Neuromuscular monitoring and postoperative residual curarization: a meta-analysis
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CRD summary
This review investigated the impact of intra-operative monitoring of neuromuscular function on the incidence of post-operative residual curarisation (PORC). The authors concluded that they could not demonstrate that monitoring decreases PORC incidence. In view of the lack of study details and issues with the meta-analysis of different study designs, these conclusions should be treated with caution.

Authors’ objectives
To investigate the impact of intra-operative monitoring of neuromuscular function on the incidence of post-operative residual curarisation (PORC). The objectives also appeared to include an investigation of the overall incidence of PORC and of a range of variables that may affect the incidence rate.

Searching
PubMed (1964 to 2006), the Cochrane Controlled Trials Register, and ISI Web of Knowledge (1975 to 2006) were searched for eligible studies published in English; the search terms were reported. The reference lists of retrieved articles were also examined. Studies were excluded if only the abstract was available.

Study selection
Study designs of evaluations included in the review
Study designs were not specified by the inclusion criteria. It appeared that studies of any design were included, amongst them randomised controlled trials (RCTs) and other comparative and non-comparative studies.

Specific interventions included in the review
Studies of the monitoring of neuromuscular functioning were eligible for inclusion, although no specific interventions were specified in the inclusion criteria.

The included interventions were conventional peripheral nerve stimulation (PNS) and objective monitoring. PNS was defined as subjective visual or tactile evaluation of responses to evoked stimulation. Objective monitoring was defined as digital real-time display of the train-of-four (TOF) ratio, a measure of the nature and magnitude of neuromuscular blockade.

Participants included in the review
Studies of adult patients were eligible for inclusion. Studies of cardiac patients were excluded. The review included patients who received total intravenous anaesthesia (TIVA), inhalational anaesthetics, or both. In some studies patients received anticholinesterases (neostigmine or pyridostigmine) to reverse the neuromuscular blockade.

Outcomes assessed in the review
Studies were eligible for inclusion if they reported the incidence of PORC. PORC was defined as a TOF ratio of less than 0.7 or less than 0.9. Studies were excluded if the primary outcome variables were unclear.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened potentially relevant studies. It was not stated how any disagreements were resolved.

Assessment of study quality
The Jadad scale was used to assess study quality; points were allocated for randomisation (0 to 2 points), double blinding (0 to 2 points) and description of withdrawals or drop-outs (0 to 1 point). Two reviewers independently
applied the criteria and resolved any disagreements by discussion.

**Data extraction**

Two reviewers independently extracted the data and resolved any disagreements by discussion.

Data on the incidence of PORC were expressed as percentages by study or study arm. Details of the type and dose of neuromuscular blocker, type and duration of anaesthesia, and the use of an antagonist were also extracted.

**Methods of synthesis**

*How were the studies combined?*

Data from each study were normalised using the Freeman-Tukey transformation before pooling in a meta-analysis. Studies were pooled using a random-effects model if there was significant heterogeneity and a fixed-effect model otherwise. Results from cohort studies and RCTs were combined in the meta-analyses to provide a pooled incidence rate for PORC, and corresponding 95% confidence interval (CI; calculated using the inverse of the Freeman-Tukey method). Separate analyses were performed by TOF ratio (<0.7 or <0.9), type of muscle relaxant (long-acting or intermediate-acting) and the use of an intra-operative neuromuscular function monitor (monitored or non-monitored). Pooled results for monitored and non-monitored patients were compared with a t-test. Three relevant studies that used mivacurium were excluded from the meta-analysis because of a lack of data on the incidence of PORC.

*How were differences between studies investigated?*

Statistical heterogeneity was assessed using chi-squared tests and the I-squared statistic, and where there was significant heterogeneity a random-effects model was used. The effects of clinical heterogeneity were investigated using a random-effects weighted linear regression model adjusting for the type of anaesthetic used (TIVA, inhalational, or both), the type of neuromuscular blocker used (long-acting or intermediate-acting) and the TOF threshold used for outcome assessment (<0.7 or <0.9). A similar model was used to investigate the effect of year of study on PORC incidence.

Two sensitivity analyses were conducted. One included only RCT data and compared the pooled incidence rates between monitored and non-monitored populations; the other compared the pooled incidence rates between RCTs and observational studies using t-tests.

**Results of the review**

The review included 24 studies (n=3,375); 13 RCTs and 11 observational studies.

The Jadad score of the included studies ranged from 1 (n=5) to 4 (n=2).

The use of neuromuscular monitoring did not have a statistically significant effect on the incidence of PORC in any of the patient groups. For patients receiving long-acting muscle relaxants with a TOF of less than 0.7, the pooled incidence rate was 0.246 (95% CI: 0.11, 0.41; 7 studies) for monitored patients and 0.422 (95% CI: 0.30, 0.55; 11 studies) for non-monitored patients. For a TOF of less than 0.9, the pooled incidence rate was 0.701 (95% CI: 0.53, 0.85; 4 studies) for monitored patients and 0.741 (95% CI: 0.53, 0.91; 5 studies) for non-monitored patients.

For patients receiving intermediate-acting muscle relaxants with a TOF of less than 0.7, the pooled incidence rate was 0.117 (95% CI: 0.04, 0.23; 8 studies) for monitored patients and 0.128 (95% CI: 0.08, 0.18; 8 studies) for non-monitored patients. For a TOF of less than 0.9, the pooled incidence rates were higher: 0.348 (95% CI: 0.13, 0.61; 84 studies) for monitored patients and 0.544 (95% CI: 0.36, 0.73; 4 studies) for non-monitored patients. For all comparisons there was evidence of considerable heterogeneity (p<0.01; I-squared values ranged from 73.5 to 97.7%).

The weighted regression model found no statistically significant effect of monitoring on the incidence of PORC, regardless of the type of neuromuscular blocker, anaesthetic technique or TOF threshold used. There was also no significant evidence of a decrease in PORC incidence over time.

Sensitivity analyses restricted to RCTs reported a significantly lower rate of PORC in monitored versus non-monitored
populations receiving long-acting neuromuscular blocking agents when using a TOF threshold of less than 0.07 (p=0.017). The incidence of PORC was higher in RCTs than in observational studies at a TOF threshold of less than 0.07, regardless of the type of muscle relaxant used. Other comparisons of the incidence of PORC by study type were not statistically significant, though the number of studies was small.

A discussion of clinical differences between the studies highlighted a number of potential confounding factors in study protocols, such as inappropriate criteria for the initiation of neuromuscular antagonism in the intervention group in one study, which the authors suggested could help to explain the heterogeneous findings. Further analyses were reported in the paper.

**Authors’ conclusions**
The review failed to demonstrate that intra-operative neuromuscular function monitoring decreases the incidence of PORC. The incidence of PORC is significantly reduced by the use of intermediate-acting compared with long-acting neuromuscular blocking drugs.

**CRD commentary**
The review objective was unclear. Initially it appeared to be limited to the effects of monitoring on the incidence of PORC but the review also reported on the effect of other variables on PORC incidence. The inclusion criteria were not fully stated but did mention eligible participants and outcomes. The search was limited and only included studies published in full in English, which might have resulted in some studies being missed. Two reviewers independently undertook the study selection and data extraction, thus reducing the risk of reviewer error and bias. The information provided about the primary studies was inadequate, with little detail of the study design other than whether the study was an RCT or not. The only indication of study quality was the Jadad score, which has limitations and is designed to assess RCTs, not observational studies.

There was considerable heterogeneity in all the subgroups pooled in the meta-analyses, and the analyses also pooled data from controlled and uncontrolled studies; the reliability of the pooled results is therefore questionable. The authors noted that the timing of outcome measures varied considerably in the included studies, which might be an additional possible source of bias. There were some sensitivity analyses of the results of the RCTs alone, but only the pooled results were presented, without any confidence intervals or individual study results; the reliability of these conclusions cannot therefore be assessed. The authors discussed some of the studies with regard to possible reasons for differences between their results in terms of patient treatment and study conduct, but this level of detail would have been better tabulated for all studies. Given these potential problems with the study pooling and lack of detail on the individual studies, the authors' conclusions should be treated with caution.

**Implications of the review for practice and research**
Practice: The authors stated that the evidence does not substantiate the view that neuromuscular monitoring reduces the incidence of PORC, but that this may be due to poor study design. They stressed the need to routinely antagonise non-depolarising neuromuscular block in order to reduce the risk of PORC.

Research: The authors did not clearly state any implications for future research.

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