisation in the recovery room is a general problem with a high incidence, in particular for long-acting NMBDs (more than 40%), but also for intermediate-acting NMBDs (more than 20%) (12, 13, 14, 15). BERG showed, in a prospective, randomised and blinded study, that residual curarisation in the recovery room caused by a long-acting NMBD is a significant risk factor for the development of postoperative pulmonary complications (16).

The time course of action of a NMBD is an intrinsic effect of the drug, but also depends on the dose administered, the period and the method of administration (bolus or infusion), individual sensitivity to the NMBD, and interaction with other drugs. Also, plasma clearance (liver uptake and excretion, renal excretion, and metabolism in plasma), active metabolites, and the effects of acidosis and hypothermia play an important part. An additional problem in determining 'clinically adequate recovery' is its precise definition: ideally, pulmonary ventilation, airway protection and maintenance of airway patency should be evaluated at the end of anaesthesia (17, 18). Certain variables of pulmonary ventilation, such as maximum inspiratory pressure and vital capacity, can be used to determine adequate neuromuscular recovery (19):

this requires spirometry. It is, however, impossible to monitor airway protection and maintenance of airway patency in clinical practice.

Therefore several other clinical indicators of sufficient recovery are used, including for example, patients' ability to open their eyes, breathe deeply, cough, lift their head and/or legs against gravity, swallow, and resist removal of a spatula from between their clenched teeth (20). These clinical tests are influenced by the effects of premedication, general anaesthetics, degree of consciousness, level of cooperation and postoperative pain. Consequently, there are contradictory results on the correlation between clinically sufficient recovery and neuromuscular transmission (NMT) monitoring (12). There are also conflicting findings about the positive effects of NMT monitoring during anaesthesia on the incidence of PORC (21, 22, 23).

Despite these disagreements, a TOF recovery, initially set at 0.7 and nowadays at 0.9, is accepted as one that correlates with sufficient clinical recovery of muscle strength (24, 25, 26, 27, 28, 29). Tactile and visual evaluation of the TOF ratio is no longer sufficient in this context because this technique can only detect residual paralysis corresponding to a TOF ratio of about 0.3–0.4. Tactile evaluation of the response to double-burst stimulation is superior to tactile evaluation of the response to TOF stimulation (30, 31, 32). Objective, quantitative monitoring is the only way to determine neuromuscular recovery (20, 33).

The high sensitivity of the pharynx to NMBDs is the basis of the proposed new standard for residual block (TOF ratio = 0.9). Early recovery occurs in central respiratory muscles such as the diaphragm and the larynx, whereas the muscles of the pharynx and the eyes recover much more slowly. Residual block is therefore more pronounced in the pharynx and the facial muscles. Recent findings suggest that a residual TOF 'fade' of up to 0.9 in the hand can be concurrent with pronounced continuing dysfunction of the pharynx and the striated muscle of the upper oesophagus (34). A TOF of less than 0.9 can thus be associated with a considerable risk of aspiration. Moreover, residual block disturbs the normal chemosensitivity of the carotid bodies by interaction with cholinergic transmission in the chemoreceptor of the glomus caroticum, causing an impaired hypoxic ventilatory response (25). Residual neuromuscular block is thus clearly a risk factor for developing postoperative pulmonary complications. However, in only a few published studies has PORC been considered a separate risk factor; it is therefore impossible to

discern the exact incidence of complications due to PORC within the multifactorial aetiology of hypoventilation, upper airway obstruction and aspiration.

Nevertheless, postoperative complications due to residual block can be both life-threatening and substantially increase the total cost of a surgical intervention. The principal cost of surgery lies in its potential side-effects and postoperative complications. Although the current drive to restrict the expense of medical care at the population level (made necessary by ageing populations and declining resources) should not be allowed to interfere with the best care for the individual patient, improving safety by the use of NMBDs does represent an important opportunity for reducing costs. However, in the 1990s and probably also in the first years of the new millennium, patients still died as a result of PORC (3).

Therefore, four steps are advocated to prevent residual block : avoid long-acting NMBDs, prevent hypothermia (which delays recovery), use objective monitoring of the neuromuscular block, and reverse any TOF ratio < 0.9. Although NMT monitoring is thus indicated for all surgical interventions, it is particularly required in the following (21, 35) :

1. long interventions, where monitoring helps avoid overdosing and the possibility of delayed recovery ;
2. altered pharmacokinetics/pharmacodynamics (pharmacokinetic changes can be expected in patients with hepatic or renal diseases) ;
3. interventions that require absence of moving or straining, where monitoring helps maintain a sufficiently deep level of block ;
4. where no reversal is preferred (in some patients, reversal agents may affect heart–lung function) ;
5. disturbed electrolyte balance, which may alter the blocking effect of some NMBDs (36) ;
6. expected drug interactions (the action of NMBDs can be potentiated or depressed by interaction with some other drugs) (36).

Despite great recent advances in the pharmacology of NMBDs, their effects, onset and recovery times are still unpredictable. The incidence of residual paralysis is still unacceptably high despite the introduction of new agents and monitoring techniques. In addition, the individual patient's response makes it difficult to predict the neuromuscular block accurately, particularly in certain disease states or conditions : the pharmacokinetic parameters of NMBDs are altered in elderly people

and those with elimination organ impairment (37, 38). Drug interactions between NMBDs and, for example, inhalational anaesthetics, local anaesthetics, anti-arrhythmics, aminoglycosides and calcium-channel blockers can influence a patient's response to NMBDs and reversal agents (36). In the light of this wide variability in the effects of NMBDs, optimisation of dosage, possible antagonisation and monitoring of NMT, and a thorough understanding of their limitations, are invaluable for best patient care, especially when continuous infusions of NMBDs are given. FAWCETT *et al.* have demonstrated that the incidence of PORC is higher after infusions of atracurium or vecuronium than after bolus dosing (13).

The specific risk with continuous NMBD administration is indeed PORC : the consequence of misinterpretation of the dose-effect relation. Dose-effect is influenced by the 'time' component in the continuous administration of drugs, the so-called pharmacological context of administration. The factor 'time' is responsible for drug accumulation and disturbs the dose-effect relation when a fixed infusion dose is administered. A possible solution to this problem is to use pharmacokinetic models, such as when hypnotics and/or opioids are administered continuously, but with NMBDs there is the great advantage that a direct-effect monitor exists that has been extensively validated (39).

So, to avoid problems with the continuous administration of NMBDs, one can :

1. optimise the dose requirement over time, as a fixed-dose regimen has a high PORC rate ;
2. measure the effect by NMT monitoring and selectively antagonise the neuromuscular block at the end of surgery ;
3. routinely antagonise the patient's neuromuscular block at the end of surgery, knowing that the classical antagonists may be harmful.

Unfortunately, NMT monitors are only seldom used in daily clinical anaesthetic practice (40). Our group has shown the absolute necessity of NMT monitoring as well as the clinically important role of optimisation techniques for continuous infusions of NMBDs. By optimising the dose in relation to duration, via NMT monitoring, the total anaesthesiological management of the patient was improved, especially when the dose-effect relation was unpredictably disturbed by pathology or type of surgery, as in anaesthesia for liver and cardiac surgery, where these two factors are very important. We studied the effects of the continuous administration of cisatracurium and rocuronium

and the necessity of NMT monitoring during protracted, major surgery without routine pharmacological reversal in patients not in organ failure (41). Even in these patients, NMT monitoring was essential for selective antagonisation and, consequently, the avoidance of complications from antagonists.

We also studied patients with organ failure and/or undergoing special surgical techniques : the dose requirements for an infusion of cisatracurium, the preferred NMBD in liver surgery, during liver transplantation (42). The fixed-dose rule was found incorrect and NMT monitoring obviously necessary in this population. Relying on NMT monitoring, we then optimised the management of anaesthesia and of a continuous infusion of cisatracurium in right-lobe living-donor liver surgery (43). We found that accurate monitoring of a cisatracurium infusion during liver transplantation had important and innovative clinical implications : the immediately postoperative extubation of high-risk patients who had been kept asleep and paralysed for hours (44).

We then drew a parallel with heart surgery where we studied, by means of NMT monitoring, the dose requirements for continuous infusions of cisatracurium and rocuronium in cardiac procedures with hypothermic cardiopulmonary bypass (45). We also found that NMT monitoring was an absolute necessity in patients undergoing off-pump coronary artery bypass surgery in whom extubation at the end of the operation was planned (46).

To conclude, the recent published data (14, 15, 41) and editorials (20, 33) warning against PORC after boluses and infusions of NMBDs mean that residual curarisation is now one of the most feared complications in anaesthesia. The consequent issue may be one of malpractice if NMT monitoring is not used and/or pharmacological antagonisation is not performed.

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