Author’s response to reviews

Title: Development of an algorithm using clinical tests to avoid post-operative residual neuromuscular block

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Development of an algorithm using clinical tests to avoid post-operative residual neuromuscular block

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BMC Anesthesiology
Dear editor,

Thank you very much for the possibility to improve our manuscript by revision.

Reviewer 1:
We thank reviewer 1 for the constructive comments.

Comment 1:
I completely agree with the authors that a sensitive test is needed for the diagnosis of PORC in the PACU. However, I think you should make clear in the discussion that decision making on extubating the patient in the OR should be based not on clinical signs but on objective neuromuscular monitoring. I realized, that the authors have the same opinion but this has to be explicitly addressed.

Answer 1:
We agree with reviewer 1 that the most effective way to avoid PORC is objective neuromuscular monitoring in combination with reversal of neuromuscular blockade. To emphasize this fact we added the red coloured parts in the introduction part (page 4, line 3):

Use of neuromuscular monitoring together with pharmacological reversal of neuromuscular blocking drugs in the operation room is able to reduce the incidence of residual paralysis in patients arriving in the postoperative care unit (PACU), especially when a quantitative monitoring device is used [1,2]

Furthermore we emphasized this issue by introduction of the red coloured words in the discussion (page 12, line 19):
There is no doubt that calibrated, quantitative neuromuscular monitoring is the gold standard to measure neuromuscular function during anaesthesia and before extubation [21].

Comment 2:

According to the results of previous surveys among anesthetists in the US and Europe, our colleagues consider the incidence of PORC much lower than it in fact is and additionally some of them rely on clinical tests with low sensitivity (such as TV or inspiratory force). Additionally, some clinicians decide not to use reversal agents before extubation at all based on their routine clinical judgment. In a recent study from Nemes et al. (Impact of reversal strategies on the incidence of postoperative residual paralysis after rocuronium relaxation without neuromuscular monitoring: A partially randomised placebo controlled trial. Eur J Anaesthesiol. 2016 Dec 26.doi: 10.1097/EJA.0000000000000585.) it has been shown that this strategy may increase the incidence of PORC. You may include a brief description on this in the discussion section in order to support the importance of your study.

Answer 2:

We agree with reviewer 1 that pharmacological reversal without objective neuromuscular monitoring is not able to prevent PORC. This underlines the importance of our study. We pointed this out with the following sentence (discussion: page 12, line 28-32):

Nevertheless, the risk to overlook residual or reoccurrence of neuromuscular block after anaesthesia, i.e. in the PACU, necessitates a valid tool for differential diagnostic reasons [22, 23]. This is undergirded by the fact that even with the use of sugammadex without neuromuscular monitoring TOFR in the PACU still remains less than 0.9 in almost 9.4% [24].

To incorporate the literature mentioned by reviewer 1 we introduced the following part (discussion: page 14, line 27):

But neither pharmacological reversal with neostigmine nor with sugammadex based on non-systematic clinical signs of muscle weakness are able to avoid PORC [39].
Literature:


Comment 3:

In fact, an important limitation of the study is that only ASA I-II patients were included. However, the material is innovative and the algorithm has to be tested in later studies among ASA III-IV patients as well.

Answer 3:

We agree with reviewer 1 that this is one limitation of our study. We pointed this out (discussion: page 14, line 42-51).

There are limitations to the present investigation. First, the algorithm was developed in a well-defined group of patients (ASA 1, 2) without organ dysfunction. Second, the relatively young study population (18-65 years) was scheduled just for elective, low risk, surgical procedures. Third, just short-acting anesthetic medication (desflurane, remifentanil) was used, enabling sufficient alertness and cooperation after extubation for the clinical assessment. Fourth, swallowing of 20 ml water as a part of the algorithm might provoke aspiration in patients with residual paralysis.

Furthermore we hinted out the future studies are necessary to examine other populations (discussion: page 15, line 8-11):

Further clinical studies are necessary to test this muscle function algorithm in other populations (ASA 3-4, age > 65 years) and varying clinical settings.
Comment 4:

My this reviewer just propose that authors include a brief description of the proposed algorithm of clinical signs that was proved to be sensitively detect TOFR 0.9 in the discussion section.

Answer 4:

Unfortunately comment 4 is ambiguous. So we tried to facilitate the understanding of the swallowing test by the following red coloured addition (page 13, line 55):

After a successfully performed 5 second arm and a 5 second head lift (node 1, node 7, Figure 3), expectedly, the simplistic test to swallow 20 ml water was not able to discriminate between TOFR < 0.9 and TOFR > 0.9 alone. Nevertheless, the swallowing test contributed to the algorithm exactly at this TOFR (node 9, Figure 3).

Reviewer 2:

Thank you very much for the comments.

Comment 1:

Introduction:

The primary outcome parameter should be defined.

Answer 1:

This study did not define any outcome parameter. Aim of the study was to develop an algorithm, which should be comparably potent identifying a residual neuromuscular blockade than the gold standard, i.e. quantitative neuromuscular monitoring. During validation of the algorithm again the algorithm was compared with other techniques to identify residual neuromuscular blockade.
The TOFR $\geq 0.7$, which is expected to avoid major complications, and TOFR $\geq 0.9$, which is typically defined as the sufficient level of recovery of neuromuscular function, were used to compare the techniques, but not in the meaning of a primary outcome variable.

Comment 2:
Methods:

Page 7, line 29: What is meant with "contralateral arm? The arm without EMG? Was EMG performed in the PACU, too? If not, why did the authors change the location of the neuromuscular measurements?

Answer 2:
The contralateral arm to the EMG arm was used for the clinical muscle function tests and for the qualitative/quantitative AMG. EMG was not performed in the PACU. After extubation it was necessary to measure EMG (one hand) parallel to the clinical judgement (other arm) to examine correlation between muscle function tests and objective neuromuscular monitoring (EMG). So it was necessary to use both arms.

Comment 3:
Statistics: Was a sample size calculation and a power analysis performed in advance? Again, what was the primary outcome parameter?

I do not possess adequate statistical knowledge with regard to that questions. Therefore I would recommend an additional statistical review.

Answer 3:
As mentioned above the TOFR $\geq 0.7$ was used as necessary level of recovery of the neuromuscular function to avoid major complications. But TOFR $\geq 0.7$ is not a primary outcome in its typical meaning, because a study comparing two or more techniques uses such an outcome value as part of the methods only. This becomes more obvious in two aspects of the study. (1) The study was designed to provoke a high prevalence of residual blockades, in order to have many cases to identify the specific improvement of the algorithm by a clinical test. (2) on the other hand, we had to use data from outcomes studies with typical prevalence to discuss the clinical meaning of the tested measures (Figure 5).
Sample size considerations therefore are meaningful for the validation of the measures to identify TOFR<0.7. We primarily focused on a measure with high sensitivity (>90%) with an accuracy of the estimate <10%. Based on these assumptions 36 patients are necessary, with TOFR < 0.7 and 36 patients with TOFR ≥ 0.7. In the development cohort 49% had TOFR ≥ 0.7 and 51% had TOFR < 0.7. 95%-confidence intervals reached from 41% to 59%. Therefore, we decided to include 100 patients for the validation assuming not less than 40 patients with TOFR < 0.7 as well as not less than 40 patients with TOFR ≥ 0.7.

A respective section is added to the statistics:

Sample size was calculated based on the assumptions that the algorithm most probably will not be able to predict TOFR ≥ 0.9, but a TOFR ≥ 0.7 is a level of recovery of the neuromuscular function possibly sufficient to avoid major complications. Therefore, we primarily focused on a high sensitivity (> 90%) with an accuracy of the estimate < 10%, resulting in a necessary sample of at least 36 patients with TOFR < 0.7 and at least 36 patients with TOFR ≥ 0.7. In the development cohort, 49% of patients had a TOFR ≥ 0.7 and 51% had a TOFR < 0.7, 95%-confidence intervals reached from 41% to 59%. Therefore, we decided to include 100 patients for the validation assuming to result in at least 40 patients with TOFR < 0.7 as well as at least 40 patients with TOFR ≥ 0.7.

Comment 4:

Results:

The rate of patients requiring reversal of the neuromuscular block is remarkably high. However, the authors address that point in the discussion.

Answer 4:

We agree with reviewer 2. We discussed this point in page 14, line 28-39:

It was not our aim to provoke extubation at such deep levels. The members of the study staff, however, routinely apply quantitative neuromuscular monitoring when paralyzing their patients and, therefore, were less experienced to work without it. Nevertheless, no patient was harmed by one of the typical complications of a residual block. This might be due to the short assessment period before reversal with 40 µg/kg neostigmine, the thorough care taking by the study staff
expecting patients with a residual block, but also the patients’ preoperative information that such a scenario might happen.

Comment 5:
Page 12, line 44: What is meant with "much less"

Answer 5:
26 (13%) patients were excluded because of bad EMG signal quality. In contrast to this just 4.5 % of patients failed to perform clinical muscle function tests. So clinical test might be more robust in this setting.

Comment 6:
Swallowing test: As already stated, the risk of a swallowing test with regard to pulmonary aspiration should be addressed in the discussion. The authors must explain, why they preferred this test.

Answer 6:
We preferred the swallowing test because the upper airway and swallowing function is the key point for defining acceptable TOFR > 0.9. CART analysis showed that the swallowing test contributed to the test exactly at a TOFR = 0.9. In contrast to this the spatula pressure test is very difficult to implement and was not so successful in the CART analysis.

We addressed the aspiration risk in the discussion as follows (page 14, line 32-40):
Although there was a potential risk of pulmonary aspiration using the swallowing test (20 ml of water), we observed no makro aspiration. Mikro aspiration could not be excluded clinically.

Comment 7:
Tables and figures: All abbreviations should be defined in the legend, including T1/T0, TOFR etc.
Answer 7:

We inserted following following red coloured abbreviation:

-(page 24, line 28): T1/T0 = first stimulation related to the baseline value

We hope that we have revised our manuscript adequately.

Yours sincerely

Dr. C. Unterbuchner.