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Manuel Maria Botelho Gomes Barbosa

Residual neuromuscular block in a post-anaesthesia care unit: a prospective study

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Trabalho efetuado sob a Orientação de:

Prof. Doutor Fernando José Pereira Alves Abelha

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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Faculdade de Medicina da Universidade do Porto, 15/03/2012

Assinatura: Manuel Maria Botelho Gomes Barbosa

Aos meus Pais

à Francisca

ao Prof. Doutor Fernando Abelha

Abstract and Keywords

Background and objective: Residual neuromuscular block is an important postoperative complication due to the use of neuromuscular blocking drugs. The aim of this study was to access the incidence of residual neuromuscular block in a post-anaesthesia care unit.

Methods: This observational prospective study was conducted in a post-anaesthesia care unit during a three-week period. Residual neuromuscular block was defined as train-of-four ratio <0.9 and objectively quantified using acceleromyography in 202 eligible patients at recovery room admission. Patients with train-of-four ratio <0.9 were re-assessed hourly. Demographic data, perioperative variables, lengths of stay in hospital and at recovery room, and critical respiratory events were recorded. Descriptive analyses of variables were used to summarize data. The Mann-Whiney *U* test, Chi-square or Fisher's exact test were used for comparisons.

Results: Residual neuromuscular block incidence in the post-anaesthesia care unit was 30.2%. Patients with residual neuromuscular block had a greater incidence of critical respiratory events (51% versus 16%, $P<0.001$) and greater incidence of each event considered independently: airway obstruction (5% versus 4%, $P=0.029$), mild-moderate hypoxemia (23% versus 2%, $P<0.001$), severe hypoxemia (7% versus 1%, $P=0.033$), respiratory failure (8% versus 1%, $P=0.031$), inability to breathe deeply (38% versus 12%, $P<0.001$) and muscular weakness (16% versus 1%, $P<0.001$). Residual neuromuscular block was more common after high risk surgery (53% versus 33%, $P=0.011$) and was more often associated with post-operative hypoactive emergence as defined by the Richmond Agitation and Sedation Scale (21% versus 6%, $P=0.001$). Length of stay in the hospital and in recovery room was not significantly different between groups.

Conclusions: This study suggests that residual neuromuscular block is common in the post-anaesthesia care unit. This condition was associated with critical respiratory events.

Keywords: Neuromuscular blockade; postoperative complications; anaesthesia recovery period; recovery room.

Introduction

When neuromuscular blocking drugs (NMBDs) are administered intraoperatively, residual neuromuscular block (RNMB) is often observed in the post-anaesthesia care unit (PACU).[1-5] Studies have established an association between RNMB and increased postoperative morbidity and mortality, critical respiratory events, and longer PACU stays.[6-8]

Train-of-four (TOF) nerve stimulation was introduced in the 1970s and is a commonly used method to access the status of neuromuscular block.[9] It is difficult to exclude residual block using qualitative monitoring of TOF (tactile or visual), because of the subjectivity involved in these observations. Quantitative methods should be preferred and acceleromyography monitoring allows an accurate quantification of small degrees of residual block.[10] The TOF ratio threshold that represents inadequate neuromuscular recovery, combined with signs and symptoms of muscle weakness, has changed over the decades. Initially, a TOF ratio >0.7 was considered to represent adequate neuromuscular recovery. However, current recommendations support a TOF ratio equal to or greater than 0.9 to ensure optimal patient safety.[11,12]

Despite the use of short-acting NMBDs and pharmacological reversal of neuromuscular block, the incidence of RNMB on arrival to the PACU can be as high as 31%-64%.[1-5,11,12]

An increase in the incidence of critical respiratory events (CRE) at the PACU even in the presence of small degrees of RNMB has been proved.[7,13-16] Many factors related to patients, surgical procedure and anaesthetic management come into play. Patient risk factors include advanced age, male sex, chronic obstructive pulmonary disease, diabetes and obesity.[14-16] Surgery-related variables include abdominal or orthopaedic surgery, emergency operation and long duration of surgery.[14-16] Finally, the anaesthetic risk factors for CREs in the PACU include the use of general anaesthesia, opioids and NMBD.[14,16]

Emergence is the transition from unconsciousness to full wakefulness, and ideally should be smooth and uneventful.[17] Inadequate emergence is characterized by a disturbance of activity level in the immediate postoperative period. It can be classified

into two subtypes: emergence delirium, characterized by agitation, restlessness and hyperactivity; and hypoactive emergence, characterized by a delayed recovery after anaesthesia. Inadequate emergence after anaesthesia is a frequent complication. Preventable risk factors for emergence delirium are induction of anaesthesia with etomidate, premedication with benzodiazepines and higher postoperative pain scores.[18] Hypoactive emergence occurs less frequently than emergence delirium and is associated with a longer postoperative hospital stay.[18] Thus, monitoring the sedation status in the PACU is important. The Richmond Agitation-Sedation Scale (RASS) has demonstrated excellent interrater reliability and criterion, construct, and face validity.[19,20]

The primary aim of this investigation was to determine the incidence of RNMB in the PACU after general anaesthesia. The secondary aim was to examine the outcome related to critical respiratory events (CREs), PACU complications and the length of PACU and hospital stay.

Methods

This study was approved by the Centro Hospitalar São João Ethics Committee, Alameda Hernâni Monteiro, 4200-319 Porto, Portugal (Chairperson Prof Filipe Nuno Alves Santos Almeida). Written informed consent was obtained from all participants.

Hospital de São João, Porto, is a 1124-bed tertiary hospital in a major metropolitan area that serves 3,000,000 people. This prospective study was conducted in a 12-bed PACU between 8:00AM and 8:00PM, Monday through Friday, over a three-week period (from May 9th to May 27th, 2011).

Inclusion criteria were the ability of patient to provide written informed consent, admission on spontaneous ventilation and intraoperative use of NMBDs. Exclusion criteria were patient refusal, incapacity of providing informed consent, a score of <25 in the mini-mental state examination (MMSE)[21], age under 18 years, foreign nationality, known neuromuscular disease, urgent/emergent surgery and also cardiac surgery, neurosurgery or other procedures that required therapeutic hypothermia.

Measurements

The neuromuscular block was defined as TOF <0.9 and it was quantified at admission to the PACU using acceleromyography of the adductor pollicis muscle (TOF-Watch®). Two surface electrodes (Kendall ARBO Electrodes®) were attached to the cleansed skin over the ulnar nerve on the volar side of the wrist. The distal electrode was positioned where a proximal bending line crosses the radial side of the flexor carpi ulnaris muscle. The proximal electrode was placed 3 cm proximal of the distal electrode. The piezoelectric transducer was placed with its largest flat side against the volar aspect of the distal phalanx of the thumb. The stimulation current was set to 50 mA. The resulting TOF ratios were obtained (4 pulses of 0.2 ms duration over 2 s at a frequency of 2 Hz). Three consecutive TOF measurements (separated by 15 s) were obtained, and the average of the 3 values was recorded. If a value differed from the others by more than 10%, an additional TOF measurement was obtained and the closest 3 ratios were averaged. Neuromuscular block was re-assessed hourly while patients maintained TOF<0.9. The initial TOF ratios were measured before any therapeutic in the PACU.

A standardized data collection sheet was completed for each patient eligible for the study. The MMSE was preformed pre-operatively, when collecting the informed consent. The Revised Cardiac Risk Index (RCRI) was assessed.[22] The patient demographic data recorded included age, gender, height, weight, American Society of Anesthesiologists physical status (ASA), pre-existing medical conditions, preoperative medications and an extensive check-list for cardiac risk. Intraoperative details included type of anaesthesia, type of surgical procedure, duration of anaesthesia, duration of surgery, intraoperative fluids (crystalloids, colloids or blood products), NMBD, time of last dose of relaxant and neuromuscular block reversers used. Patients' tympanic temperature, blood pressure, cardiac frequency, peripheral oxygen saturation and mean TOF ratio were recorded on admission to the PACU. The length of PACU stay, the neck perimeter, and occurrence of CREs were also recorded. Each CRE was defined on the data collection sheet using the following criteria:[7]

1. Upper airway obstruction requiring an intervention (jaw thrust, oral or nasal airway);
2. Mild-moderate hypoxemia [oxygen saturations (SpO_2) of 93%-90%];
3. Severe hypoxemia (SpO_2 <90%);
4. Signs of respiratory distress or impending ventilator failure (respiratory rate >20 breaths per minute, accessory muscle use, tracheal tug);
5. Inability to breathe deeply when requested;
6. Symptoms of respiratory or upper airway muscle weakness (difficulty breathing, swallowing or speaking);
7. Patient requiring reintubation in the PACU;
8. Clinical evidence or suspicion of pulmonary aspiration after tracheal extubation (gastric contents observed in the oropharynx and hypoxemia).

Inadequate emergence was classified in its different forms according to the Richmond Agitation-Sedation Scale (RASS) applied at discharge.[19,20] Emergence delirium was defined as a RASS score $\geq$+1, and hypoactive emergence was defined as a RASS score $\leq$−2.[18]

PACU discharge times were recorded by PACU nurses not involved in this study.

Statistical analysis

Descriptive analyses of variables were used to summarize data.

Ordinal and continuous data found not to follow a normal distribution, based on the Kolmogorov–Smirnov test for normality of the underlying population, are presented as median and interquartile range. Normally distributed data is presented as mean and standard deviation (SD).

An univariate analysis was performed to identify determinants for RNMB using the Mann-Whitney *U* test to compare continuous variables and Chi-square or Fisher's exact test to compare proportions between two groups of subjects.

Differences were considered statistically significant when P was <0.05.

Data was analysed using SPSS software for Windows Version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

From the 357 patients consecutively admitted in the PACU during the study period, a total of 202 patients were studied. Seventeen patients were excluded: 7 patients were admitted in a surgical intensive care unit, 3 patients were incapable of providing informed consent or had a Mini Mental Status Examination <25, 3 patients were not submitted to surgery, 1 patient was submitted to neurosurgical surgery, 1 was less than 18 years old, 1 did not speak Portuguese and 1 refused to participate. One hundred and thirty-seven patients did not meet the inclusion criteria. One patient was not assessed due to the impossibility to perform TOF measurements as planed (patient had plaster on both arms).

In this study were included 79 (39%) male and 123 (61%) female patients. The median patient age was 54 years (41 – 66) and body mass index was 26 kg m^{-2} (23 – 30). Forty-five patients (22%) were scored as ASA I, 132 (65%) as ASA II, 24 (12%) as ASA III and 1 (1%) as ASA IV. Seventy-nine patients (39%) underwent high risk surgery. Fifty-three patients (26%) presented CRE: 40 (20%) were unable to breathe deeply when requested, 20 (10%) developed mild-moderate hypoxemia, 11 (5%) symptoms of respiratory or upper airway muscle weakness, 7 (4%) signs of respiratory distress, 5 (3%) severe hypoxemia and 3 (2%) upper airway obstruction. (Table 1)

On arrival in the PACU, 61 patients (30.2%) were found to have RNMB with a mean TOF ratio of 75% (62-84). (Tables 1 and 2)

The incidence of CRE in the PACU was 26%. Patients with RNMB had a CRE incidence significantly high when compared to patients with adequate recovery of neuromuscular transmission [31 (51%) versus 22 (16%), $P<0.001$]. This also applies to each CRE independently: airway obstruction (5% versus 4%, $P=0.029$), mild-moderate hypoxemia (23% versus 2%, $P<0.001$), severe hypoxemia (7% versus 1%, $P=0.033$), respiratory failure (8% versus 1%, $P=0.031$), inability to breathe deeply (38% versus 12%, $P<0.001$) and muscular weakness (16% versus 1%, $P<0.001$). (Table 3)

Time from last dose of relaxant to arrival in PACU was shorter in patients with RNMB [63 min (47-105) versus 90 min (64-124), $P=0.012$]. Neostigmine had been

administered to 98% of patients with RNMB and to 81% of patients with TOF>0.9. (Table 2)

RNMB was also significantly more common after high risk surgery, as defined by the Revised Cardiac Risk Index (53% versus 33%, *P*=0.011). Patients with TOF<0.90 were more often associated with post-operative hypoactive emergence as defined by the Richmond Agitation and Sedation Scale (21% versus 6%, *P*=0.001). (Table 2)

Patients with and without RNMB did not differ in terms of age, gender, body mass index or ASA physical status. Length of hospital and PACU stays were also not different for patients with RNMB.

Discussion

The main findings of this study were that residual neuromuscular block was very frequent in the post-anaesthesia care unit and that it had an incidence of 30.2%. In addition, RNMB was more common after high-risk surgery and was associated with a shorter time interval between last dose of NMBD and admission to the PACU. Residual block was also associated with a higher incidence of post-operative critical respiratory events and hypoactive emergence.

Many European institutions have reported the practice of not administering reversal agents.[1,2,23] In the hospital where this study took place, however, it is common practice to use reversal agents in all patients as standard of care. This may account for the clinically significant but relatively low RNMB incidence of 30.2% observed. Many factors contribute to RNMB, including demographic variables such as history of chronic obstructive lung disease, the type and duration of surgery, major abdominal and thoracic surgery, general anaesthesia (as opposed to regional anaesthesia) and anaesthesia involving pancuronium.[13,14,24] These risk factors were controlled in the present study. (Table 2)

The incidence of CRE in this study was 26%. The group with RNMB presented a higher incidence of CRE when compared with the group with adequate neuromuscular recovery. This can be explained by the many risk factors for CREs, as already stated.

Interestingly, the percentage of patients to whom neostigmine was administered was higher in the RNMB group than in the group with adequate neuromuscular recovery. (Table 2) This is somewhat unexpected and an observer effect may have affected the decision-making process. Although most of the anaesthesiologists routinely administered a relaxant reversal, some might have used subjective criteria. In the latter situation, patients that received neostigmine were probably already at a higher risk of developing RNMB (due to a shorter time interval since the last dose of NMBD and the end of surgery, for example). On the other hand, patients with a longer time interval since the last dose of NMBD and the end of surgery may have not received neostigmine because RNMB was not likely. This might have led to the administration of relaxant reversal more frequently in patients that were bound to have RNMB anyway.

Two other associations were found. First, the patients that underwent high risk surgery presented a higher incidence of RNMB in the PACU. High risk surgery was defined according to the Revised Cardiac Risk Index (RCRI).[22] The RCRI is a score defined to predict major cardiac events in non-cardiac surgery. It states six independent predictors and one of them is "high risk surgical procedure", which includes intraperitoneal, intrathoracic and suprainguinal vascular surgery.

Second, patients with RNMB were more hypoactive in the PACU. Hypoactive emergence was defined according to the RASS score (RASS ≤ -2).[18] Abdominal surgery is a stated risk factor associated with hypoactive delirium.[25] In this way, abdominal surgery might be connected to the association found between high risk surgery and the incidence of RNMB and also the fact that patients with RNMB were more prone to the development of hypoactive delirium.

Although a recent study has suggested that RNMB delayed recovery room discharge no difference was detected between the two groups in the present study.[8] Hospital stays were also non-statistically different between groups. Duration of anaesthesia and duration of surgery were not associated with RNMB either.

The results of this study must be considered within the context of its limitations. This was an observational prospective study. There was no intervention on anaesthetic practices before, during or after surgery and all treatments and therapeutics were of the responsibility of the colleague assigned to PACU duty that day. The data collection took place during a limited period of time, resulting in a reduced sample size. In addition, the sample of patients may not have been representative of all cases due to sampling bias. Notably neglected were patients under 18 years-old; foreign patients; patients submitted to ambulatory, emergent/urgent, cardiac and neurosurgery; patients admitted to the long-term PACU; and patients not operated in the Central Operating Room. One cannot exclude that other non-measured factors may have acted as confounders in this study. Finally, acceleromyography is a quantitative method but there are technical and operator-related issues that must be taken into account. Therefore, some interpersonal variability and random error cannot be excluded. To minimise this, TOF-measurement training took place prior to the data collection. It must also be recognized that even high stimulating currents such as the 50 mV used may not be supramaximal in some patients.

Nevertheless, this study has clinical implications. Departmental guidelines should encourage the use of quantitative neuromuscular transmission monitoring on all patients receiving NMBD. This evidence is not as obvious when reversal agents are used routinely.[26] Special attention to these patients must be taken in the PACU setting, as they have a higher risk of postoperative complications, as shown.

Intraoperative acceleromyographic monitoring was shown to reduce the risk of RNMB and CRE in the PACU.[27] Future studies should confirm this suggestion and fundament new guidelines to reduce RNMB and its complications.

In conclusion, the RNMB incidence in the PACU throughout this study was 30.2%. An association between RNMB and increased CRE incidence, high risk surgery and hypoactive emergence was also observed.

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Tables

Table 1 Characteristics of patients

	(*n* = 202)
Age (years)	54 (41-66)
Sex (male/female)	79 (39) / 123 (61)
BMI (kg m^{-2})	26 (23-30)
ASA	
I/II	117 (88)
III/IV/V	25 (12)
RCRI	
High-risk type of surgery	79 (39)
Ischemic heart disease	8 (4)
History of congestive heart failure	9 (5)
History of cerebrovascular disease	2 (1)
Insulin therapy for diabetes	17 (8)
Preoperative serum creatinine >2.0 mg dL^{-1}	4 (4)
RCRI	
RCRI ≤2	195 (96)
RCRI >2	7 (4)
COPD	9 (5)
Hypertension	73 (36)
Hyperlipidaemia	53 (26)
Risk of surgery	
Minor	29 (14)
Medium	156 (77)
Major	17 (8)
Type of anaesthesia	
General anaesthesia	181 (90)
Combined anaesthesia	21 (10)
Intraoperative fluids	
Intravenous crystalloids (L)	1.642 ± 1.218
Intravenous colloids (L)	39.6 ± 160.6
Packed erythrocytes (Units)	11.1 ± 62.6
Fresh frozen plasma (Units)	0 ± 0

Duration of surgery (min)	105 (70-162)
Duration of anaesthesia (min)	140 (100-210)
Temperature at PACU admission (ºC)	35.2 (34.8-35.6)
<35ºC	80 (40)
Length of PACU stay (min)	100 (73-140)
Length of Hospital stay (days)	4 (2-7)
At PACU admission	
Systolic blood pressure (mmHg)	130 ± 25
Diastolic blood pressure (mmHg)	70 ± 14
Heart rate (bpm)	76 ± 17
SpO_2 (%)	96 ± 4
TOF mean	90 ± 15
TOF mean <90	30.2%
TOF mean <80	18.3%
TOF mean <70	12.4%
TOF mean <60	7%
Critical Respiratory Events	53 (26)
Upper airway obstruction	3 (2)
Mild-moderate hypoxia	20 (10)
Severe hypoxia	5 (3)
Respiratory distress	7 (4)
Inability to breathe deepely	40 (20)
Upper airway muscle weakness	11 (5)

Values are number (percentage), median (range) or mean ± SD. ASA, American Society of Anesthesiologists physical status; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PACU, post-anaesthesia care unit; RCRI, revised cardiac risk index; SD, standard deviation; TOF, train-of-four ratio.

Table 2 Characteristics of patients with (TOFm <90) and without (TOFm >90) neuromuscular residual block

	TOFm <90 (*n* = 61)	TOFm >90 (*n* = 141)	*P*
Age (years)	55 (41-68)	53 (41-65)	0.666
Sex (male/female)	21(34) / 40(66)	58 (41) / 83 (59)	0.370
BMI (kg m^{-2})	26 (24-31)	26 (23-30)	0.878
ASA			0.834
I/II	53 (87)	124 (86)	
III/IV/V	8 (13)	17 (12)	
RCRI			
High-risk type of surgery	32 (53)	47 (33)	0.011
Ischemic heart disease	4 (7)	4 (3)	0.213
History of congestive heart failure	2 (3)	7 (5)	0.594
History of cerebrovascular disease	1 (2)	1 (1)	0.540
Insulin therapy for diabetes	5 (8)	12 (9)	0.941
Preoperative serum creatinine >2.0mg dL^{-1}	2 (3)	6 (4)	0.744
RCRI			0.924
RCRI ≤2	59 (97)	136 (96)	
RCRI >2	2 (3)	5 (2)	
Duration of surgery (min)	105 (70-158)	100 (70-163)	0.646
Duration of anaesthesia (min)	140 (100-210)	140 (98-210)	0.975
Time (min) from last dose of NMBD to arrival in PACU	63 (47-105)	90 (64-124)	0.012
Patients given suxamethonium	13 (22)	17 (12)	0.059
Patients given neostigmine	59 (98)	115 (81)	0.005
Post-operative hypoactive (RASS≤2)	13 (21)	8 (6)	0.001
Temperature at PACU admission (ºC)	35.2 (34.8-35.5)	35.2 (34.8-35.8)	0.463
<35ºC	27 (44)	53 (38)	
SpO_2 at PACU admission (%)	97 (95-99)	96 (95-98)	0.148
TOF mean (%)	75 (62-84)	97 (95-99)	<0.001
Length of PACU stay (min)	100 (74-136)	100 (73-140)	0.901
Length of Hospital stay (days)	5 (2-7)	4 (2-7)	0.422

Values are number (percentage), median (range) or mean ± SD. ASA, American Society of Anesthesiologists physical status; BMI, body mass index; NMBD, neuromuscular blocking drug; PACU, post-anaesthesia care unit; RASS, Richmond agitation-sedation scale; RCRI, revised cardiac risk index; SD, standard deviation; SpO_2, oxygen saturation; TOFm, train-of-four ratio mean.

Table 3 Incidence of critical respiratory events in patients with (TOFm <90) and without (TOFm >90) neuromuscular residual block in the post-anaesthesia care unit

	TOFm <90 (*n* = 61)	TOFm >90 (*n* = 141)	*P*
Critical Respiratory Events	**31 (51)**	**22 (16)**	**<0.001**
Upper airway obstruction	3 (5)	6 (4)	0.029
Mild-moderate hypoxia	14 (23)	6 (4)	<0.001
Severe hypoxia	4 (7)	1 (1)	0.033
Respiratory distress	5 (8)	2 (1)	0.031
Inability to breathe deepely	23 (38)	17 (12)	<0.001
Upper airway muscle weakness	10 (16)	1 (1)	<0.001

Values are number (percentage) of patients. TOFm, train-of-four ratio mean.

Appendix

European Journal of Anaesthesiology

Online Submission and Review System

Guidance for Authors on the Preparation and Submission of Manuscripts to the European Journal of Anaesthesiology

Note: These instructions comply with those formulated by the International Committee of Medical Journal Editors (ICMJE). For further details, authors should consult the following article: International Committee of Medical Journal Editors. "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" *New Engl J Med* 1997, **336**:309–315. The complete document appears at http://www.icmje.org.

Scope

The *European Journal of Anaesthesiology* (EJA) publishes original work of high scientific quality in the field of anaesthesiology, pain, emergency medicine and intensive care. Preference is given to experimental work or clinical observation in man, and to laboratory work of clinical relevance. The journal also publishes commissioned reviews by an authority, abstracts of scientific meetings, editorials, commentaries, special articles and correspondence are also included.

Points to consider before submission

We have prepared a standard covering letter to accompany your submission. Please complete and submit the letter with your manuscript.

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We ask you to confirm that your paper has not been published in its current form or a substantially similar form (in print or electronically, including on a web site), that it has not been accepted for publication elsewhere, and that it is not under consideration by another publication. The ICMJE has provided details of what is and what is not duplicate or redundant publication. If you are in doubt (particularly in the case of material that you have posted on a web site), we ask you to proceed with your submission but to include a copy of the relevant previously published work or work under consideration by other journals. In the standard covering letter to the editors, draw attention to any published work that concerns the same patients or subjects as the present paper.

Conflicts of interest

Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sorces of funding should be acknowledged in the manuscript (see paragraph: Acknowledgements).

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The protection of a patient's right to privacy is essential. Please send copies of patients' consent forms on which patients or other subjects of your experiments clearly grant permission for the publication of photographs or other material that might identify them. If the consent form for your research did not specifically include this, please obtain it or remove the identifying material.

A statement to the effect that such consent had been obtained must be included in the 'Methods' section of your paper and an example of the consent form you used must be uploaded with your manuscript.

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All articles dealing with original human or animal data must include a statement on ethics approval at the beginning of the Methods section. This paragraph must contain the following information: the name and address of the ethics committee responsible; the protocol number that was attributed by this ethics committee; the name of the Chairperson of the ethics committee (or the person who approved the protocol) and the date of approval by the ethics committee.

The paragraph could read, for example:

Ethics: Ethical approval for this study (Ethical Committee N° NAC 207) was provided by the Ethical Committee NAC of Geneva University Hospitals, Geneva, Switzerland (Chairperson Prof N. Dupont) on 12 February 2007.

In addition, for studies conducted on human participants you must state clearly that you obtained written informed consent from the study participants; please also look at the latest version of the Declaration of Helsinki. Similarly, for experiments involving animals you must state the care of animal and licensing guidelines under which the study was performed. If ethics clearance was not necessary, or if there was any deviation from these standard ethical requests, please state why it was not required. Please note that the editors may ask you to provide evidence of ethical approval. If you have approval from a National Drug Agency (or similar) please state this and provide details, this can be particularly useful when discussing the use of unlicensed drugs.

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All persons designated as authors should qualify for authorship and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. One or more authors should take responsibility for the integrity of the work as a whole, from inception to

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1.5 spacing should be used throughout the manuscript, which should include the following sections, each starting on a separate page: Title Page, Abstract and Keywords, Text, Acknowledgements, References, Tables and Figures, and captions. Margins should be not less than 3 cm. Pages should be numbered consecutively, beginning with the Title Page, and the page number should be placed in the top right hand corner of each page. Two letter abbreviations should be avoided. Longer abbreviations should be defined on their first appearance in the text; those not accepted by international bodies should be avoided.

Presentation of papers

Title Page

The Title Page should carry the full title of the paper and a short title to be used as a ‘running head’ (and which should be so identified). Please, include the study design in the title; for instance, “randomized trial”, or “systematic review”. The first name, middle initial and last name of each author and their affiliations should appear. Academic degrees should not be stated. If the work is to be attributed to a department or institution, its full name should be included. The name and address of the corresponding

author and the name and address of the author to whom requests for reprints should be made should also appear on the Title Page.

Structured Abstract

For original articles (for systematic reviews and meta-analyses, see below), the second page should carry an abstract, which will be printed at the beginning of the paper and should not be more than 350 words. Use the following headings and information as appropriate (which are adapted from the BMJ and JAMA websites :

Context: Explaining the clinical (or other) importance of the study question.

Objective(s): Including a clear statement of the main aim(s) of the study and the major hypothesis tested or research question posed.

Design: For example, randomised-controlled, case control, crossover, or observational study, survey, diagnostic test etc .

Setting: Include the level of care e.g. primary, secondary; number of participating centres. Be general rather than give the name of the specific centre, but give the geographical location if this is important. Include the dates of the study period.

Patients or other participants: Numbers entering and completing the study, sex, and ethnic group if appropriate. Give clear definitions of how selected, entry and exclusion criteria. For animal studies, this information should be included in the Design or Setting section.

Intervention(s): What, how, when and for how long. This heading can be deleted if there were no interventions but should normally be included for randomised controlled trials, cross over trials, and before and after studies.

Main outcome measures: Those planned in protocol, those finally measured (if different, explain why).

Results: Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance.

Conclusions: Primary conclusions and their implications, suggest areas for further research if appropriate.

Trial registration: If appropriate, the trial registration should be stated at the end of the abstract, for example: “Trial registration: Clinicaltrials.gov identifier: NCT00405977.”

The abstract should be usable as it stands by abstracting journals. Because of this it should contain some numerical data (if appropriate), not just statistical statements, and it should not contain abbreviations or references.

For systematic reviews and meta-analyses, use the following headings and information:

Context:

Objective(s):

Data sources: Where included studies were retrieved from? Include years searched.

Eligibility criteria: Describe inclusion and non-inclusion criteria of selected studies.

Results:

Conclusions:

Key Words

The abstract should be followed by a list of 3–10 key words or short phrases which will assist the cross-indexing of the article. When possible, the terms used should be from the Medical Subject Headings list of the National Library of Medicine.

Text

The remainder of the text should be divided into sections headed Introduction, Methods (including ethical and statistical information), Results, and Discussion (including a conclusion).

Acknowledgements

The acknowledgements section should contain two distinct statements:

1. *Assistance with the study*. Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions.

2. *Conflict of interest and sources of funding*. You must make reference to all relevant conflicts of interest and sources of funding under a separate sub-heading. If there are no conflicts of interest or sources of funding please state: none declared.

For example:

Acknowledgements

We would like to thank Dr John A. Smith for his assistance with the study.

Conflicts of interest and sources of funding

This work was supported by the Department of Anaesthesiology, London Hospital, London, UK.

A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organisation Y, and C is on the speaker's bureau for Organisation X. For the remaining authors none were declared.

References

Number references consecutively in the order in which they are first mentioned in the text. Identify references in the text, tables and legends using superscripted Arabic numerals that are placed after the punctuation. References cited only in tables or in legends to figures should be numbered in accordance with the sequence established by the first identification in the text of the particular table or illustration.

Use the Vancouver reference system as adopted by the U.S. National Library of Medicine ensuring that all journal titles conform to Index Medicus approved abbreviations. If in doubt, look up the reference list of a recent paper published in the *European Journal of Anaesthesiology*.

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Books

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Chapter in a book:

Pessayre D, Feldmann G, Haouzi D, Fau D, Moreau A, Neumann M. Hepatocyte apoptosis triggered by natural substances (cytokines, other endogenous molecules and foreign toxins). In Cameron RG, Feuer G (editors): *Apoptosis and its Modulation by*

Drugs. Handbook of Experimental Pharmacology. Berlin: Springer-Verlag; 2000, pp. 59-108.

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References to tables should be made in order of appearance in the text and should be in Arabic numerals in parentheses, e.g. (Table 1). Each table should be typed on a separate sheet in 1.5 spacing. Tables should not be submitted as photographs. Each table should have a brief title as a heading. Vertical rules should not be used. Place explanatory matter in footnotes, not in the heading. Authors are discouraged from using abbreviations in tables. If abbreviations are necessary then please explain them in the table's footnotes. Identify statistical measures of variations, such as standard deviation (SD) and standard error of the mean (SEM).

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Scientific measurements should be given in SI units. Blood pressure, however, may be expressed in mmHg and haemoglobin as g dL-1.

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• A checklist for editors and reviewers (not for publication) showing that you have described the recommended respective key points in your report.

Maximum length of reports of randomised controlled trials is 3500 words. Please provide a structured abstract (max. 250 words).

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Authors are requested to report these in accordance with the PRISMA (Transparent Reporting of Systematic Reviews and Meta-Analyses) Statement [www.prisma-statement.org]. This ensures that enough information is provided for editors, peer reviewers, and readers to see how the study was performed and to judge whether the findings are likely to be reliable. Please provide the following:

• A flow chart showing the progress of retrieved reports through the review

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Conventional (non-systematic) Narrative Reviews

There are three sources of narrative reviews – commissioned, non-commissioned or invited, for instance, on the basis of a Refresher Course lecture presented at the annual Euroanaesthesia meeting.

We welcome the submission of review articles and prospective authors are invited to contact the Editor-in-Chief to discuss their proposed topic. However, all review articles undergo peer review after submission and final acceptance is not guaranteed.

Narrative reviews should start by posing a clear question they aim to answer or with a clear description of the intended educational aim. While such reviews do not include a systematic search, they should be compiled after a careful search of the available, recent literature taking care to avoid any personal bias. They should be based on the synthesis of statements that summarise the literature using appropriate references. Summary tables may be included and figures copied (with permission) from important papers in the field may help readers understand the subject matter.

The manuscript should have a maximum length of 3500 words. Please include a title page (see paragraph: Title Page) and an acknowledgement statement (see paragraph: Acknowledgement). Please provide an unstructured abstract (maximum 350 words) which should summarise the most important conclusions.

Practice Guidelines

In general, published statements intended to guide clinical care (e.g., Guidelines, Practice Parameters, Recommendations, Consensus Statements, Position Papers) should describe:

1. The clinical problem to be addressed;
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3. A review of the evidence for the statement (if available), and;
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As more than one group or society may issue statements on the same topic, this often results in confusion amongst clinicians. To minimize confusion and to enhance transparency, such statements should begin with the following bulleted phrases, followed by brief comments addressing each phrase:

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- Why does this statement differ from existing guidelines?

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Editorials discuss issues that are not directly related to published material. Editorials are usually commissioned. Editorials should be up to 1500 words long with no more than 15 references. Please include a title page giving all authors' names, addresses, email addresses, phone and fax numbers, as well as an Acknowledgement statement (see paragraph: Acknowledgements) and signed copyright forms. Editorials do not have an abstract.

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Commentaries discuss issues that are directly related to published material. Commentaries accompany original articles, critically appraise their results and put their conclusions into a wider context. Commentaries are always commissioned and should be up to 1000 words long with no more than 10 references. Commentaries do not have an abstract. Please include a title page giving the author's name, address, email address, phone and fax numbers, as well as an Acknowledgement statement (see paragraph: Acknowledgements) and signed copyright forms.

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In this section, we publish case reports, letters and replies. Items in the Correspondence section are peer reviewed. Please look at a very recent copy of the European Journal of Anaesthesiology to see how the material should be presented. The format (layout) for the Correspondence section is quite different from our other articles. The absolute maximum is 1000 words, which must include the space for any tables and illustrations (this is approximately two sides of printed matter in the Journal). References are limited to seven. For case reports please send copies of patient consent forms which clearly grant permission for the publication of photographs or other material that might identify the patient. A statement to the effect that such consent had been obtained must be included in your paper.

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