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ORIGINAL RESEARCH

Development and validation of an android-based application for anaesthesia neuromuscular monitoring

Hugo Carvalho[1] · **Michael Verdonck**[2] · **Johan Berghmans**[3] · **Jan Poelaert**[1]

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Abstract
Quantitative neuromuscular block (NMB) assessment is an internationally recognised necessity in anesthesia care whenever neuromuscular blocking agents are administered. Despite this, the incidence of residual neuromuscular block and its associated major respiratory morbidity and mortality remain unacceptably high considering its preventable nature. Recent surveys show that quantitative NMB assessment is not consistently employed by anesthesiologists. Availability, price and practical concerns are some of the factors determining this phenomenon. Clinically assess and validate an Android cell phone application conceived specifically for NMB Monitoring in the anesthesia setting. Twenty-two adult ASA I to III patients scheduled to undergo elective surgical procedures under general anaesthesia requiring administration of a neuromuscular blocking agent were included. After anaesthesia induction, the grade of neuromuscular block was assessed at multiple independent time-points by paired comparison of the train of four (TOF) Ratios obtained by a Stimpod™ accelerometer and the currently developed application. Accelerometric measurements were made at the patient's hand after retrograde supramaximal stimulation of the ipsilateral ulnar nerve. TOF-ratios were subjected to bias analysis with 0.001 as the a priori established clinical significance cut-off. The difference between the two methods averaged 0.0004 (95% limits of agreement: ±0.12), with 83.3% of the differences being under 0.05. This average inter-method difference was not significantly different than the a priori hypothesized difference cut-off of 0.001 ($p = 0.78$). Lin's concordance correlation coefficient and Pearson's correlation were both of 0.98. The custom developed Android application proved accurate for diagnosis of residual neuromuscular block.

Keywords Anaesthesia · Neuromuscular monitoring · Android · Mobile application · App · Cellphone

1 Introduction

Since Harold Randall Griffith pioneered by the use of curare during anaesthesia by administering it to a young man during an appendectomy in Montreal, the practice of anaesthesia has completely changed and the world of Neuromuscular Blocking has been thoroughly fine-tuned [1]: increased knowledge and clinical experience, development of new Neuromuscular Blocking Agents (NMBA) with fewer side-effects and well-studied pharmacokinetic profiles, introduction of new antagonizing drugs such as Sugammadex, as well as refinement of neuromuscular block measuring instruments [2]. NMBAs are routinely administered to patients in a multiplicity of anaesthetic settings, and the possibility and availability of instruments allowing the accurate measurement of the degree of neuromuscular block has raised the standards of their use and reversal. The absence of a residual neuromuscular blockade is now widely considered an anesthetic must, as incomplete recovery has been long-established as a strong contributor to post-anesthesia morbidity and mortality [3, 4]. In order to evaluate this recovery, one recurs to the evaluation of the number and intensity of muscular contractions elicited by specific electrical nerve stimulation. This evaluation can either be done subjectively/qualitatively (visual/tactile assessment) or objectively/quantitatively (peripheral device use with numeric quantification). Considering the proven

Hugo Carvalho and Michael Verdonck have contributed equally to this work.

✉ Hugo Carvalho
Carvalho.hn@gmail.com

[1] Dienst Anesthesiologie en Perioperatieve Geneeskunde, Universitair Ziekenhuis Brussel, Brussels, Belgium

[2] Business Informatics Research Group, Universiteit Gent, Ghent, Belgium

[3] Dienst Anesthesie en Reanimatie, ZNA Middelheim, Antwerp, Belgium

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inconsistent, inter/intra-variable and inaccurate character of the human senses to estimate adequate neuromuscular recovery after NMBA use, the proper assessment of neuromuscular recovery can only be done by means of objective methods [3]. Within this last category one can make use of mechanomyography (force of contraction measurement, the physiological gold standard method), Electromyography (measurement of the amplitude of compound muscle action potential), kinemyography (unidimensional piezoelectric transducer-measured muscle movement), phonomyography (sound intensity provoked by muscular activity) an acceleromyography (uni/multidirectional muscle acceleration measurement). Once mechanomyography has a highly impractical and time-consuming setup, it is not used in daily practice. Accelerometry, on the other hand, not only entails more practicality but also a clinically acceptable sensibility and sensitivity for neuromuscular evaluation, being thus the most commonly used quantitative neuromuscular assessment method in daily anesthesia practice.

For purpose of accelerometric contraction analysis, one of the most widely used electrical stimulation patterns is the TOF: transcutaneous application of a series of 4 square-wave supra-maximal electrical stimuli over the course of a nerve of choice (most commonly the ulnar nerve). These are applied at a frequency of 2 Hz, and each with a duration of 0.2 ms. These stimuli elicit a motor response on the adductor pollicis muscle, which on its turn dictates the adduction of the thumb. The acceleration of this movement can be followed by means of an uni/multi-directional accelerometer attached to the thumb. The ratio of the acceleration of the 4th and 1st elicited contractions is called the TOF-ratio—a clinically and scientifically established method of assessing neuromuscular block recovery. A value of 1 translates a full recovery of the muscular function of a patient. In modern Anesthesia, the bar for deeming recovery as adequate has been set at a minimum of a TOF-ratio of >0.9, with some authors advocating a ratio of 1 as the only acceptable and complications-avoiding result [3, 5–9].

Although an effective measurement of muscular recovery parameters is necessary, daily clinical limitations and habits dictate other practices [6–9]. A significant share of anesthesiologists (up to 20%) never uses quantitative monitoring after NMBA use [6]. Medical devices are expensive and not always available for immediate use. Some devices are also only able to deliver the electrical impulses, but not to measure acceleromyographic parameters. These limitations often force anaesthetists to undertake on-the-spot guess-practices (assuming recovery based on a particular NMBA's half-life and its last administered dose), or "d'office" actions (standard NMBA reversal) to determine if a patient has adequately recovered. These methods are inherently associated with major pitfalls, and result frequently in unnoticed residual neuromuscular block (incidence up to 60%) [8, 9]. These iatrogenic side-effects and are major determinants of a high postoperative respiratory morbidity and mortality (up to 65% incidence when associated with residual neuromuscular block) [6–11].

In this study we aim to assess the capability of a dedicated smartphone application to transform and incorporate a Smartphone's accelerometric data to accurately measure TOF-ratio in an anaesthesia setting and to compare it to commercially used and established neuromuscular block measuring devices.

2 Methods

2.1 Study design

The present study was set up as a prospective, interventional, longitudinal, and quantitative clinical trial.

This trial was conducted in accordance with the established protocol after approval by the Medical Ethical Committee of the ZNA Middelheim Hospital (Board License 009-OG 031, ZNA Middelheim, Antwerp, Belgium) and followed current Good Clinical Practice guidelines and applicable law(s). Compliance with these standards provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Helsinki declaration on patient safety in anaesthesia, and that the clinical trial data are credible. Informed consent was obtained from all individual participants included in the study.

2.2 Patient population

2.2.1 Inclusion criteria

Patients above the age of 18 with an American Society of Anaesthesiology (ASA) physical status classification I to III scheduled to undergo elective surgical procedures under general anaesthesia requiring use of a non-depolarizing neuromuscular blocking agent (according to clinical practice at ZNA Middelheim) will be eligible as potential participants.

2.2.2 Exclusion criteria

- Known or suspected central or peripheral neuropathies of any etiology
- Muscular dystrophies
- Skin burns and trauma at measurement sites (arms).
- Musculo-tendinopathies of the arms and hands.
- All conditions that might be judged to alter appropriate peripheral neuromuscular conduction. Examples include: documented peripheral neuropathy of any etiology (Guillian–Barre syndrome, diabetic/alcoholic polyneuropa-

thy,…), trauma, distal compartment syndrome, and overt peripheral oedema with increased compartimental pressure.
- Fragile skin impeding placement of electrocardiogram electrodes at measurement sites.
- Allergy to ECG electrodes
- Intra-operative position impeding proper use of any of the two used neuromuscular monitors.
- Device failure (either the TOF monitoring device or the cellphone)
- Failure to properly stabilize the patient's hand in supination (so that the smartphone won't dislocate itself during measurements)
- Patient premedication judged to interfere with cognitive function and thus thought to affect proper comprehension of the study concept and informed consent (example: excessive sedation/confusion due to premedication with benzodiazepines)

2.2.3 Replacement of subjects

Continuous inclusion of new patients, with replacement of drop-outs on a 1:1 basis.

2.2.4 Restrictions and prohibitions for the subjects

None.

2.3 Protocol

After reviewing the medical records of the patient, he/she was informed about the study during pre-anaesthesia interview by the investigator himself. The final signed informed consent was obtained at the day of surgery.

Patient premedication (midazolam/alprazolam) was variably employed as per institutional practice and according to the clinical scenario.

After patient transport into the holding area at the operation theatre, the sign-in ("check-in") procedure took place, after which the patient was transported to the designated operation room.

At the operating theatre, standard patient monitoring was attached to the patient (oxygen saturation/plethysmography), 3 or 5-lead ECG, NIBP and extra monitoring devices placed on a case-to-case basis and according to institutional practice, and a peripheral intravenous line was cannulated.

Before anaesthesia induction, one of the patient's arms (measuring side) was positioned in a proper padded arm support. Subsequently there was confirmation of an arm abduction under 90°, hand in neutral supine position, and absence of pressure points. Active feedback on position was requested from the patient before final arm fixation.

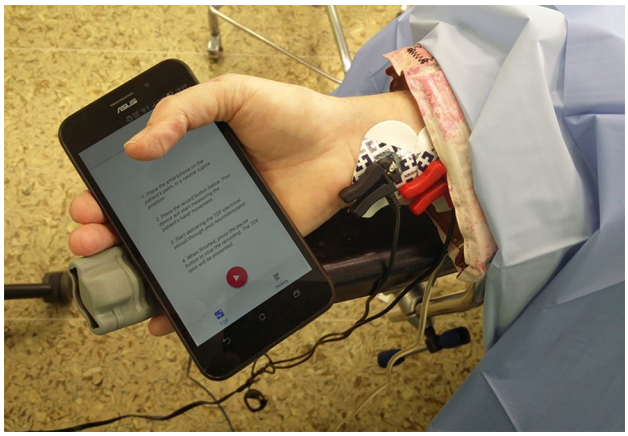

Fig. 1 Neutral cellphone hand positioning

Fig. 2 Illustration of the auxillliary tape fixation. Upper and lower poles of the cellphone fixated to the hand dorsum in a continuous fashion (single tape line). Lateral cellphone edges bounded by the tenar eminance and palmar surface of the middle phalanges (not taped)

After proper positioning, anaesthesia induction took place. A hypnotic and an opioid analgesic agent were administered, and after confirmation of a "can ventilate" scenario, a non-depolarizing neuromuscular blocking agent (NMBA) was administered and an naso/orotracheal tube inserted according to need. Anaesthesia maintenance was achieved with Sevoflurane and/or Propofol + Remifentanil according to need. Boli of opioids or NMBAs were also given according to need. Post-operative preventive anti-nociceptive medication administration as per in-house protocol (diclofenac, paracetamol, tradonal according to need, age class and possible contraindications).

According to Stimpod's product specifications, placement of the Negative and Positive electrodes of the Neuromuscular monitor/stimulator over the course of the nervus ulnaris at the level of the distal forearm. Attachment of Stimpod's accelerometer to the ipsilateral thumb of the patient (Figs. 1, 2).

Neuromuscular block degree measurement began after post-induction full anaesthetic stabilization of the patient

provided four adductor pollicis muscle contractions were present after supramaximal stimulation of the nervus ulnaris in a Train of Four pattern (four impulses at 2 Hz frequency). Measurements were consistently made in pairs to avoid inducing a time-dependent recovery bias. A minimum 50 s rest-period between each measurement (within a pair) was employed.

Firstly, the TOF-ratio measurement with the Stimpod accelerometer was done, after which the thumb accelerometer was removed. Subsequently, the cellphone was positioned in the hand of the patient in a neutral and non-forcing fashion (Fig. 1). Bilateral medical grade tape was used to neutrally and non-restrictively fix the cellphone to the palm (Fig. 2). Before recording the TOF Ratio with the app, one set of TOF contractions was delivered with the single purpose of neutralizing the cellphone's position in the hand, and thus minimizing a dislocation bias in the measurement series. After this neutralizing stimuli, a rest period of 15 s was employed, after which the actual TOF stimulation and ratio measurement by the cellphone application was done.

This measuring sequence was repeated throughout the anaesthesia period whenever it was deemed that no gross movement interference from the surgical table was present.

At the end of the surgery, reversal of neuromuscular block was only undertaken if needed and based on data provided by the Stimpod only.

All measuring devices were removed before patient awakening.

Quality measurement was assured by data recording by the principal investigator.

2.4 Statistical analysis

Sample size was calculated based on specification of the maximum accepted width of the confidence intervals for the agreement of measures [12–14].

In the absence of past comparison studies between NMB monitoring devices with indication of clear cut-offs associated with clinical morbidity and mortality, we dynamically adapted power calculation based on post-hoc results and empiric assumption of what would be an acceptable accuracy for an inter-method difference. In this line of thought, a total of 117 data pairs (thus, a total of 234) measurements were required for a study with the following characteristics:

- $\alpha = 0.05$
- $\beta = 0.05$
- Expected mean of differences: 0.0003
- Expected standard deviation of differences: 0.05
- Maximum allowed difference between methods: 0.13
- Proportion of measuring techniques per patient: 1:1

The individual demographic parameters as well as their variability in the population were calculated.

The main method agreement analysis was based on the "Bland–Altman random effects method for repeated measures data" [12].

Pre-statistical confirmation of a normal distribution was confirmed recurring to the Kolmogorov–Smirnov test (Univariate variable distribution analysis), after which a paired sample t-test was used to properly place confidence intervals on the Bland–Altman Plot.

Data analysis will be performed with SPSS (IBM Corp. IBM SPSS Statistics for Mac., Armonk, NY: IBM Corp.).

Power analysis was performed both a priori and post-hoc with G*Power (Statistical Power Analyses for Windows and Mac, Release 3.1.9.3, 2018, Heinrich-Heine-Universität Düsseldorf).

3 Results

The current study successfully included a total of 22 patients, corresponding to a sample size of 142 data pairs (284 measurement points), a value above the required 117

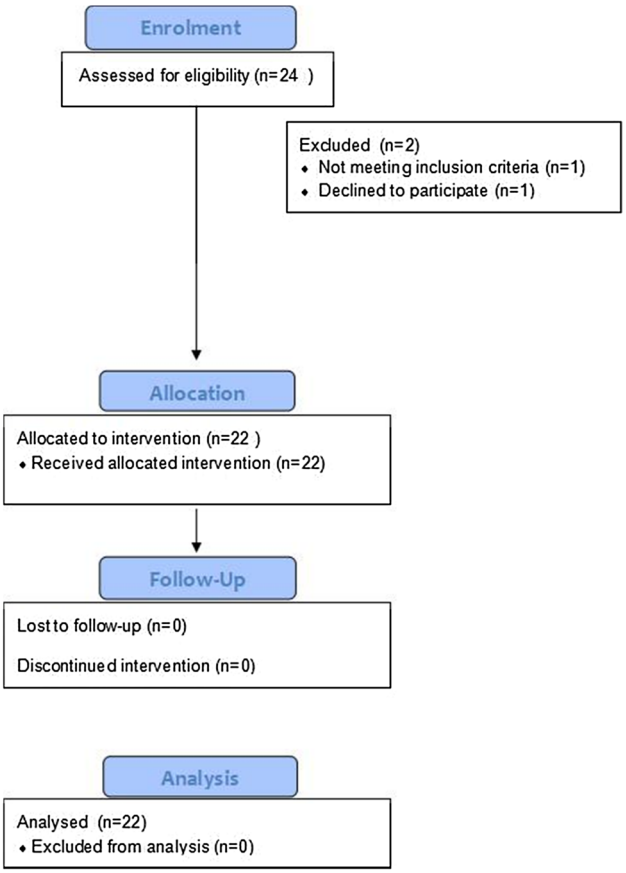

Fig. 3 CONSORT flow diagram

Table 1 Study's population demographics and anesthetic details

Patients (n)	
Male	11 (50%)
Female	11 (50%)
Average weight (kg)	68.7 (43–103)
Average height (cm)	168 (154–187)
BMI (kg/m^2)	24.1 (154–187)
Average anesthesia time (min)	131 (26–599)
Airway (n)	
Orotracheal tube	17 (77%)
Nasotracheal tube	2 (9%)
Laryngeal mask	3 (14%)
Anesthesia induction type (n)	
IV	22 (100%)
Anesthesia maintenance type (n)	
Sevoflurane	21 (95%)
TIVA (Propofol + Ultiva TCi)	1 (5%)
NMBA used	
Rocuronium	6 (27%)
Atracurium	12 (55%)
Mivacurium	4 (18%)
Surgery subspecialty (n)	
General surgery	12 (55%)
Obstetrics	1 (5%)
Neurosurgery (cranial)	2 (9%)
Nose–ear–throat	1 (5%)
Ophthalmology	2 (9%)
Maxillofacial	2 (9%)
Vascular	1 (5%)
Orthopedics	1 (5%)

Presented values correspond to patient numbers, with the corresponding study's population percentage between parenthesis

BMI body mass index, *NMBA* neuromuscular blocking agent

data pairs for the specified power characteristics. The study's CONSORT flow diagram is displayed in Fig. 3. The population's demographics and corresponding anesthetic details are displayed in Table 1.

The 142 data pairs were tested through means of a paired sample t-test for means, with an cut-off significance TOF Ratio (range 0–1) of 0.001. A difference between the two TOF measuring methods significantly different from the hypothesized could not be found ($p = 0.78$, t-stat $= -0.27$, t-critical two tail $= 1.98$, 141 degrees of freedom). In fact, the two measuring methods had an average difference (d) of 0.0003 (Standard deviation 0.05, Upper Limit of agreement 0.12, lower limit of agreement -0.12, $\alpha = 0.05$). Based on this difference analysis, a Bland–Altman plot was constructed (Fig. 4), together with the classical linear regression equation (Fig. 5).

The variance within both measurement methods was of 0.10. The Pearson correlation product between the two methods was of 0.98. Lin's concordance correlation coefficient (ρc) was of 0.983 (95% CI 0.976–0.987).

The proportion of measurements whose absolute difference was within a threshold of 0.05 was of 83.3%.

4 Discussion

This method-agreement study showed a significantly low (0.0003) difference between the TOF-ratio calculated with a dedicated android cell phone application and the one obtained by the Stimpod accelerometer. This small degree of difference is highly unlikely to be of clinical significance, although there are no studies suggesting cut-offs for comparison purposes.

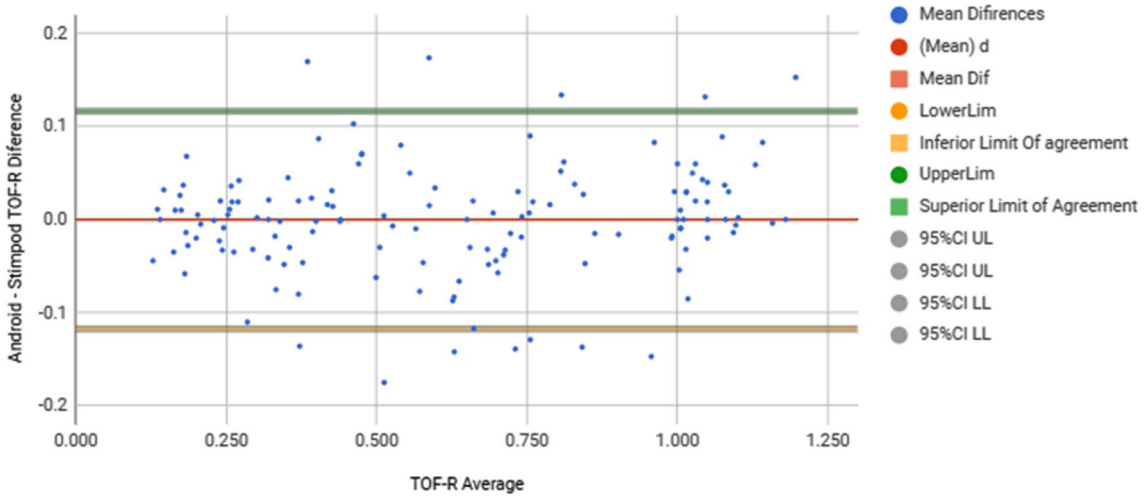

Fig. 4 Bland–Altman plot. Lines: *Red* average difference; *Green* upper limit of agreement; *Yellow* lower limit of agreement. *95% CI* 95% Confidence Interval, *UL* upper limit of agreement, *LL* lower limit of agreement. Point overlap indicated by increased spot density

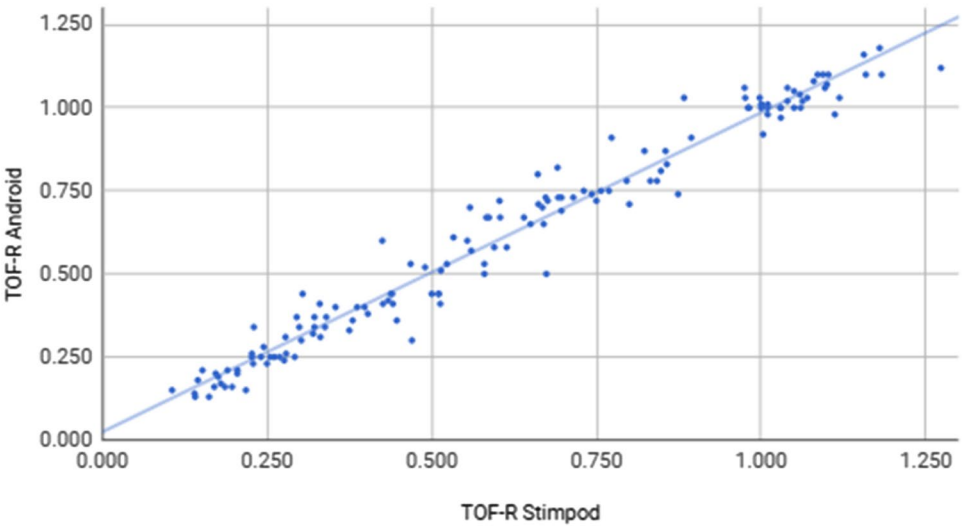

Fig. 5 Scatter plot. Regression line equation: $0.961x + 0.0245$ ($R^2 = 0.966$)

Considering the obtained 95% confidence intervals for this inter-method difference (±0.12), the developed application has revealed itself clinically relevant and valid for an accurate diagnosis of residual neuromuscular block, where qualitative assessment methods (tactile and visual estimation) have consistently proved to fail [15–17].

Again, considering the 95% confidence intervals, there is still insufficient data to confidently affirm that the app will confidently diagnose a TOF higher than 0.9, implying a cut-off for a safe extubation. As per example, the obtained 10%-wide confidence intervals mean that an App-shown TOF Ratio of 0.9 can both be 0.8. as 1.0, two situations requiring different approaches (antagonize or wait, versus safely extubate, respectively). Extra data points are needed to confidently narrow the application's confidence range, for which there is ongoing patient enrollment in the study. There is also ongoing algorithmic a signal processing improvement in this sense, for which independent and parallel method comparison data series were set-up.

The application employment revealed itself practical, harmless for the patient and user friendly (Fig. 6). The fact that it can be carried on the pocket of every anesthetist is one of its strongest positive points. It has the possibility to fill the gap where no accelerometric measuring devices are available, and allows a purposeful upcycling of neurostimulators without incorporated accelerometric sensors. Another advantage of the developed app was the absence of the need for calibration, which has shown to condition performance of some commercially available accelerometers [18]. The standard setting of high sensitivity accelerometric sensing (100 Hz) in combination with adaptive data display and dynamic algorithmic TOF calculation meant that no signal gain modulation needed to be introduced. In no situation was a contraction movement missed when compared with the Stimpod™. On the contrary, it happened in often happened that four contractions were sensed by the application, while only 3 or 2 were displayed by the Stimpod.

The cellphone measurement approach does have its limitations, and the inter and intra-model variability cannot be ignored. Different devices use different components, which naturally introduces unaccounted-for variability. Considering however that the sensitive range of incorporated cell phone accelerometers is equal to (or sometimes better) than those of commercialized for anaesthesia use, there is no immediate reason to assume a default solely based on insufficient primary component quality.

Another limitation of the use of a cellphone as a TOF-ratio measuring device is the fact that contractions themselves can dislocate it, further invalidating any subsequent measurements. We tackled this in the same way as current anaesthesia accelerometers: fixation. For this purpose, the cell phone was attached with medical grade tape to the hand in a way to prevent its projection, but that did not restrict the hand's movement. Confirmation of its positioning within the hand was assured in every measurement moment.

Another limitation is inherent to method comparison studies and refers to the validity of the used comparator as an actual gold standard. In fact, although accelerometry is clinically used in anesthesia for diagnostic purposes, it is actually a surrogate measure and a practical alternative to the actual gold-standard—mechanomyography.

As vector analysis can easily be misinterpreted, movement signal processing and analysis constitutes a significant aspect of this project. Bounce and rebound movements need to be properly interpreted and excluded when present for proper data selection. Movement artifacts are a possible confounding effect for every method based on

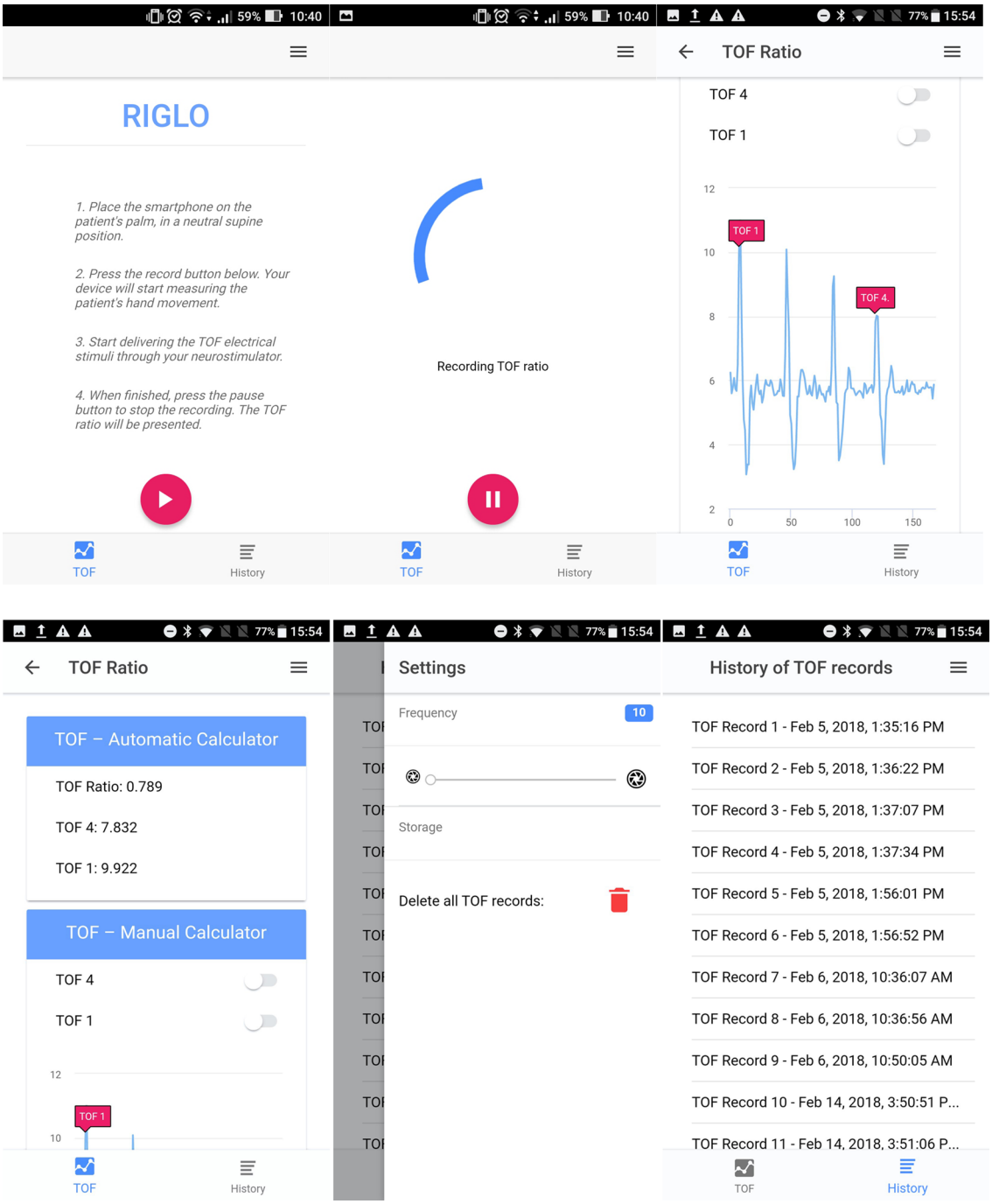

Fig. 6 Application's Interface. *Clockwise*: 1—intro screen, 2—during recording, 3—result display graph. 4—Result display with automatic TOF calculator, 5—settings Menu, 6—record history record

movement analysis. For this purpose, the current app was developed in a cloud environment and collected data at multiple simultaneous frequencies. This facilitated the offline time-interpretation of movement and elimination of high and low pass filters, a previously referred problem on iOS [19]. Our programming code, initially tailored for the Android environment, was also conceived for simultaneous collection of sensor data on an individual basis. This allowed us not only to collect raw individualized data per sensor component, as well to individually incorporate each sub-element on our computing algorithm in order to properly evaluate and weight each input. The collected

encrypted data served also as a base for offline continuous algorithm refinement through self-learning networks (machine learning), the ultimate objective being the reduction of intervariability of signal interpretation by the user, providing feedback as well as optimization of proper TOF Ratio calculation.

5 Conclusion

The currently developed anaesthesia neuromuscular monitoring application revealed itself accurate for proper quantitative diagnosing of residual neuromuscular block during anesthesia. Reliability on it for assertive determination of a TOF Ratio > 0.9 is still not possible and the application is ongoing refinement for this purpose.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Review Article

CLINICAL PRACTICE

Forty years of neuromuscular monitoring and postoperative residual curarisation: a meta-analysis and evaluation of confidence in network meta-analysis

Hugo Carvalho[1,*,†], Michael Verdonck[1,2,†], Wilfried Cools[3], Lieselot Geerts[4], Patrice Forget[5] and Jan Poelaert[1]

[1]Department of Anaesthesia and Perioperative Medicine, Universitair Ziekenhuis Brussel, Brussels, Belgium, [2]Business Informatics Research Group, University of Ghent, Belgium, [3]Interfaculty Center Data Processing & Statistics, Vrije Universiteit Brussel, Brussels, Belgium, [4]Department of Anesthesiology, University of Ghent, Ghent, Belgium and [5]Department of Anaesthesia, NHS Grampian, Institute of Applied Health Sciences, Epidemiology Group, School of Medicine, Medical Science and Nutrition, University of Aberdeen, Aberdeen, UK

*Corresponding author. E-mail: carvalho.hn@gmail.com

†H. Carvalho and M. Verdonck contributed equally to the present work.

Abstract

Background: The reported incidence of postoperative residual curarisation (PORC) is still unacceptably high. The capacity of intraoperative neuromuscular monitoring (NMM) to reduce the incidence of PORC has yet to be established from pooled clinical studies. We conducted a meta-analysis of data from 1979 to 2019 to reanalyse this relationship.
Methods: English language, peer-reviewed, and operation room adult anaesthesia setting articles published between 1979 and 2019 were searched for on PubMed, Cochrane Central Register of Controlled Trials, ISI-WoK, and Scopus. The primary outcome was PORC incidence as defined by an at- or post-extubation train-of-four ratio (TOFR) of lower than 0.7, 0.9, or 1.0. Additional collected variables included the duration of action of neuromuscular blocking agents (NMBAs) used, sugammadex or neostigmine use, and the technique of anaesthesia maintenance.
Results: Fifty-three studies (109 study arms, 12 664 patients) were included. The pooled PORC incidence associated with the use of intermediate duration NMBAs and quantitative NMM was 0.115 (95% confidence interval [CI], 0.057–0.188). This was significantly lower than the PORC rate for both qualitative NMM (0.306; 95% CI, 0.09–0.411) and no NMM (0.331; 95% CI, 0.234–0.435). Anaesthesia type did not significantly affect PORC incidence. Sugammadex use was associated with lower PORC rates. The GRADE global level of evidence was very low and the refined assessment of the network meta-analysis by means of a confidence in network meta-analysis raised concerns on within- and across-study bias.
Conclusions: Quantitative NMM outperforms both subjective and no NMM monitoring in reducing PORC as defined by a TOFR of <0.9.

Keywords: meta-analysis; neuromuscular block; neuromuscular monitoring; postoperative residual curarisation; train-of-four; train-of-four ratio

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Editor's key points

- The authors performed a network meta-analysis to summarise evidence regarding the influence of methods of neuromuscular monitoring on the incidence of postoperative residual neuromuscular block.
- Quantitative neuromuscular monitoring was associated with a significantly lower incidence of residual neuromuscular block than qualitative monitoring (or the use of no monitoring).
- High-quality trials are required to confirm the findings of this meta-analysis.

Neuromuscular blocking agents (NMBAs) are part of the daily anaesthetic practice worldwide. In the USA alone, 51.4 million surgical procedures per annum are estimated to take place.[1] In Europe, estimations approximate 34.8 million procedures.[2] Combined worldwide estimates put forward a global volume of 234.4 million surgical procedures per year.[2] The proportion of these in which NMBAs are used is not accurately known and can be only speculated upon.[1]

Despite international recognition of quantitative neuromuscular monitoring (NMM) as an absolute and core necessity in modern anaesthesia care, the incidence of postoperative residual curarisation (PORC) as a result of ineffective or absent NMM remains unacceptably high (up to 60%) – especially considering its preventable nature.[1,3]

The substandard NMM adoption is attributed to both logistical/material factors (limited availability, suboptimal practicality/ergonomics, time pressure), and to operator-related phenomena (undereducation, overconfidence).[3–6]

Although clinical intuition and expert opinion put NMM forward as essential for PORC prevention, indexed literature reports heterogeneous findings, and this subject has only been addressed once by means of a meta-analysis.[7] Pooling studies from 1979 to 2005, Naguib and colleagues[7] and Viby-Mogensen and colleagues[8] have counter-intuitively failed to statistically demonstrate that intraoperative NMM leads to PORC prevention.

This analysis aims to reanalyse evidence for the effect of different subtypes of intraoperative NMM on PORC. Building on the original meta-analysis, published data to date have been pooled for re-analysis and complemented with a Confidence In Network Meta-analysis (CINeMA).[7]

Methods

Before commencement, the protocolised meta-analysis was registered on the PROSPERO Database (ID 137975, registration number CRD42020137975).

The literature search strategy involved the following databases: PubMed, Cochrane Central Register of Controlled Trials, ISI Web of Knowledge, and Scopus. The keywords used were: Curarisation, Postoperative, Neuromuscular blockers, Muscle relaxants, Residual block, Residual curarisation. Inclusion criteria were: publication between January 2006 and May 2019; English language; peer-reviewed; human adult studies; operating room anaesthesia setting. Exclusion criteria were: abstracts; editorials; paediatric, cardiac surgery, and neuromuscular disorder patients; duplicate populations.

The reported outcome was the incidence of PORC as defined by an at- or post-extubation train-of-four ratio (TOFR) of lower than 0.7, 0.9, or 1.0. The cut-off of 0.7 was included for historical reasons. As reported by Naguib and colleagues,[7] earlier studies used this value for PORC definition. Conversely, more recent studies have reported on a threshold of 1.0.[9–13] Thus, this value was also included.

Data were screened by HC, MV, and LG, with full-text review of potential eligible studies. Disagreements were disputed by referring to a third co-author (WC, PF, JP). A standardised pre-piloted Excel form was used to extract data from the included studies. Extracted information included: study name, authorship, and publication date; participant number subdivided per study arms; study setting; study population and recruitment dates; intervention (intraoperative NMM type, stimulating current in milliamperes) and control conditions; NMBA used and dose; NMBA duration category (short, intermediate, or long); type of anaesthesia (TIVA, volatile anaesthesia [VA], or combined); duration of anaesthesia; use of neostigmine or sugammadex; outcome (PORC defined by a TOFR <0.7, <0.9, or <1.0) and timing of measurement; Oxford quality scoring system and Cochrane Collaboration's risk of bias.[14] Short duration of action NMBAs included the drug succinylcholine. Intermediate duration NMBAs included atracurium, cisatracurium, mivacurium, vecuronium, and rocuronium. Long duration of action NMBAs included gallamine, pancuronium, and *d*-tubocurarine. Missing data were requested from study authors by means of e-mail contact.

The level of certainty was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group guidance.[15,16]

To the constructed database involving articles from 2006 onwards, those of the meta-analysis of Naguib and colleagues[7] (1979–2006) were added. These were similarly re-analysed.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram representing the data processing is presented in Figure 1. The pooled studies and main collected variables are displayed in Table 1.

Statistical analysis

The goal of the primary analysis was to examine whether PORC (defined by post-extubation TOFR values above the cut-off of 0.7, 0.9, or 1.0) was more or less likely depending on the type of NMM used intraoperatively: no monitoring, qualitative monitoring (peripheral nerve stimulation [PNS]), or quantitative monitoring (TOFR quantification). In so far as possible, the evaluation also accounted for the duration category of NMBAs used intraoperatively (short, intermediate, or long duration of action), use of antagonising drugs (sugammadex or neostigmine), type of anaesthesia maintenance technique (VA, TIVA, or both), and year of publication.

The statistical processing of the present meta-analysis was grossly identical to that of Naguib and colleagues, with differences detailed below. A three-level mixed-effect model was used to analyse one or more proportions per study obtained in different conditions.[64] The proportions in each of the relevant conditions were transformed in order to normalise them using the Freeman–Tukey arcsine transformation which resulted in effect size estimates (proportion) and variance. Secondly, these transformed effect sizes were pooled using a linear mixed model conditional on these variances. The lowest of the three levels consisted of the Freeman–Tukey transformed proportions with

appropriately transformed variances. A second-level defined the conditions under which these proportions were obtained, including information, for example on the type of intraoperative NMM/NMBA. The third level was necessary to identify the study so that within-study correlations between proportions can be incorporated. In contrast to Naguib and colleagues and in order to accommodate the embedding of sometimes more than one proportion within a study, an extra level was considered in the statistical model which incorporated within study correlations. Therefore, instead of the originally described DeSimeon and Laird's method, the restricted maximum likelihood (REML) method was used for the computation of estimations.[64] Similar to the original meta-analysis of Naguib, the resulting estimates were then back-transformed to the proportion scale for interpretation purposes.

For all models, assuming the simplest of mixed models, the test for heterogeneity and moderators were significant, suggesting a benefit of inclusion of at least a random intercept in as far as part of these models. The used I^2 test for heterogeneity was linked to the simplest of mixed models only, in which it reflected the variance explained by the second level or equivalently, the intraclass correlation. The more complex model used in the present analysis added an additional variance to the equation, and therefore did not strictly map on the I^2 statistic.

The analysis was repeated twice, once for the proportions related to the TOFR cut-off of 0.9 and once for the proportions related to the 0.7 cut-off. Pairwise contrasts were used to compare the three types of monitoring with Shaffer adjusted *P*-values. A forest plot was used to illustrate the back-transformed proportions for the various studies and their pooled proportions.

An intercorrelation analysis preceded the abovementioned calculations in order to put forward a statistical model without confounding multicollinearity issues. In fact, because of the high intercorrelation concerns between some of the collected variables, a model encompassing all relevant information could not be created. For this purpose, a model accounting for the monitoring type, NMBA duration category, and type of anaesthesia maintenance (main model) was used as the central model to answer the main questions within the present meta-analysis. A secondary analysis addressed the effect of variables such as pharmacological antagonism in combination

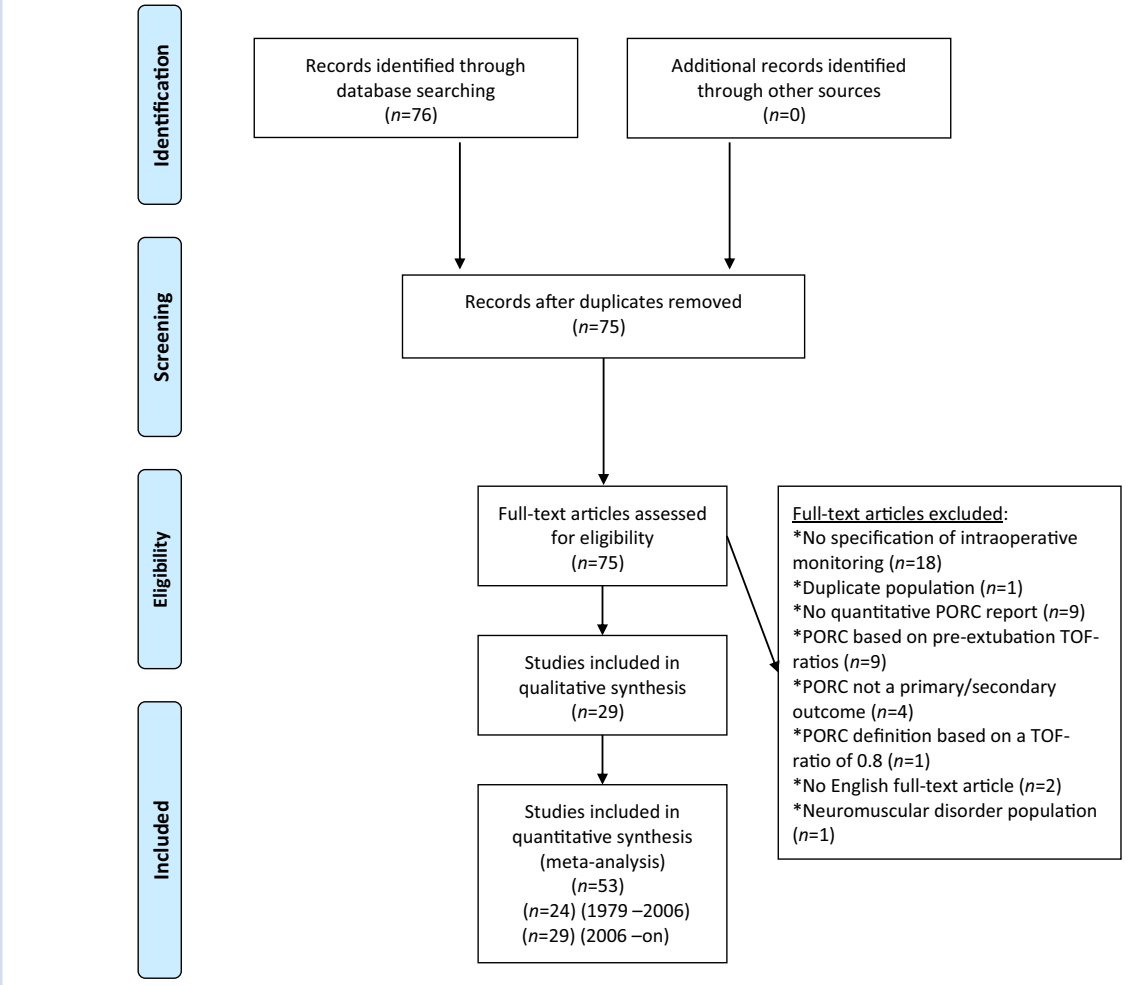

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

Table 1 Summary of studies included in the meta-analysis. PORC determination time point: point in time at which the train-of-four ratio (TOFR) was measured and used to define the presence or absence of PORC according to the selected TOFR cut-off. NMM, neuromuscular monitoring; NR, not reported; PFT, pulmonary function tests; PORC, postoperative residual curarisation; VA, volatile anaesthesia

Year	Authors	Primary outcome	*n*	NMB duration category	Type of anaesthesia maintenance	Intraoperative NMM	NMB antagonism	PORC (TOF <0.7) (*n*)	PORC (TOF <0.9) (*n*)	PORC (TOF <1.0) (*n*)	PORC determination time point	NMM method for PORC definition
1979	Viby-Mogensen and colleagues[17]	PORC	72	Long	NR	None	Neostigmine (67)	30	52	NR	At PACU arrival	Mechanomyography
1984	Lennmarken and Löfström[18]	PORC	48	Long	VA	None	Neostigmine	12	NR	NR	At the PACU (time point not specified)	Mechanomyography
1986	Beemer and Rozental[19]	PORC	100	Long	VA	None	Neostigmine	21	40	NR	At PACU arrival	Not mentioned.
1988	Andersen and colleagues[20]	PORC	30	Intermediate	VA	None	Neostigmine	0	NR	NR	After PACU arrival (time point not specified)	Mechanomyography
			30	Long	VA	None	Neostigmine	6	NR	NR		
1989	Howardy-Hansen and colleagues[21]	PORC	9	Intermediate	VA	NR	Neostigmine	0	NR	NR	At PACU arrival	Mechanomyography
			10	Long	VA	NR	Neostigmine	5	NR	NR		
1990	Pedersen and colleagues[22]	PORC	20	Long	VA	Qualitative	Neostigmine	12	NR	NR	At PACU arrival	Mechanomyography
			20	Long	VA	None	Neostigmine	12	NR	NR		
			20	Intermediate	VA	Qualitative	Neostigmine	8	NR	NR		
			20	Intermediate	VA	None	Neostigmine	3	NR	NR		
1991	Brull and colleagues[23]	PORC	29	Long	VA	Qualitative	Neostigmine	13	NR	NR	Within 15 min of PACU arrival	Unclear
			25	Intermediate	VA	Qualitative	Neostigmine	2	NR	NR		
1991	Ueda and colleagues[24]	PORC	30	Long	NR	None	Neostigmine	25	28	NR	At PACU arrival	Mechanomyography
			60	Long	NR	Qualitative	Neostigmine	19	53	NR		
1995	Shorten and colleagues[25]	PORC	20	Long	VA	Qualitative	Neostigmine	3	NR	NR	At the PACU (20 min after neostigmine administration)	Electromyography
			19	Long	VA	None	Neostigmine	9	NR	NR		
1995	Fawcett and colleagues[26]	PORC	88	Intermediate	NR	Qualitative	Neostigmine	14	74	NR	At PACU arrival	Electromyography
			62	Intermediate	NR	None	Neostigmine	10	52	NR		
1995	Mortensen and colleagues[27]	PORC	21	Long	VA (5), Both (16)	None	Neostigmine	11	17	NR	Immediately after extubation	Acceleromyography
			19	Long	VA (3), Both (16)	Quantitative	Neostigmine	1	10	NR		
1996	Kopman and colleagues[28]	PORC	56	Long	VA (29), TIVA (27)	Qualitative	Neostigmine	2	36	NR	Intraoperatively (5 and 10 min after reversal) and PACU (if TOFR after reversal <0.9)	Mechanomyography
1998	Fruergaard and colleagues[29]	PORC	30	Long	NR	None	Neostigmine	17	25	NR	Immediately after extubation	Mechanomyography
			29	Long	NR	Qualitative	Neostigmine	7	20	NR		
2000	Bissinger and colleagues[30]	PORC Hypoxia Hypercarbia	49	Long	VA (30), TIVA (19)	None	Neostigmine	10	NR	NR	After PACU arrival (at least more than 10 min after arrival)	Acceleromyography
			27	Intermediate	VA (18), TIVA (9)	None	Neostigmine	2	NR	NR		

Continued

Table 1 Continued

Year	Authors	Primary outcome	n	NMB duration category	Type of anaesthesia maintenance	Intraoperative NMM	NMB antagonism	PORC (TOF <0.7) (n)	PORC (TOF <0.9) (n)	PORC (TOF <1.0) (n)	PORC determination time point	NMM method for PORC definition
2000	Baillard and colleagues[31]	PORC	568	Intermediate	TIVA	None (557) Qualitative (11)	Neostigmine (1)	239	NR	NR	At PACU arrival	Acceleromyography
2001	Hayes and colleagues[32]	PORC	19	Intermediate	NR	Qualitative	Neostigmine	NR	13	NR	At PACU Arrival	Acceleromyography
			18	Intermediate	NR	Qualitative	Neostigmine	NR	6	NR		
			24	Intermediate	NR	Qualitative	Neostigmine	NR	8	NR		
			31	Intermediate	NR	None	Neostigmine	NR	19	NR		
			32	Intermediate	NR	None	Neostigmine	NR	20	NR		
			24	Intermediate	NR	None	Neostigmine	NR	11	NR		
2002	Kim and colleagues[33]	PORC	364	Intermediate	VA	None	Pyridostigmine	90	NR	NR	At PACU Arrival	Acceleromyography
			238	Intermediate	VA	None	Pyridostigmine	35	NR	NR		
2002	Gatke and colleagues[34]	PORC	60	Intermediate	TIVA	Quantitative	Neostigmine	1	9	NR	At extubation	Mechanomyography
			60	Intermediate	TIVA	None	Neostigmine	6	18	NR		
2002	Cammu and colleagues[35]	PORC	15	Intermediate	TIVA	Quantitative	Neostigmine (11)	0	0	NR	At extubation	Electromyography
			15	Intermediate	TIVA	Quantitative	Neostigmine (14)	1	1	NR		
2003	Debaene and colleagues[36]	PORC	79	Intermediate	VA	None	None	13	33	NR	At PACU arrival	Acceleromyography
			47	Intermediate	VA	None	None	8	22	NR		
			400	Intermediate	VA	None	None	64	180	NR		
2004	Kopman and colleagues[37]	PORC	30	Intermediate	VA	Qualitative	Neostigmine	0	2	NR	5, 10, and 15 min after neostigmine reversal	Electromyography
			30	Intermediate	VA	Qualitative	Neostigmine	0	5	NR		
2005	Murphy and colleagues[38]	PORC	120	Intermediate	VA	Qualitative	Neostigmine	9	38	NR	At extubation and PACU	Acceleromyography
2005	Baillard and colleagues[39]	PORC	218	Intermediate	NR	Quantitative (131)	Neostigmine (92)	NR	8	NR	At PACU arrival	Acceleromyography
2005	Kopman and colleagues[40]	PORC	20	Intermediate	VA	Quantitative	Neostigmine	8	19	NR	5, 10, 15, and 20 min after neostigmine reversal	Acceleromyography
			20	Intermediate	VA	Quantitative	Neostigmine	9	19	NR		
2006	Khan and colleagues[41]	PORC	49	Intermediate	NR	None	Neostigmine	17	NR	NR	At PACU arrival	Acceleromyography
			58	Intermediate	NR	None	Neostigmine	10	NR	NR		
2007	Maybauer and colleagues[42]	PORC	142	Intermediate	TIVA	Quantitative	None	NR	62	NR	At extubation	Acceleromyography
			175	Intermediate	TIVA	Quantitative	None	NR	99	NR		
2008	Murphy and colleagues[43]	PORC and Respiratory Events	42	Intermediate	VA	Qualitative	Neostigmine	31	7	NR	15 min after PACU admission	Acceleromyography
			42	Intermediate	VA	Qualitative	Neostigmine	0	4	NR		
2008	Murphy and colleagues[44]	PORC	89	Intermediate	VA	Quantitative	Neostigmine	0	4	NR	At PACU arrival	Acceleromyography
			90	Intermediate	VA	Qualitative	Neostigmine	12	15	NR		
2010	Baykara and colleagues[12]	PORC	130	Intermediate	TIVA	None	Neostigmine	12	39	67	At PACU arrival	Acceleromyography
2011	Murphy[45]	PORC	76	Intermediate	VA	Quantitative	Neostigmine	3	11	NR	At PACU arrival	Acceleromyography
			74	Intermediate	VA	Qualitative	Neostigmine	14	37	NR		
2012	Thilen and colleagues[46]	PORC	99	Intermediate	VA	Qualitative	Neostigmine	NR	51	NR	Within 5 min of arrival at the PACU	Acceleromyography
			51	Intermediate	VA	Qualitative	Neostigmine	NR	11	NR		
2012	Kaan and colleagues[47]	PORC	28	Intermediate	VA	None	Neostigmine	NR	3	NR	At PACU arrival	Acceleromyography
			29	Intermediate	VA	None	Neostigmine	NR	5	NR		
			27	Intermediate	VA	None	Neostigmine	NR	3	NR		

Continued

Table 1 Continued

Year	Authors	Primary outcome	*n*	NMB duration category	Type of anaesthesia maintenance	Intraoperative NMM	NMB antagonism	PORC (TOF <0.7) (*n*)	PORC (TOF <0.9) (*n*)	PORC (TOF <1.0) (*n*)	PORC determination time point	NMM method for PORC definition
2012	Kumar and colleagues[48]	PFT, PORC	50	Intermediate	VA	None	Neostigmine	NR	23	NR	At PACU arrival	Acceleromyography
			50	Intermediate	VA	None	Neostigmine	NR	33	NR		
			50	Intermediate	VA	None	Neostigmine	NR	30	NR		
2012	Omar[49]	PORC	23	Intermediate	VA	Quantitative	Neostigmine	3	8	NR	At PACU arrival.	Acceleromyography
			23	Intermediate	VA	Quantitative	Neostigmine	0	2	NR		
2013	Kotake and colleagues[50]	PORC	23	Intermediate	VA (17) TIVA (6)	None	None	NR	3	16	After tracheal extubation	Acceleromyography
			109	Intermediate	VA (73) TIVA (36)	None	Neostigmine	NR	26	73		
			117	Intermediate	VA (80) TIVA (37)	None	Sugammadex	NR	5	54		
2013	Pietraszewski and colleagues[10]	PORC	184	Intermediate	VA	None	None	49	51	12	Within 10 min of arrival at the PACU	Acceleromyography
			231	Intermediate	VA	None	None	46	132	53		
2014	Kocaturk and colleagues[51]	PORC	51	Intermediate	VA	None	Neostigmine	NR	4	NR	At PACU arrival	Acceleromyography
			94	Intermediate	VA	None	Neostigmine	NR	13	NR		
			63	Intermediate	VA	None	Neostigmine	NR	5	NR		
2015	Brueckmann and colleagues[52]	PORC	64	Intermediate	NR	Quantitative	Sugammadex	NR	0	NR	At PACU arrival	Acceleromyography
			10	Intermediate	NR	None	Sugammadex	NR	0	NR		
2015	Murphy[9] and colleagues	PORC	150	Intermediate	VA	Qualitative	Neostigmine	9	45	NR	At PACU arrival	Acceleromyography
			149	Intermediate	VA	Qualitative	Neostigmine	25	86	NR		
2015	El-Tahan and colleagues[53]	PORC	33	Intermediate	VA	Quantitative	Neostigmine	0	2	NR	15 min after PACU arrival	Kinemyography
2015	Rahe-Meyer and colleagues[54]	PORC	69	Intermediate	VA (21) TIVA (47)	Quantitative	Sugammadex	NR	0	NR	At tracheal extubation	Acceleromyography
			67	Intermediate	VA (16) TIVA (53)	Quantitative	None	NR	0	NR		
2016	Yazar and colleagues[55]	PORC	60	Intermediate	VA	Quantitative	Sugammadex	NR	1	NR	5 min after PACU arrival	Acceleromyography
2016	Errando and colleagues[56]	PORC	285	Intermediate	NR	NR	NR	NR	58	NR	At PACU arrival	Acceleromyography
			433	Intermediate	NR	None	NR	NR	132	NR		
2016	Carron and colleagues[37]	Neuromuscular monitoring cost analysis, PORC	128	Intermediate	VA (102) TIVA (26)	Quantitative	Sugammadex	0	0	NR	At tracheal extubation	Not reported.
			128	Intermediate	VA (96) TIVA (32)	Quantitative	Neostigmine	16	41	NR		
			96	Intermediate	VA (71) TIVA (25)	Quantitative	Neostigmine, Sugammadex	61	27	NR		
			96	Intermediate	VA (76) TIVA (20)	Quantitative	Neostigmine	9	14	NR		
2016	Feltracco and colleagues[11]		60	Intermediate	TIVA	Quantitative	Neostigmine	0	2	0	At the PACU (15 min after extubation)	Acceleromyography
			60	Intermediate	TIVA	Quantitative	Neostigmine	0	4	0		
2016	González-Cardenas and colleagues[57]	PORC	228	Intermediate	NR	Quantitative	Neostigmine (17) Sugammadex (15)	NR	21	NR	At PACU arrival	Acceleromyography
2017	Santos and colleagues[13]	PORC	62	Intermediate	VA	None	Neostigmine	NR	NR	28	At PACU arrival	Acceleromyography
			60	Intermediate	VA	None	Neostigmine	NR	NR	15		
2018	Murphy and colleagues[58]	PORC	47	Intermediate	VA	Quantitative	Neostigmine	NR	0	NR	15 min after PACU arrival	Acceleromyography
			43	Intermediate	VA	Quantitative	None	NR	0	NR		

Continued

Table 1 Continued

Year	Authors	Primary outcome	n	NMB duration category	Type of anaesthesia maintenance	Intraoperative NMM	NMB antagonism	PORC (TOF <0.7) (n)	PORC (TOF <0.9) (n)	PORC (TOF <1.0) (n)	PORC determination time point	NMM method for PORC definition
2018	Thilen and colleagues[59]	PORC	41	Intermediate	VA	Qualitative	Neostigmine	1	22	NR	At tracheal extubation	Acceleromyography
			38	Intermediate	VA	Qualitative	Neostigmine	12	14	NR		
2018	Kirmeier and colleagues[60]	Pulmonary complications after NMBAs	4182	Short, Intermediate, Long	NR	Quantitative	Neostigmine (1874)	NR	1343	NR	At extubation	Not reported
2019	Koo and colleagues[61]	Endoscopic surgical conditions (PORC, secondary endpoint)	53	Intermediate	VA	Quantitative	Sugammadex	NR	0	NR	At the PACU (no time point specification)	Acceleromyography
			51	Intermediate	VA	Quantitative	Sugammadex	NR	0	NR		
2019	Saager and colleagues[62]	PORC	171	NR	NR	Qualitative	Neostigmine	NR	112	NR	At tracheal extubation	Acceleromyography
			2	NR	NR	Qualitative	None	NR	1	NR		
			81	NR	NR	None	Neostigmine	NR	51	NR		
			1	NR	NR	None	None	NR	0	NR		
2019	Wardhana and colleagues[63]	PORC	36	Intermediate	VA	None	Neostigmine	NR	6	NR	At PACU arrival	Acceleromyography
			36	Intermediate	VA	Quantitative	Neostigmine	NR	1	NR		

with monitoring type and anaesthesia maintenance but without NMBA duration category. Another secondary analysis addressed the trend over time with publication year in combination with NMM type only. No sensitivity analysis was planned.

Data were classified as missing only if not reported in the original article and eventual accompanying supplements, and only after attempts to contact the corresponding authors were unsuccessful. Further statistical processing was carried out by removing the missing data from the analysis for which missingness at random was assumed.

Selective outcome reporting and publication biases were assessed using the Egger's test and an evaluation of the asymmetry in funnel plots according to Cochrane guidelines.[14,15,65]

The meta-analysis was performed with the R package metafor (R version 3.6.2, 12 December 2019; Metafor package 2.1–0).[66]

A CINeMA was used for purposes of confidence analysis in the network meta-analysis (NMA).[16,67]

A six-node treatment network was graphically summarised and used as base for the later bias relationship presentation within the network (supplementary material). The elements included herein were the duration category of the NMBA (short, intermediate, long) and NMM category (no, qualitative, and quantitative). The included nodes and their relationships derive from their practical combination in the clinical setting. No alternative network geometries were explored.

In the CINeMA analysis, incorporated quality domains were: within-study bias; across-studies bias; indirectness; imprecision: heterogeneity; and incoherence. This analysis referred to the findings relating to the PORC TOFR cut-off of 0.9. Data were listed in 'arm per arm' fashion, with unreported data within a specific study leading to its exclusion from the global CINeMA analysis. Outcome was binarily analysed (presence *vs* absence of PORC) based on a random-effects analysis model with risk ratio (RR) as the effect measure. The PRISMA extension statement for the NMA is provided as a supplementary file.

Results

The proportions obtained in 53 studies were pooled with a three-level mixed model conditional on observed variances. Twenty-four of these studies refer to the period between 1979 and 2006 and were upcycled and re-analysed from the original meta-analysis of Naguib and colleagues.[7] Further indexed database searches referring to the period from 2006 up to May 2019 ultimately yielded 29 additional studies. A total of 12 664 patients were included in the analysis, distributed through a total of 109 study arms. There were no additional studies awaiting classification.

Short-acting NMBAs were used in only one of the studies and were thus excluded from the analysis.[60] Long-acting NMBAs were given to a total of 665 patients, with the remaining majority receiving intermediate-acting NMBAs (n=11 556). In one study with four intervention arms and a total of 255 patients, the duration category of the NMBA could not be identified.[62] Neostigmine was used in 6272 patients, and sugammadex in 663 patients. The remaining patients had either unreported antagonist use or an unclear reversal drug allocation that precluded an unbiased analysis. Only one study included the use of pyridostigmine.[33]

A potent inhalation agent was used as the single anaesthesia maintenance technique in 4631 patients. TIVA was used in 1622 patients. Combined use of volatile anaesthesia and TIVA was used in 111 patients. The remaining cases had either unreported or unclear anaesthesia maintenance technique allocation.

In 4416 patients, no intraoperative NMM was used. Qualitative monitoring was used on 1528 patients, and 6181 were monitored by means of a quantitative device.

The initial intercorrelation analysis showed that when considering only the monitoring type and NMBA duration category, there was no multicollinearity impeding their combination into an additive model. The top-up with additional predictors (anaesthesia type and pharmacological antagonism) raised a clear multicollinearity issue, as the drug duration category was strongly correlated to pharmacological antagonism and publication year. Pharmacological antagonism was on itself strongly related to the publication year. Although publication year related in proximity to data collection year, this might not always be the case, and heterogeneity exists for this purpose.

The relation of both the type of NMBA and of pharmacological antagonism with the publication year complicates drawing conclusions on whether changes in PORC proportions relate to changes in procedure or other changes over time. The correlation coefficients obtained when focusing solely on the intermediate duration NMBA, the most prevalent NMBA category, are as follows: NMM type *vs* publication year, −0.005; NMM type *vs* anaesthesia maintenance type, 0.047; NMM type *vs* antagonist use, 0.233; anaesthesia maintenance type *vs* publication year, −0.293; antagonism use *vs* publication year, 0.287; anaesthesia maintenance type *vs* antagonist use, −0.287.

Not all combinations of intraoperative NMM and NMBA were frequent within the constructed data set. In addition, as stated above, some studied variables were not reported in some of the included studies. At least marginally all three possible combinations of pharmacological antagonism (none, neostigmine, sugammadex) and all three types of anaesthesia maintenance options (potent inhalation agent, TIVA, or both) were observed at least seven times.

Only the intermediate and long-duration NMBA category in combination with the different intraoperative NMM modalities (none, qualitative or quantitative) were kept for further analysis.

Considering the above-mentioned factors, the statistical analysis was subdivided into three different models:

1. *Main model*: a model that included the variables NMM type, NMBA category, and anaesthesia maintenance type.
2. *Antagonist model*: encompassed the NMM category, anaesthesia maintenance type, and pharmacological antagonism as variables.
3. *Trend model*: a model combining the NMM type and publication year in order to make an evolution analysis of monitoring use.

The *main model* retained a total of 51 study arms, part of 39 studies. The *antagonist model, by excluding the NMBA duration category*, held 76 study arms for analysis. Finally, the *trend model* trimmed the observations down to 69.

In all statistical models, analysis of the primary outcome was subdivided according to the TOFR cut-off used for its definition: 0.7, 0.9, and 1. It appeared that data on the PORC with 1.0 TOFR cut-off were not often available, resulting in only five observed proportions. It was therefore excluded from the analysis. Data on PORC associated with the use of pyridostigmine resulted in only two observed proportions and was similarly excluded from the analysis.

Main model

TOFR cut-off 0.7

For the cut-off at 0.7, the analysis suggests that there is no sufficient evidence to conclude on any effect of the type of anaesthesia maintenance to exist. Significant differences between monitoring methods could not be statistically objectivated, and 95% confidence intervals (95% CI) for the different NMM and NMBA combinations overlapped.

Results of the test for residual heterogeneity (QE (32df)=378.47, $P=7.76\times10^{-54}$) and for moderators (QM(6df)=148.27, $P=1.9\times10^{-29}$) were strongly significant.

The variances at the study level and the within-study level (different types of effect) are 0.0125 (27), 0.0217 (38) with the number of unique instances within parentheses. The corresponding forest plot includes the observed proportions and is available as supplementary material.

TOFR cut-off 0.9

The analysis suggests that quantitative monitoring results in lower PORC than both no (coefficient of 0.208; 95% CI, 0.048 to 0.368; $P=0.005$) and qualitative NMM (coefficient of −0.269; 95% CI, −0.423 to −0.114; $P<0.001$). No differences between the NMBA duration category were suggested (coefficient of −0.340; 95% CI, −0.761 to 0.082; $P=0.157$). Qualitative NMM was not significantly different from no NMM (coefficient of −0.061; 95% CI, −0.269 to 0.147; $P=0.866$). Similar to the 0.7 cut-off, there is no suggestion that anaesthesia type influences cumulative PORC proportions.

The test for residual heterogeneity (QE (29df)=803.20, $P=2.46\times10^{-150}$) and for moderators (QM(6df)=139.49, $P=1.28\times10^{-27}$) were strongly significant. The variances at and within study level were 0.0689 (30) and 0.0025 (35), respectively, with the number of unique instances within parentheses.

The forest plot is presented as supplementary material. Owing to the paucity of observations for the combinations of qualitative monitoring and both TIVA and the combination of TIVA and a potent inhalation agent, no back-transformed pooled proportions could be computed.

Considering the absence of an effect of anaesthesia type, a model pooling the PORC rates independently of anaesthesia type was used in order to clearly summarise the findings of this meta-analysis (Table 2). Within this model, quantitative monitoring resulted in lower PORC proportions than both none (coefficient=0.260; 95% CI, 0.144 to 0.376; $P<0.001$) or qualitative intraoperative NMM (coefficient=0.234; 95% CI, 0.119 to 0.348; $P<0.001$). Qualitative monitoring did not significantly differ from no monitoring (coefficient=0.026; 95% CI, −0.082 to 0.135; $P=0.919$). The strong significance of residual heterogeneity (QE (45df)=1178.63, $P=1.83\times10^{-217}$) and moderator tests (QM(4df)=230.31, $P=1.13\times10^{-48}$) was maintained. A model-concordant forest plot is presented in Figure 2.

Antagonist model

TOFR cut-off 0.7

This sub-analysis suggests only a difference between quantitative and no NMM (coefficient=0.264; 95% CI, 0.051 to 0.477;

Table 2 Summary of findings for intermediate NMBAs and PORC defined by a TOF ratio <0.9. PORC, postoperative residual curarisation; TOF ratio, train of four ratio; NMM, neuromuscular monitoring; NMBA, neuromuscular blocking agent; CI, confidence interval

Quantitative *vs* quantitative *vs* no NMM									
Patients: Adult patients. Setting: Elective surgical procedures under general anaesthesia in operation room setting requiring administration of intermediate duration NMBAs. Intervention: Quantitative or qualitative neuromuscular monitoring. Comparison: No neuromuscular monitoring.									
Outcome	**Absolute risk (95% CI)**			**Relative risk**			**Number of studies**		
	Quantitative NMM	**Qualitative NMM**	**No NMM**	**Quantitative *vs* no NMM**	**Qualitative *vs* no NMM**	**Quantitative *vs* qualitative NMM**	**Quantitative NMM**	**Qualitative NMM**	**No NMM**
PORC (TOF ratio <0.9)	0.119 (0.061; 0.191)	0.311 (0.216; 0.415)	0.338 (0.243; 0.440)	0.352	0.920	0.383	18	11	20

P=0.009). Neither pharmacological antagonism nor anaesthesia maintenance type seem to influence PORC. Residual heterogeneity testing (QE (32df)=334.94, $P=3.56\times10^{-52}$) and moderator testing (QM(7df)=147.30, $P=1.50\times10^{-28}$) showed strong significance. The variances at and within study level are 0.0073 (27) and 0.0298 (39), respectively, with the number of unique instances within parentheses.

TOFR cut-off 0.9

Quantitative monitoring yielded lower PORC proportions than qualitative (coefficient=−0.259; 95% CI, −0.413 to −0.106; *P*<0.001) and no NMM (coefficient=0.214; 95% CI, 0.055 to 0.372; *P*=0.004). Qualitative monitoring did not differ significantly from no monitoring (coefficient=−0.047; 95% CI, −0.253 to 0.159; *P*=0.932). Sugammadex was associated with lower PORC than neostigmine (coefficient=0.196; 95% CI, 0.060 to 0.332; *P*=0.002). The forest plot for the pooled PORC proportions is given in the supplementary material.

Results of the test for residual heterogeneity (QE (33df)=678.84, $P=1.33\times10^{-121}$) and for moderators (QM(7df)=145.49, $P=3.60\times10^{-28}$) are again strongly significant. The variances at the study level and the within study level (different types of effect) are 0.0714 (30) and 0.0023 (40), respectively, with the number of unique instances within parentheses.

Trend model

TOFR cut-off 0.7

The analysis suggests that there is only a small difference between quantitative and no NMM (coefficient=0.221; 95% CI, 0.012 to 0.430; *P*=0.035). There is a consistent reduction of PORC incidence with time, although with the variance coefficients' CIs assuming both positive and negative values (coefficient=−0.006; 95% CI, −0.014 to 0.003; *P*=0.295). The isolated proportions plot is available as supplementary material.

Results of the test for residual heterogeneity (QE (42df)=450.10, $P=9.17\times10^{-70}$) and for moderators (QM(4df)=225.06, $P=1.53\times10^{-47}$) were strongly significant. The variances at and within study level are, respectively, 0.0075 (32) and 0.0273 (46), with the number of unique instances within parentheses.

TOFR cut-off 0.9

The analysis confirms the earlier difference between quantitative and qualitative (coefficient of −0.236; 95% CI, −0.343 to −0.129; *P*<0.001), and of no NMM (coefficient=0.246; 95% CI, 0.136 to 0.355; *P*<0.001), with the latter yielding higher PORC proportions. PORC significantly decreased over time (*P*=0.001). Isolated plotting of proportions is represented in Fig 3.

Again, residual heterogeneity (QE (48df)=1649.48, $P=3.13\times10^{-314}$) and moderators (QM(4df)=264.66, $P=4.52\times10^{-56}$) tests were strongly significant. The variances at and within study level are, respectively, 0.0620 (41) and 0.0009 (52), with the number of unique instances within parentheses.

Confidence in network meta-analysis

A network plotting of bias relationship within the present meta-analysis was made selectively for the PORC TOFR cut-

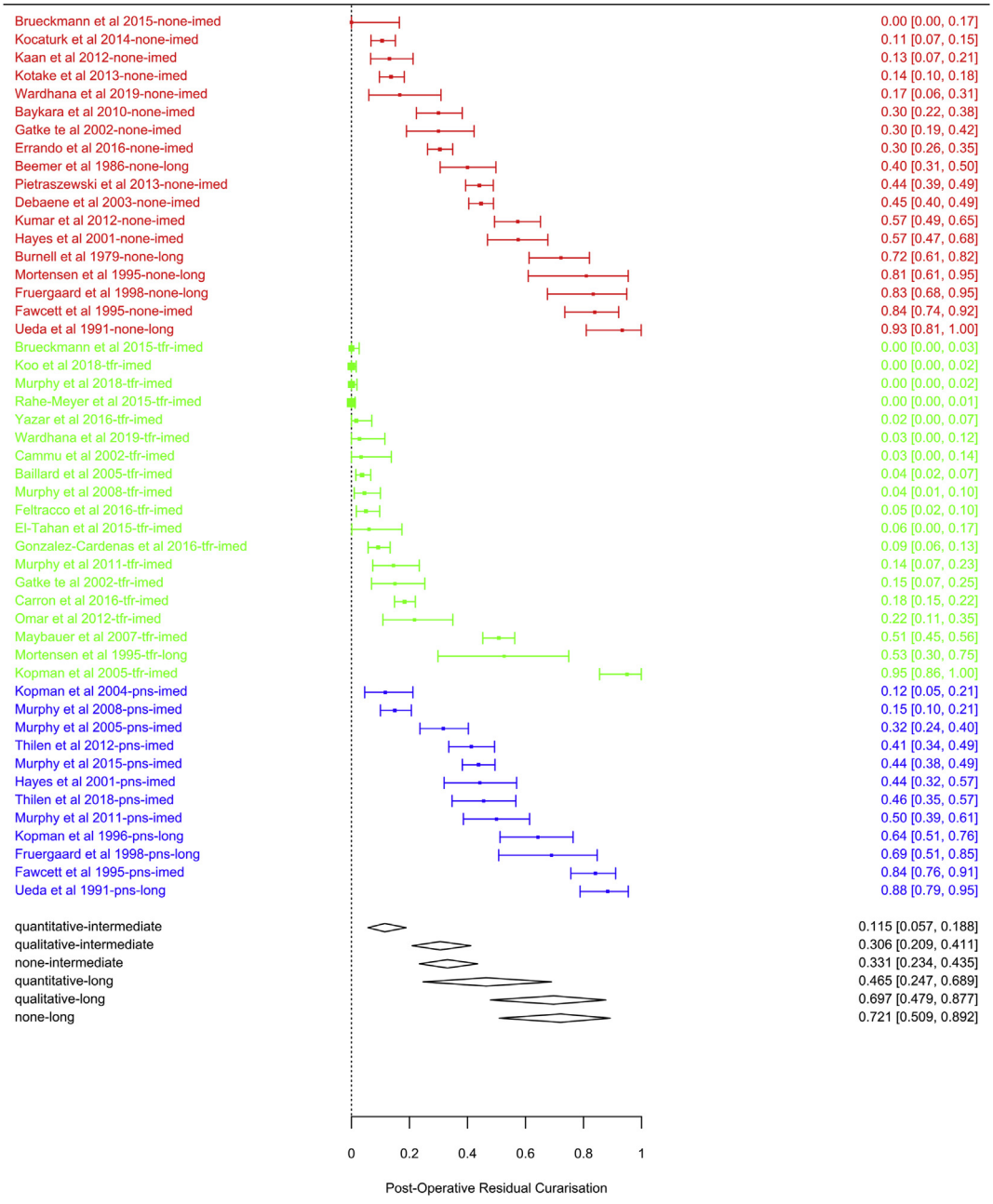

Fig 2. Main model with subtracted anaesthesia type, cut-off 0.9; Forest plot; pooled postoperative residual curarisation PORC proportions. Study arm label structure (left): Author, publication year, NMM subtype, NMBA duration category. Individual and pooled PORC rates and respective 95% confidence intervals presented on the right-hand side of the plot. NMM, neuromuscular monitoring subtype; none (red), no NMM; pns (blue), qualitative NMM; tft (green), quantitative monitoring; imed, intermediate duration NMBAs; long, long duration NMBAs. For intermediate-duration NMBAs, the use of quantitative neuromuscular monitoring is associated with lower PORC rates when compared with both no monitoring and qualitative monitoring, as exemplified by the absence of overlap of the respective confidence intervals.

off of 0.9 within the Main model. This selectivity pertained to the international recognition of this cut-off as the most clinically relevant for PORC definition.[3] The CINeMA analysis was based on a total of 82 study arms (17 excluded because of missing data). Risk of Bias and Indirectness as per Cochrane guidelines were summarised as averages, and RR was used as size of effect measure with a conservative cut-off of 0.1.[15,16]

Cohen's kappa coefficient relating to the inter-rater agreement for the summarised Cochrane Risk of Bias averages was of 0.797 (standard error, 0.056; 95% CI, 0.687 to 0.906).

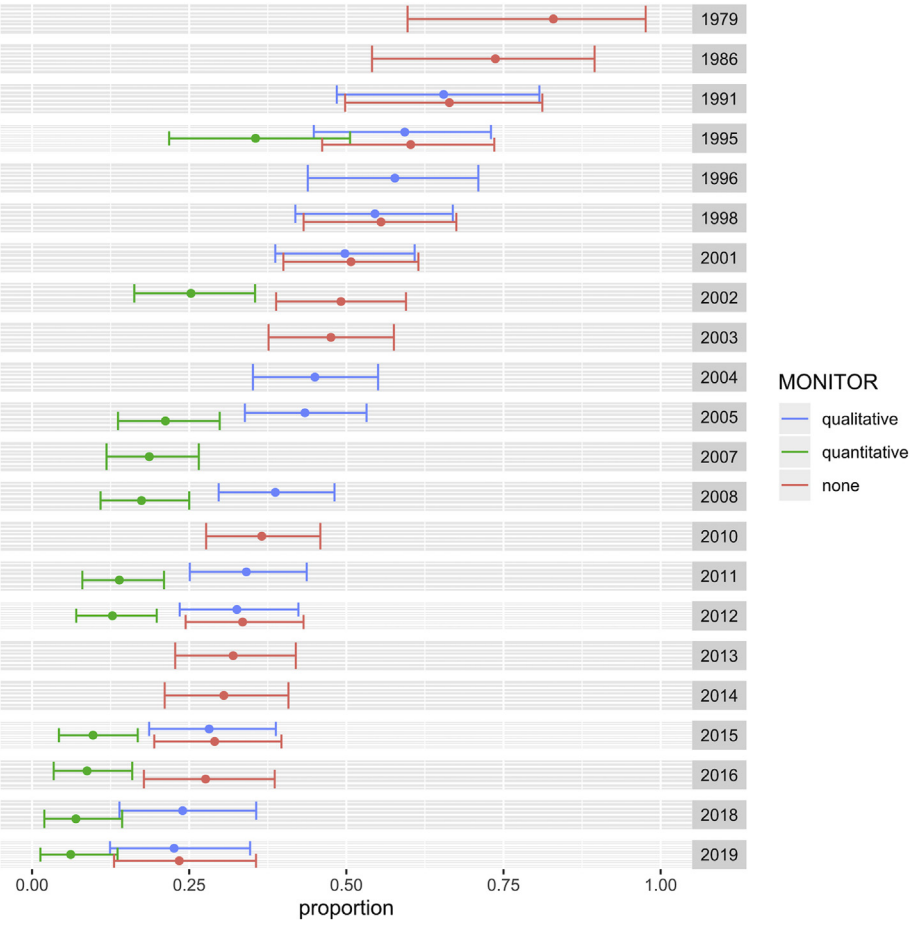

Fig 3. Trend model, cut-off 0.9. Isolated proportion plotting – publication year *vs* neuromuscular monitoring type (monitor). There is a global reduction in the incidence of PORC with time, independently of the subtype of neuromuscular monitoring. Although the chronological decrease is most evident when no monitoring is used, the PORC are consistently higher when compared with quantitative monitoring.

The network plot (Supplementary material) illustrates the bias relationship for the different comparisons. The average risk of bias contribution per binary comparison is also available as supplementary material.

Direct evidence for the majority of the comparisons of interest was available, being absent for the comparisons of long-duration NMBAs and quantitative NMM, and for short duration NMBAs and no/qualitative NMM. In fact, direct comparative evidence was present for the comparisons between Intermediate-duration NMBAs (A) and all the different monitoring modalities (D, no monitoring; E, qualitative monitoring; F, quantitative monitoring).

There were moderate within-study bias concerns for the conclusions drawn for the abovementioned comparisons. All are suspect for across-study bias.

In terms of Indirectness rating, all of the abovementioned comparisons rated low on bias risk (illustrations available as supplementary material).

Imprecision analysis raised no concerns for the selected RR cut-off of 0.1, meaning there was agreement in relation to a clinically important effect. Quantitatively speaking, this is translated by the following estimates and ranges: Intermediate NMBA and No monitoring: RR=1 [0.941;1.062], I^2=0%, τ^2=0; Intermediate NMBA and qualitative monitoring: RR=1 [0.930;1.075], I^2=0%, τ^2=0; Intermediate NMBA and quantitative monitoring: RR=1 [0.927,1.079], I^2=0%, τ^2=0.

In terms of heterogeneity, no concerns were raised. The estimated value of between-study variance for the network meta-analysis was 0, with confidence and prediction intervals agreeing in relation to the clinically important effect. There were similarly no concerns raised for incoherence within the network. A random-effects design-by-treatment interaction model for global testing yielded for this purpose a χ^2 statistic of 0 based on two degrees of freedom analysis (P=1). The CINeMA summary of results is presented in Table 3.

Publication bias was assessed by means of the Egger test, and by graphing residual values against the corresponding standard error in a funnel plot.[65] The process was repeated for every statistical analysis model and for every analysed TOFR cut-off. Both bias-assessment methodologies indicated no serious systematic heterogeneity bias (Fig. 4). One study clearly shows a proportion that is different from what would be expected based on the available information in the model.[40]

Table 3 CINeMA analysis – summary. CINeMA, Confidence In Network Meta-analysis; NMBA, neuromuscular blocking agent.

Comparison	Study arms (n)	Within-study bias	Across-studies bias	Indirectness	Imprecision	Heterogeneity	Incoherence
Intermediate NMBA and no monitoring	26	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns
Intermediate NMBA and qualitative monitoring	17	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns
Intermediate NMBA and quantitative monitoring	29	Some concerns	Suspected	No concerns	No concerns	No concerns	No concerns

The summary of findings for the clinically relevant TOFR cut-off of 0.9 is presented in a standard Cochrane format in Table 2.[15] Bias grading has been specifically assessed by means of the CINeMA analysis as discussed above. Each individual study's per domain GRADE Assessment for Risk of Bias is available for consultation in the supplementary material.[14,15]

Discussion

In contrast with the work of Naguib and colleagues,[7] the present meta-analysis suggests that intraoperative NMM does significantly reduce PORC. When considering a TOFR cut-off of 0.7, no significant difference can be found between NMM subtypes, in spite of a tendency for objective monitoring to

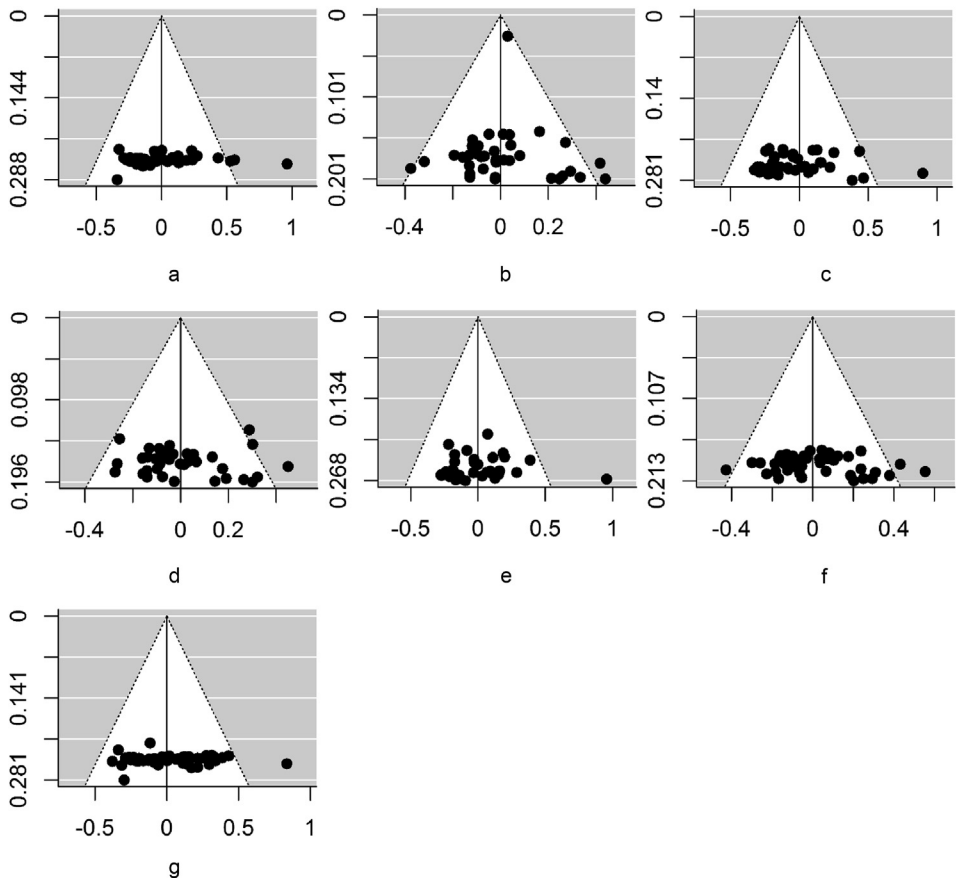

Fig 4. Funnel plotting per statistical model and TOF ratio cut-off. X axis: residual value; y axis: standard error. (a) Main Model with subtracted anesthesia type; cut-off 0.9. (b) Antagonist model, cut-off 0.7. (c) Antagonist model, cut-off 0.9. (d) Main model, cut-off 0.7. (e) Main model, cut-off 0.9. (f) Trend model, cut-off 0.7. (g) Trend model, cut-off 0.9. There is no serious indication of any systematic heterogeneity bias. For the antagonist model with a cut-off of 0.7, one study clearly shows a proportion that is different from what would be expected based on the available information in the model.[24]

yield lower PORC proportions. Nonetheless, data analysis in the light of a more consensually accepted TOFR cut-off (0.9), reveals that objective monitoring significantly outperforms both subjective and absent monitoring.[12] The growing awareness for PORC and consistent reporting of high PORC rates with its associated negative clinical impact might partially explain this shift.[4,6,68–70] Publishing of consensus groups' updates on monitoring standards have also given this phenomenon a momentum.[3,69] This has additionally been paralleled with the marketing of new quantitative neuromuscular monitors and equivalent practical solutions.[71–73]

The observation in the original meta-analysis that long-duration NMBAs are associated with a higher PORC incidence than its intermediate counterparts was not held statistically within the present study, although a same-sided trend was present.[7] This must be interpreted in light of the relative absence of recent studies involving long-duration NMBAs. In fact, from the year 2006 onwards, no additional articles involving long-acting NMBAs have been found. The most recent of these date back to 2000 and were already included in the original meta-analysis.[7,30] Considering that long-duration NMBAs are rarely used in modern western anaesthesia practice, this fact probably carries more historical than clinical relevance.

Concerning intermediate-duration NMBAs (used on 91% of the pooled patient population), no sub-analysis could be performed to study the effect of NMBA dosing on PORC. In fact, although the majority of studies did register cumulative administered doses, an anthropometric- and time-adjusted dose reporting (expressed as ED_{95} equivalent dose kg^{-1} h^{-1}) was scarce. This precluded what would be a representative analysis of the dosing effect.

The studies included in this meta-analysis are not fully homogeneous from a methodological point of view. In fact, the first heterogeneity aspect lies on the definition of the primary outcome itself. Although PORC is consistently defined throughout the included studies by means of a fixed TOFR (0.7, 0.9, or 1.0), the time point and method of measurement varied considerably. In fact, timing ranged from an immediate post-extubation moment,[27,29,34,38,42,50,54,59,60,62] to measurement post-PACU arrival or at a fixed time point.[41,47–49,51,53,56–58,63] Some studies did not specify the measurement time point at the PACU at all.[55] Globally considered, 84 of the 109 included study arms (77%) reported PORC based on TOFRs measured at the PACU.[9–13,17–26,28,30–33,33,38,39,41,43–46,49,51–53,55–58,61,63]

Additional intra-study heterogeneity is introduced by the fact that measurements after PACU arrival were not consistently standardised. Moreover, there was no reporting on transport times between the operating room and the PACU, nor mention of a possible correction factor.

Monitoring techniques similarly presented interstudy heterogeneity. Although most study arms (88%) reported using either accelero- or kinemyographic techniques, electro- or mechanomyographic methods were used in smaller proportions (eight and five of the 109 study arms, respectively). It has been shown that accelero- and kinemyography can significantly diverge not only between themselves, but also from electromyography and mechanomyography.[74–80] It is similarly unclear if movement artefact prophylactic measures were adopted whenever accelero- or kinemyography was used, and if supra-maximal current was used for electrical ulnar nerve stimulation. In fact, only 14 studies have explicitly protocolised usage of supra-maximal currents.[25,27,30,33–35,38,40,42,47,51,54,55,59] Moreover, the reliance of accelero- or kinemyographic techniques on movement for their measurements, associated with the fact that most of the PORC measurements took place on awake patients (thus possibly moving) and with the fact that these techniques have been used in the great majority of the included studies (35 out of 53, or 66%) to confirm the presence or absence of PORC, has to be seen as an important limitation on the global accuracy of the pooled primary outcome.

The presence of a strong relation between some of the collected variables impeded the construction of a larger PORC analysis model. Consequently, more restricted models were used to answer specific questions. Specifically, when considering the influence of the anaesthesia maintenance technique, the variable could be analysed in the light of the NMBA and type of monitoring use, but not co-corrected for pharmacological antagonism or publication year. The generalised absence of reporting on time- and anthropometric-corrected dosing of NMBAs further restricted a holistic analysis. In the light of these restrictions, although it is physiologically recognised that potent inhalation agents prolong neuromuscular block, their use does not seem to play a significant role according to our results.[81–84] The same conclusion applies to TIVA. These results align with those of Naguib and colleagues.[7]

Similar to the anaesthesia maintenance technique, the effect of pharmacological antagonism is similarly based on more restricted statistical models. The analysis is further complicated by significant inter- and intrastudy heterogeneity issues concerning the time of antagonist administration. For the cut-off of 0.9, the analysis suggests lower PORC incidences with sugammadex. Besides the pharmacological principles underlying its established efficacy and efficiency, the fact that sugammadex is less subject to the variable efficacy effects because of heterogeneity in administration timing might explain the obtained results. Again, no accounting for dosing took place in significance testing for this purpose.

The pharmacological selectivity of sugammadex, the heterogeneity of the NMBAs used in the included studies, the non-holistic nature of the statistical models used, and the relative smaller number of patients receiving sugammadex in comparison with neostigmine (663 *vs* 6272, respectively) should be assumed as possible confounders when drawing conclusions related to sugammadex use. Notwithstanding the undisputable usefulness of a pharmacological milestone such as sugammadex, it is important to reiterate that although it reduces PORC, it does not eliminate it. Reported heuristics and overconfidence concerns with respect to NMM in general preemptively suggest a potential false sense of security that might be associated with sugammadex use.[4–6] As shown within the present analysis, sugammadex does not eliminate PORC and its use and monitoring should be guided by appropriate quantitative NMM. The use of infra-therapeutic dosing schemes ('vial-saving' dosing strategies) reinforces this need.[85,86]

The present analysis did not control for variables that are similarly known to potentiate neuromuscular block (temperature, antibiotics, ionic imbalances, among others). Present inferences are thus dependent on active control of these factors within the included studies, which is sub-optimally reported.

When considering the yearly evolution of PORC, one observes a progressive reduction independent of the monitoring modality and cut-off. The differences are clearer when reporting on a TOFR of 0.9. Curiously, one observes a similar

reduction of the PORC rates for the less accurate NMM modalities (none or qualitative). Moreover, these are reduced through time to a proportionally greater extent than those with quantitative monitoring. In the light of the absence of flagrant publication bias signs, such positive evolution might translate the increased awareness and sensibilisation efforts within the anaesthesia community.[3–6,39] Unfortunately, a possible underlying effect of the almost effective extinction of long-duration NMBAs could not be analysed because of collinearity issues.

Within the year-dependent PORC variation analysis, one should acknowledge the potential intra-category bias as result of the inherent limitations of each of the different quantitative monitoring modalities used for the quantification of PORC. In fact, the accurate but now virtually extinct mechanomyography has been progressively replaced by kine- or acceleromyographic technologies. Within the included studies, its last reported use dates back to 2002.[34] The more practical and user-friendly nature of acceleromyography comes at a known practicality/accuracy trade-off because of its susceptibility to well-described overestimation artefacts. These could potentially overestimate the reduction of PORC over time.[35,75–80]

The fact that acceleromyography has been used as the exclusive PORC quantification method on every study included after the year 2005 (cumulatively, 69.2% of the included studies) illustrates the potential magnitude of this effect.

Nonetheless, it should be emphasised that the clinical implications of the conclusions relating to qualitative monitoring are not invalidated by the possible aforementioned bias. In fact, despite increasing awareness and cumulative PORC incidence reduction over time even with qualitative methods, the fact that the latter failed to statistically differentiate itself from the absence of monitoring is not obviated. This conclusion bears particular relevance amid reports of a still high proportional use of qualitative NMM and tendencies of overconfidence and overestimation in terms of NMM management.[4–6]

The abovementioned acceleromyographic limitations have recently been resurfaced as grounds for the enforcement of stricter cut-offs for the definition of PORC. In fact, a *post-hoc* analysis of the POPULAR study has put forward a 7.8% point adjusted risk reduction in postoperative pulmonary complications associated with the raising of the TOFR cut-off for extubation from 0.9 to 0.95.[60,87,88] This recognition of the importance of full neuromuscular recovery is similarly seen in publications using unity as the recovery cut-off.[10,50] Owing to the paucity of studies using these more restrictive TOFR values, a pooled analysis in the light of these raised cut-offs was not possible. Although a concordant widening of the difference gap between quantitative and qualitative/absent NMM modalities is intuitively expected when raising the TOFR, only the systematised anaesthetic community adoption of these cut-offs will allow a later reiteration of their superiority.

Finally, the present analysis should be interpreted with the accompanying confidence analysis in the network meta-analysis. Although the CINeMA analysis did not raise overwhelming concerns on the likelihood of the conclusions of this meta-analysis to be modified by upcoming trials (geometric simplicity, stable heterogeneity, imprecision, indirectness, and incoherence), significant within- and across-study bias concerns were found relating to the relationship between intermediate-duration neuromuscular blocking agents and all neuromuscular monitoring modalities. The individual GRADE classification reflects similarly an overwhelming dominance of studies with a very low level of evidence. These are additional limiting issues that should be considered for the interpretation of the forwarded conclusions. Ideally, these should be addressed in the design of future studies.

Authors' contributions

All authors were involved in design, execution, analysis and interpretation of the work; drafting or revising the manuscript critically for important intellectual content; giving final approval of the version to be published; taking accountability for all aspects of the work, including accuracy and validity of the contents, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

The authors declare that they have no conflict of interest.

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Willy Gepts (Univeristair Ziekenhuis Brussel, Brussels, Belgium).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.05.063.

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Acceptance of mHealth among health professionals: a case study on anesthesia practitioners

Hugo Carvalho[1*†], Michael Verdonck[1,2†], Patrice Forget[3] and Jan Poelaert[1]

Abstract

Background: mHealth, the practice of medicine aided by mobile devices is a growing market. Although the offer on Anesthesia applications (Apps) is quite prolific, representative formal assessments on the views of anesthesia practitioners on its use and potential place in daily practice is lacking. This survey aimed thus to cross-assess the Belgian anesthesia population on the use of smartphone Apps and peripherals.

Methods: The survey was exclusively distributed as an online anonymous questionnaire. Sharing took place via hyperlink forwarding by the Belgian Society for Anesthesia and Reanimation (BSAR) and by the Belgian Association for Regional Anesthesia (BARA) to all registered members. The first answer took place on 5 September 2018, the last on 22 January 2019.

Results: Three hundred forty-nine answers were obtained (26.9% corresponding to trainees, 73.1% to specialists). Anesthesiologists were positively confident that Apps and peripherals could help improve anesthesia care (57.0 and 47.9%, respectively, scored 4 or 5, in a scale from 0 to 5). Trainees were significantly more confident than specialists on both mobile Apps (71.2% and 51.8%, respectively; $p = 0.001$) and peripherals (77.7% and 45.1%, respectively; $p = 0.09$).
The usefulness of Apps and Peripherals was rated 1 or below (on a 0 to 5 scale), respectively, by 9.5 and 14.6% of the total surveyed population, being specialists proportionally less confident in Smartphone peripherals than trainees ($p = 0.008$). Mobile apps are actively used by a significantly higher proportional number of trainees (67.0% vs. 37.3%, respectively; $p = 0.000001$).
The preferred category of mobile Apps was dose-calculating applications (39.15%), followed by digital books (21.1%) and Apps for active perioperative monitoring (20.0%).

Conclusions: Belgian Anesthesia practitioners show a global positive attitude towards smartphone Apps and Peripherals, with trainees trending to be more confident than specialists.

Trial registration: ClinicalTrials.gov database Identifier: NCT03750084. Retrospectively registered on 21 November 2018.

Keywords: Anesthesia, mHealth, Smartphone application, Smartphone peripherals, Apps

* Correspondence: carvalho.hn@gmail.com
†Hugo Carvalho and Michael Verdonck contributed equally to this work.
[1]Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium
Full list of author information is available at the end of the article

Background

Smartphones are a ubiquitous phenomenon. The massive production of these multisensory devices has reduced their overall cost and increased their societal penetrance. Their high processing capacity entails a rather useful leverage for healthcare in general, a sector where data is abundant and its processing relevant for clinical decision-making [1, 2]. These advantageous features have been quickly assimilated by anesthesiologists, and dedicated anesthesia applications for various perioperative purposes have been continuously sprouting [3]. Medical device manufacturers have been similarly leveraging on this versatility in order to commercialize smartphone plug-in devices (also known as smartphone peripherals) that can be used for diagnostic purposes. These include, among others, echography probes (Butterfly™, Clarius™, Philips Lumify™), video laryngoscopes (Airtraq™ Phone adapter) and stetoscopes (StethIO™).

Commonly referred to as "mHealth" (abbreviation for Mobile Health), the practice of medicine aided by mobile devices is a growing market. In the United States of America (USA), this sector has been estimated to be worth more than 28 billion dollars in 2018, and predicted to surpass the 100 billion dollar barrier by 2023 [4]. Despite its exponential growth, regulation has been lagging behind and Food and Drug Administration (FDA) data shows that from a pool of more than 150,000 mobile applications (Apps) within the Health/Wellness category, only around 200 (0.1%) had been submitted to standardized governmental validation procedures [5].

Despite the high mobile applications output, formal surveying of the views of anesthesia providers on these applications is scarce [3, 5]. Green et al. have conducted one of the most complete, although non-representative, studies on the pattern of utilization of smartphone applications by anesthesiologists in the USA [3].

The aim of the present survey was to specifically cross-assess the Belgian anesthesia population on this same subject, as well as to discuss the results with respect to the current legal European framework around mHealth.

Methods

The present study was approved by Ethical Committee of the Universitair Ziekenhuis Brussel, Belgium (Reference 2018/435, B.U.N. 143201837927), and registered at the ClinicalTrials.gov database (Identifier: NCT03750084). The survey was specifically developed for the present study and has not been published elsewhere. The targeted population referred to active (practising) Belgian anesthesiologists (both trainees and specialists), and the a priori established aim was the assessment of the confidence level of this population on both smartphone applications and dedicated smartphone peripherals within daily anesthesia practice. Future development expectations/desires were also to be assessed. Assessment of user experience was not within the scope of the present study.

The survey was not piloted and was exclusively distributed as an online anonymous questionnaire (Google™ Forms platform) for traceability purposes. Sharing took place via hyperlink distribution by the Belgian Society for Anaesthesia and Reanimation (BSAR) and by the Belgian Association for Regional Anaesthesia (BARA) to all registered members. The first answer took place on 5 September 2018, the last on 22 January 2019.

The original survey is available as a supplementary file as well as online at: https://goo.gl/forms/7job24qgFOPXpUD12

It was divided in two main sections: one pertaining to Smartphone Applications themselves, another to Smartphone Peripherals. Each section was identically subdivided and sequentially evaluated the following topics:

- Confidence that Smartphone applications / peripherals can help improve Anesthesia care and why.
- Phase of perioperative care in which Smartphone applications / peripherals are most useful.
- Which sort of Smartphone applications appeal the user the most.
- Which Smartphone applications / peripherals the user employs in his/her daily practice.
- What are the user's wishes on the development of future Smartphone applications / peripherals.

The survey has been structured based on the Technology Acceptance Model (TAM), an information systems theory that describes how users come to accept and use new technologies [6, 7]. The model suggests that when users are presented with a new technology, two primary factors influence their decision about how and when they will use it: (1) Perceived ease of use, which is determined by the degree to which a person believes that using a particular technique would be free of effort; and (2) Perceived usefulness, referring to the degree in which a person believes that a technique will be effective in achieving the intended modelling objective. The aforementioned model and associated measures were concordantly translated into the current survey to assess how respondents perceived the acceptance of mobile applications and peripherals within anesthesia. More specifically, participants had to answer several questions – using multiple-item scales with a Likert structure – which measured both the perceived usefulness and perceived ease of use. The reliability and validity of these type assessments has been assessed in several similar research efforts [8–11].

Questions were in their majority presented to the surveyees with a categorical structure. Dichotomous, nominal and contingency questions were used to categorize individuals as well as the contextual use of

Apps and Peripherals. Confidence levels were assessed by a Likert-type scale with balanced keying in order to allow for discrete quantitative comparisons. A score of 3 was considered the positivism transition point (considered to "Improve Anesthesia Care"), and a score of 4 or 5 was considered as positively trending confidence. Optional open text questions were used for detailing the reasons for the selected subjective confidence level.

Data reporting for the total population and for each subgroup (consultants/trainees) was descriptive in nature and precision reported with 95% Confidence Intervals [95%CI]. The inter-group confidence level comparisons based on the multi-point (ordinal) rating scales levels were carried out by means of binary reconversion of the Likert scale into two mutually exclusive intervals (one encompassing the ratings 0 to 3, and the second 4 to 5), and by sequential non-parametric analysis by means of Chi-square testing with a significance cut-off of 0.05. Identical methodology was used for the analysis of inter-group differences in terms of active use of Apps or Peripherals to aid Anesthesia care.

Results

A total of 349 answers were obtained. Ninety-four (26.9%) responses were of Belgian Anesthesia trainees, 255 (73.1%) from Belgian Anesthesia consultants. A majority of the answering specialists (21.7%) had no dedicated subspecialty activities or were all-round specialists (Fig. 1). Anesthesiologists with an orthopedic anesthesia subspecialty accounted for 17.6% of the total, followed by cardio-thoracic anesthesiologists (14.3%), Pediatric Anesthesiologists (13.4%), Pain Clinic specialists (12.8%), Neuro-anesthesiologists (6.5%) and Intensive care specialists (6.0%). The remainder subspecialties were underrepresented (less than 1.8%).

When asked on how confident they were that Smartphone Applications (Apps) or Smartphone Peripherals (Peripherals) could improve anesthesia care, a majority of the Belgian anesthesiologists were positively confident (score of 4 or 5, on a 0 to 5 categorical scale) that these could indeed help improve anesthesia care (57.0% [95%CI: 51.8–62.2%] and 47.9% [95%CI: 42.7–53.1%], respectively, scored 4 or 5) (Fig. 2). When subanalyzing the data per experience group, anesthesia trainees demonstrated a significantly higher degree of optimism (score of 4 or 5, out of 5) on Mobile Apps compared to consultants (71.3% [95%CI: 62.1–80.4%] and 51.8% [95%CI: 45.6 57.9%], respectively) (X^2 [1, $N = 349$] = 10.6696, $p = 0.001$) (Fig. 3). This positivity trend was maintained for Smartphone peripherals (77.7% [95%CI: 69.3–86.1%] and 45.1% [95%CI: 39.0–51.2%], respectively), although no statistical significance was retained (X^2 [1, $N = 349$] = 2.8754, $p = 0.090$) (Fig. 4).

Nine and a half percent [95%CI: 6.4–12.6%] of the surveyees (consultants and trainees combined) rated Apps' usefulness in Anesthesia as 1 or below (on a 0 to 5 scale), and 14.6% [95%CI: 10.9–18.3%] gave the same rating when asked about Peripherals. Inter-group analysis for this rating showed no statistical significance between trainees and consultants for Apps (X^2 [1, $N = 349$] = 2.5711, $p = 0.108833$). On the other hand, smartphone peripherals were significantly more negatively rated by consultants than by trainees (X^2 [1, N = 349] = 6.9839, $p = 0.008225$).

From all the responders, 45. 3% [95%CI: 40.0–50.5%] actively used Apps to aid their anesthesia practice, compared to only 3.2% [95%CI: 1.3–5.0%] that use Peripherals in their daily anesthesia practice. Again, subanalysis of the answers per training group showed that trainees actively use mobile apps in a significantly higher proportion when compared to consultants (67.0% [95%CI:

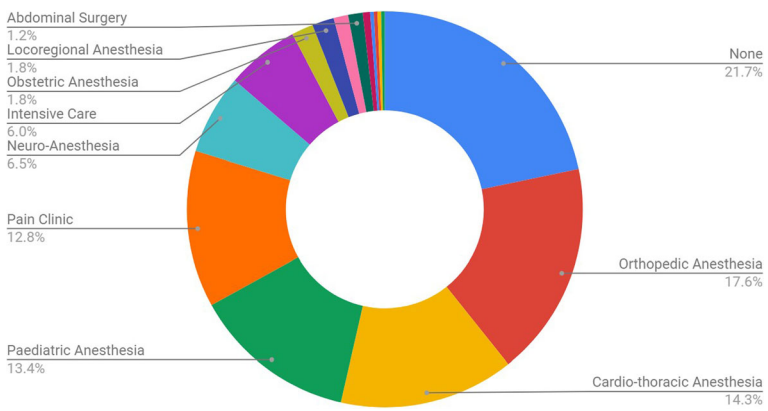

Fig. 1 Subspecialty stacked distribution of responding Anesthesia Specialists (one specialist can be accounted for more than once if he holds multiple subspecialty competences). Percentages represent the total number of surveyees per specific category relative to total number of surveyees

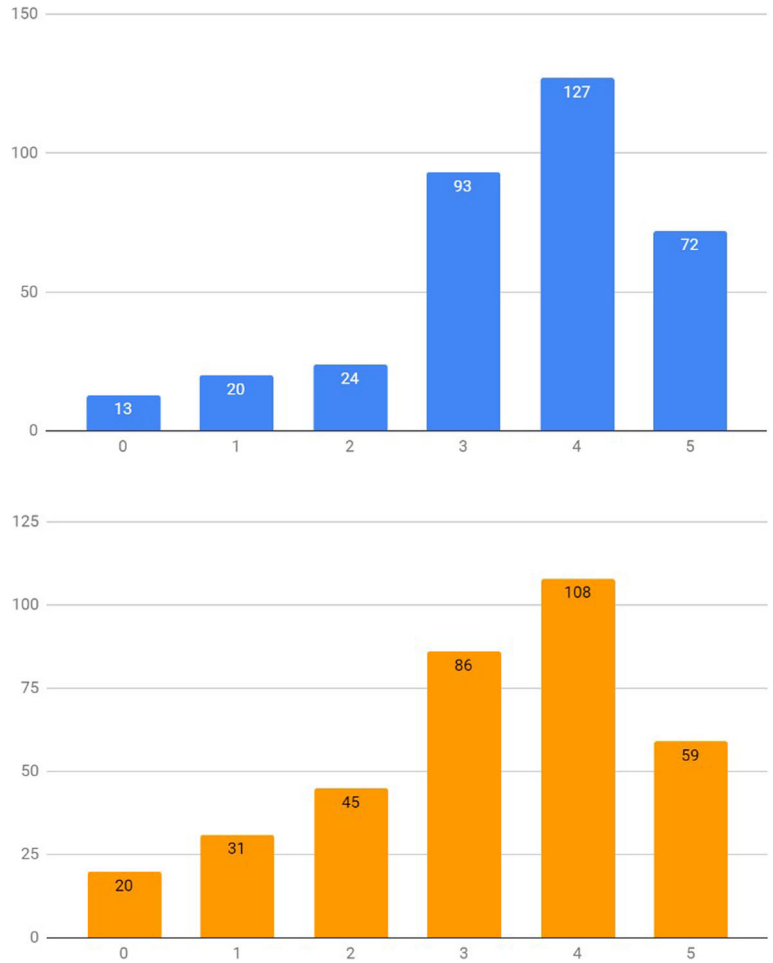

Fig. 2 Apps (left - blue) vs Peripherals (right - orange) - Confidence level (scale: 0 to 5). x axis – Confidence level category, y axis – absolute number of survey answers ("How confident are you that Smartphone Apps can help improve anesthesia care?" / "How confident are you that combining your smartphone with a dedicated monitoring peripheral can help improve anesthesia care?")

57.5–76.5%] and 37.3% [95%CI: 31.3–43.2%], respectively) (X^2 [1, N = 349] = 24.5615, p = 0.000001) (Table 1). No statistically significant inter-group difference was found in terms of active peripherals use) (X^2 [1, N = 349] = 0.4421, p = 0.506108) (Table 1).

When questioned on which App category was more appealing, 39.15% [95%CI: 34.0–44.3] of total responders gave preference to dose-calculating applications (dynamic [TCI modelling] and static [fixed dose calculation] apps). The next bigger App preference were Digital Books (21.12% [95%CI: 16.8–25.4%]), followed by Applications used for perioperative monitoring (20.0% [95%CI: 15.8–24.2%]) and interactive anatomy models (12.39% [95%CI: 8.9–15.8%]) (Fig. 5).

Concerning the perioperative care phase in which Applications or Peripherals could be more useful, 71.1% [95%CI: 66.3–75.9%] and 57.0% [95%CI: 51.8–62.2%], respectively, considered them to have a potential use in all phases of the perioperative care (Figs. 6 and 7).

The categories in which anesthesiologists would like to see development of smartphone peripheral devices are illustrated in Fig. 8.

Discussion

In general, these survey results agree with the findings of Green et al. on the American anesthesiologists population, where apps enjoy a significant degree of confidence and are believed to have a potential use on all phases of perioperative care [3]. Peripherals also enjoy a high confidence on potential use, rating 47.9% [95%CI: 42.7–53.1%] of the responders their confidence as 80% or higher that these can be useful in Anesthesia care. Nine and a half percent [95%CI: 6.4–12.6%] of the surveyees rated Apps' usefulness in anesthesia as 1 or bellow (on a 0 to 5 scale), and 14.6% [95%CI: 10.9–18.3%] gave the same rating when asked about Peripherals. Thus, Apps enjoy both a greater degree of optimisms as well as a lower degree of disbelief in comparison to Peripherals. The

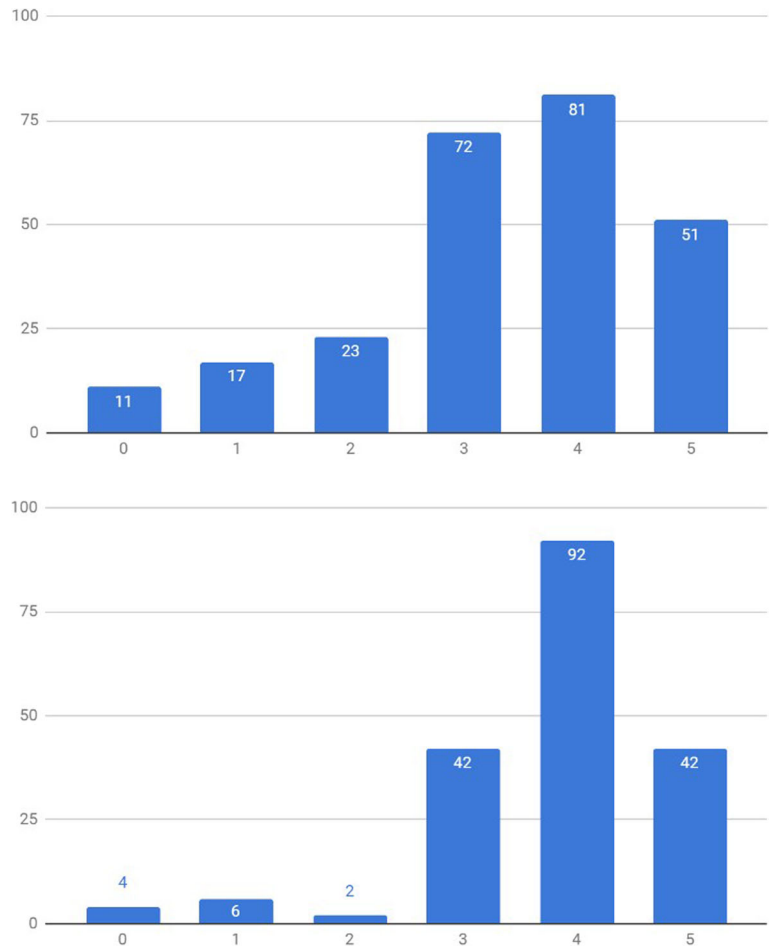

Fig. 3 Apps Confidence level (scale: 0 to 5): Specialists (left) vs Trainees (right). x axis – Confidence level category, y axis – absolute number of survey answers

reasons for this discrepancy were not evaluated by this questionnaire, but one can speculate that the underdeveloped regulated market of smartphone peripherals for diagnostic aid is still not firmly established within today's anesthesia practice. Although the major players have already created a dedicated peripherals market branch (f.e., the Philips Lumifym® portable echography series), convincing of practitioners on their usefulness is still needed. Curiously, when asked on which peripherals they wanted to see developed, 61.7% of the anesthesiologists answered "Echography". This is nonetheless one of the more exploited areas in terms of Anesthesia smartphone peripherals, and has been explored both by the major players in the medical device industry (Philips™, Airtraq™), as well as by less known and upcoming competitors (Clarius™, Butterfly™). From the total of 66 individuals providing a written rationale for their confidence levels on mobile peripheral devices, 6 (9.1%) suggested that although they did know of the existence of such products, they still found them economically inaccessible. Other, however, suggested they had no knowledge of such devices. Another possible reason that might contribute to the greater disbelief possibly relates to the medical use of an originally partially non-medical device. Although it seems logical that controlled CE-labelling (Conformité Européenne) of smartphone peripherals for medical use might help overcome this phenomenon, a subjective factor cannot be underestimated. Just like heavy, well designed and good fitting over-head headphones feel subconsciously better than in-ear equivalents, traditional anesthesia monitors might still convey more confidence [12].

Another curious pattern observed on the surveyees' answers was the fact that although 57.0% [95%CI: 51.8–62.2%] considered Apps useful (classification of 4 or 5 out of 5), only 45.3% [95%CI: 40.0–50.5%] reported actually using them in their daily practice. The gap was proportionally bigger when analysing smartphone peripherals (47.9% [95%CI: 42.7–53.1%], and 3.2% [95%CI: 1. 3–5.0%], respectively), although the latter easier to justify in light of the underdeveloped smartphone peripherals

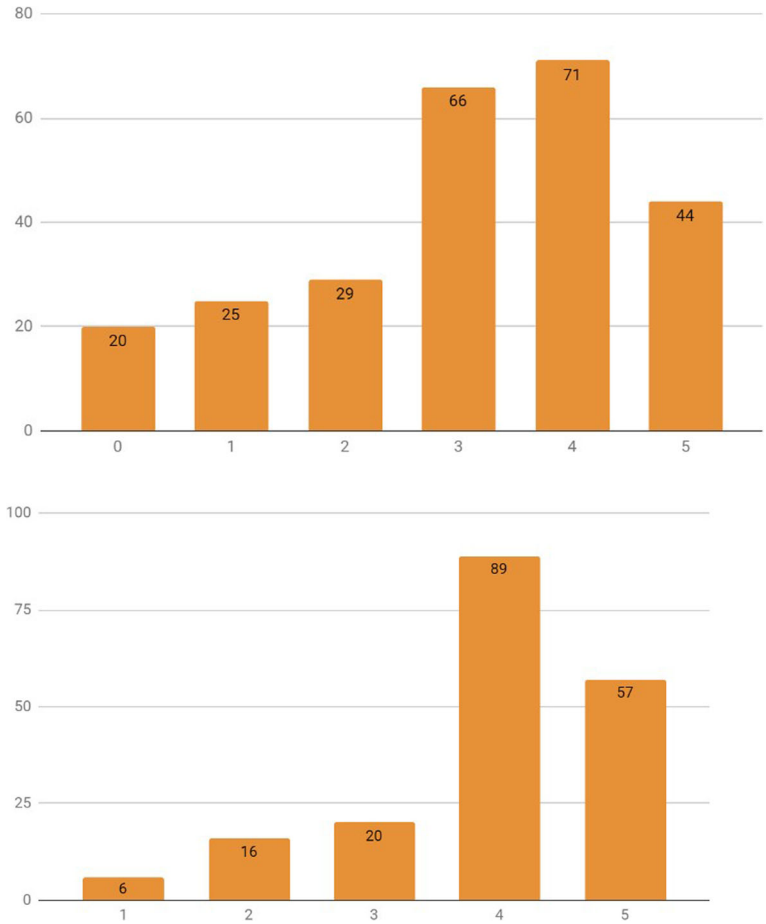

Fig. 4 Peripherals Confidence level (scale: 0 to 5): Specialists (left) vs. trainees (right). x axis – Confidence level category, y axis – absolute number of survey answers

market. This Smartphone "Confidence - Active use" gap might be explained by a yet unripe and ununiformed anesthesia app market. A perceptive phenomenon of unrealistic and consequently unfulfilled expectations by users must also be considered as possible, although formal prospective user experience assessments are needed for this purpose.

In line with the study of Green et al., dosage apps were chosen by the majority as the most useful [3]. Digital books and perioperative apps followed. Such choice pattern is not counter-intuitive considering the still limited interactivity between handheld devices and anesthesia monitoring devices, although such justification is purely speculative as formal assessments to this point are lacking. The increasing focus on portability and cross-connectivity might lead to a pattern change, and future studies would be useful to analyse a trend shift.

Table 1 Active Usage of Mobile Apps and Peripherals per subgroup

	Apps	Peripherals
Specialists	95 (37.3%)	9 (3.5%)
Trainees	63 (67.0%)	2 (1.2%)
Total	158 (45.3%)	11 (3.2%)

Cell values represent the absolute number of individuals. Within parenthesis the percentages are relative to total of individuals within the same cell line-group (i.e., relative to either specialists, trainees or total surveyees)

The observed positive disposition towards mHealth usage as well as its focus on mobile apps is apparent on indexed literature analysis. In fact, notwithstanding a possible positive publication bias, the publication of mHealth applications within all domains of healthcare has been steadily increasing [13]. Curiously, and notwithstanding the fact that representative reports on global mHealth usage patterns are lacking, analysis of an individual application's trends have shown a higher penetration of these low cost aids in low income countries [14].

Within the anesthesia domain, developed applications range from crisis management support apps, to postoperative pain assessment, but also to non-medical topics such as logistic optimisation of Operation room

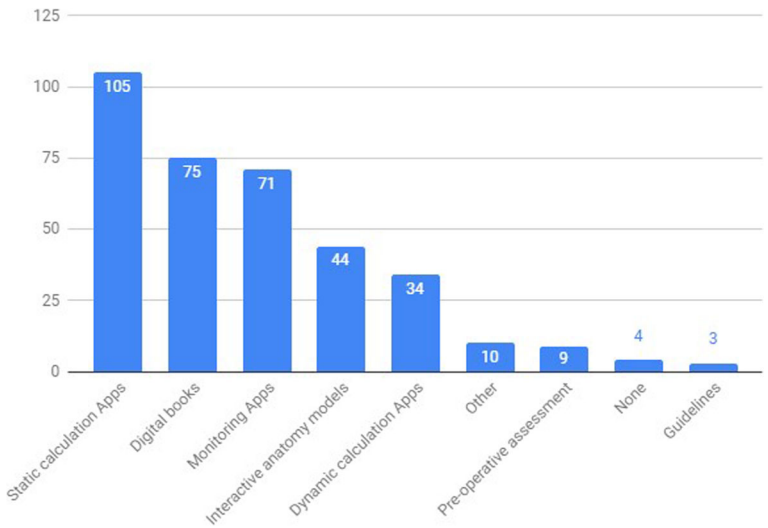

Fig. 5 Categorization of the most appealing Apps ("Which kind of Apps appeal you the most?"). x axis – App category, y axis – absolute number of survey answers

supplies [15–17]. Most of these reports are descriptive and lack usability testing to allow a direct comparison to the present study's results.

As opposed to the study of Green et al., our group found significant differences between anesthesia trainees and specialists. Although there was a global positivity trend towards mobile apps in both groups, training anesthesiologists displayed a significantly higher confidence on mobile apps than consultants (71.3% vs 51.8%, respectively, $p = 0.001$). This positivity trend was similarly true for smartphone peripherals (45.1% vs 77.7%, respectively), although this difference didn't retain statistical significant on further difference testing ($p = 0.09$). Besides the evident cultural and contextual medical practice differences between the sampled subjects (American vs. European), the collected data on both studies is insufficient to put forward a phenomenological explanation.

According to data from the Belgian National Institute for Health and Disability Insurance (RIZIV / INAMI), in the beginning of 2016, Belgium had 2441 active anesthesia specialists (certified specialists and trainees) [18]. This sets this survey's cross-sectional percentage at 14.2% of the total active Belgian anesthesiologists, 13.2% of the certified Belgian anesthesiologists, and 17.5% of the Belgian anesthesiology trainees. Concerning the accredited specialists (diploma-holding), it is however not known if all of them are dedicated in exclusivity to anesthesia-related fields such as Intensive care, Emergency or Chronic Pain. It is thus possible that the

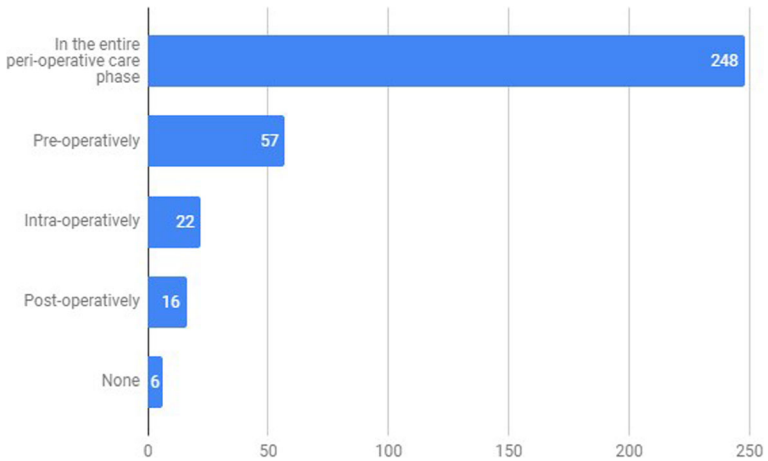

Fig. 6 Phase in which Smartphone Apps can be more useful ("In which phase of perioperative care can Smartphone Apps be more useful?"). x axis – absolute number of survey answers, y axis – Perioperative phase category

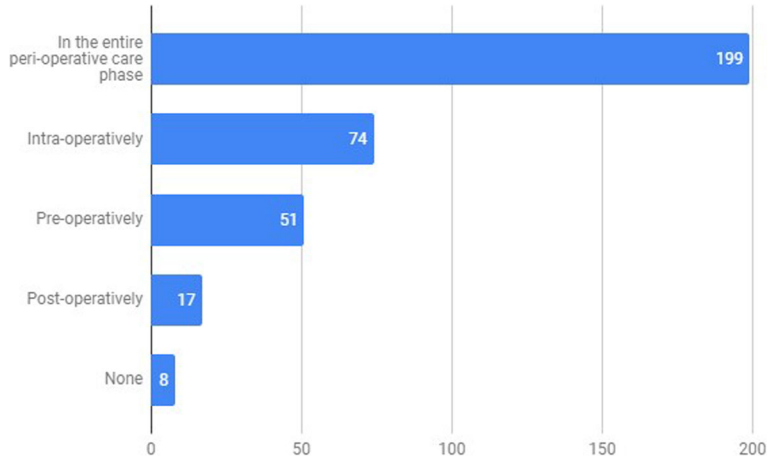

Fig. 7 Phase in which Smartphone Peripherals can be more useful ("In which phase of perioperative care can Smartphone Peripherals be more useful?"). x axis – absolute number of survey answers, y axis – Perioperative phase category

representability percentage of this survey is different than calculated, although practically very difficult to confirm.

These definitely promising technologies are increasingly being introduced in our daily practice and play an important facilitating role. However, one must not forget that these freely available tools are not always subject to formal approval procedures that scientifically validate their clinical use. Most of these are part of the off-label/"use at own risk" category (commonly referred to as "Grey Area Apps") - applications freely available without formal evaluation of their function for their stated (medical) use [8]. Taking this into mind, the European Union (EU) has created between 2016 and 2017 a workgroup for the development of mHealth assessment guidelines [19]. However, the group was not able to endorse concrete guidelines by failure to reach a minimal intragroup consensus [20]. As of this moment, Grey Area Apps remain unregulated. There is, however, a non-binding "privacy code of conduct on mobile health apps" that outlines the core values that should guide mobile health application development [21]. It provides a theoretical competitive advantage against non-conform Applications and speeds up an eventual CE-label request. As for applications aiming for a formal regulated national market entry, compliance with the EU regulation 2017/745 (from 5 April 2017) is mandatory. Together with the EU norm 2017/746, they regulate the European market of medical devices since May 2017. European Union state members fall, thus, under these norms.

It is self-evident that mobile Applications and Peripherals are quickly permeating all phases of Healthcare, with the right steps are being taken for their scientific, national and intracontinental integration [22–33]. Peripherals still lag behind mobile applications although

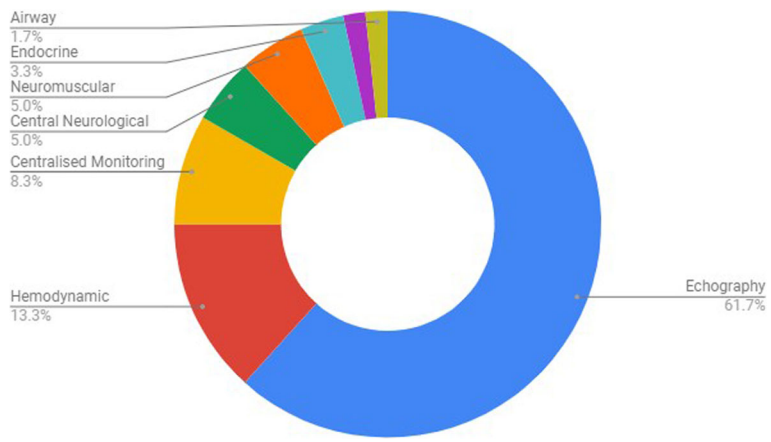

Fig. 8 Wishes for smartphone peripheral device development per monitoring category ("Which peripherals would you like to see developed in the coming future?"). Percentages represent the total number of votes per specific category relative to total number of votes

they constitute an economically and clinically important area. Care must still be taken considering the majority of available Apps fall within the unregulated category of "Grey Area Apps". Last, but not least, care is necessary in avoiding over-reliability/dependency on Apps, with the consequent side-tracking of basic clinical skills. Notwithstanding this warning note, the education potential of apps as supplement to classical learning techniques is increasingly being explored with some educational centers incorporating such solutions within anesthesia training programmes [34]. The development of applicationS should ideally use a user-centered design for and optimal and successful adoption [15].

The present study is limited in the fact that it doesn't directly address user experience. Initially designed primarily to address the acceptance of Apps and Peripherals, user experience and expectations were left out in the need for a compromise between brevity and completeness. A mixed-method experience analysis would be a relevant top-up survey that would allow this quantification as well as to potentially guide App and Peripheral development based on end user experience and expectations. Secondly, the survey is further limited in the fact that the transversal population assessment was estimated at 14.3% (349 out of 2441 active anesthesia specialists), raising the obvious concern of non-responder bias. Finally, the fact that digital books have been considered Apps might constitute a classification bias depending on surveyee interpretation. In fact, digital books might also come in non-app form (for example as *.pdf or *.chm format), which could potentially affect the perception of the respondents.

Conclusions

Belgian Anesthesia practitioners show a positive attitude towards smartphone-based solutions within Anesthesia care, mirroring international reported trends within other medical sectors. There is evidence of an international recognition of the potential of these technologies within the healthcare domain, with consequently rising regulatory efforts from medical societies and national legislative bodies.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12871-020-00958-3.

Additional file 1. Original survey used for the present study.

Abbreviations

Apps: Mobile Applications; BARA: Belgian Association for Regional Anesthesia; BSAR: Belgian Society for Anesthesia and Reanimation; CE: Conformité Européenne; EU: European Union; FDA: Food and Drug Administration; mHealth: Mobile Health; RIZIV/INAMI: Belgian National Institute for Health and Disability Insurance; TAM: Technology Acceptance Model; USA: United States of America; VUB: Vrije Universiteit Brussel

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Authors' contributions

HNC and MV contributed to the design and the methods, HNC and MV acquired the data, HNC and MV analysed the data and are responsible for the integrity of the data and the analyses, all the authors contributed to the interpretation, HNC and MV redacted the first draft, reviewed and modified by PF and JP. All the authors approved the final version.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by Ethical Committee of the Universitair Ziekenhuis Brussel, Belgium (Reference 2018/435, B.U.N. 143201837927). Written informed consent was obtained from all survey participants.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium. [2]Business Informatics Research Group, Universiteit Gent, Ghent, Belgium. [3]Institute of Applied Health Sciences, NHS Grampian, University of Aberdeen, Aberdeen, UK.

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