The influence of body mass index on sensorimotor block and vasopressor requirement during spinal anaesthesia for elective caesarean section

By

Dr. Tshebeletso Christian Ngaka
NGKTSH001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfillment of the requirements for the degree:

Master of Medicine in Anaesthesiology

Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Date of Submission: 27 January 2016

Supervisor: Prof Robert A. Dyer
Department of Anaesthesia, University of Cape Town

DECLARATION

I, *Dr. Tshebeletso Christian Ngaka*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate
Signature removed

Date: 27 January 2016

ACKNOWLEDGEMENTS

Professor Robert A. Dyer
For introducing this topic to me and guiding me every step of the way. His support and mentorship is what helped complete this project, and his attention to detail has inspired me to strive for excellence in my career.

My colleagues
For identifying the patients meeting the criteria for the study and informing me timely in order to recruit.

Portia Ngaka, my wife
For her unconditional support throughout my career and always encouraging me to do better.

TABLE OF CONTENTS

List of abbreviations

SA	Spinal anaesthesia
BMI	Body mass index
BP	Blood pressure
HR	Heart rate
MAP	Mean arterial pressure
SASA	South African Society of Anaesthesiologists
CS	Caesarean section
CSE	Combined spinal epidural
CSA	Continuous spinal anaesthesia
LD	Low dose
CD	Conventional dose
CI	Confidence interval
ECG	Electrocardiogram
WHO	World Health Organisation
HREC	Human Research Ethics Committe

Part A: Study protocol

As approved by the Departmental Research and Human Research Ethics Committees, University of Cape Town.

The influence of body mass index on sensorimotor block and vasopressor requirement during spinal anaesthesia for elective caesarean section

Introduction and aim of study

Spinal anaesthesia (SA) using local anaesthetics and opiates is the preferred anaesthetic technique for elective and emergency caesarian section in both non-obese and morbidly obese parturients. Hypotension following induction of SA is a common event[1] leading to maternal dizziness, nausea and vomiting and impaired placental perfusion and fetal acidaemia. In limited resource settings such as peripheral hospitals in South Africa, combined spinal – epidural anaesthesia, which allows for a reduction of the initial spinal dose and subsequent epidural top-up, is not a feasible option, particularly in the emergency situation. Therefore single shot SA is favoured in most cases.

A recent meta-analysis suggests that any reduction of the bupivacaine dose during single shot SA in the non-obese population to less than 10 mg, results in a significantly increased requirement for analgesic supplementation, and possibly conversion to general anaesthesia.[2] Maternal weight may be a significant variable in predicting block height and consequent hypotension and the need for inotropes/vasopressors. Many obstetric anaesthetists do adjust their dose regimen in morbidly obese patients, with a view to achieving adequate surgical anaesthesia while minimizing haemodynamic side effects. Current practice at our institution is to use the same standard dose of local anaesthetic and opiate for SA for caesarean section in both non-obese and morbidly obese parturients, since prolonged surgical time in obese patients is an important consideration. In addition, a recent investigation suggests that the ED95 for spinal bupivacaine in obese patients is similar to that in non-obese patients.[3] Conversion to general anaesthesia for caesarean section in morbidly obese patients is associated with a significantly increased maternal and fetal risk.[4] Therefore this study will compare an identical dose of spinal

bupivacaine of 10 mg, plus 10 µg fentanyl, in non-obese and morbidly obese patients.

The primary outcome variable will be:

- Vasopressor requirement (mean phenylephrine dose in the first 30 minutes after induction of SA)

The secondary outcome variables will be:

- Maximum block height (touch and cold modalities)
- Time to regression to T6 of block height as assessed by cold sensation, and to T10 as assessed by touch
- Adequacy of anaesthesia, as measured by requirement for analgesic supplementation and conversion to general anaesthesia
- Measurements of motor block: hand grip strength and peak expiratory flow
- Maternal side-effects such as nausea and vomiting
- Neonatal umbilical arterial blood gas values, and Apgar scores

Hypothesis

The hypothesis of this study is that there will be no difference between the groups with regard to vasopressor requirement.

Patients and Methods

Approval for the study will be obtained from the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town. The study will be performed at the Groote Schuur Hospital Maternity Centre and at Mowbray Maternity Hospital. Written informed consent will be obtained at the time of recruitment. Two groups of 25 patients per group requiring elective caesarean section will be recruited. One group will comprise women with normal body mass index (BMI), defined as 32 kg/m^2, and the other group will comprise morbidly obese parturients with a BMI of ≥ 40 kg/m^2.

Inclusion criteria will be:

- ASA Class 1 and 2
- Gestational age 37 completed weeks
- Singleton pregnancy
- Elective caesarean section

Exclusion criteria will be:

- Patient refusal
- Pre-existing hypertension, or preeclampsia
- Any contraindication to SA
- Multiple pregnancy
- Urgent or emergency caesarean section
- Gestational age < 37 completed weeks
- Patients in whom obstetric haemorrhage is likely, i.e.
    - More than 2 previous caesarean sections
    - Placenta praevia
- Labour
- Inability to understand the procedure for testing for dermatome height of the neuraxial block
- Failed SA

Prior to the surgical procedure, each patient will be visited in the ward by the anaesthesiologist, who will familiarise her with the testing procedure to determine the dermatome level of the neuraxial block using light touch and cold sensation.

On arrival in theatre, IV access will be secured with at least an 18G cannula, 30 mL of 0.3 M Sodium Citrate will be administered per os and intravenous Cefazolin, 1 or 2 g depending on maternal weight below or above 80 kg. Standard monitoring will be applied as per South African Society of Anaesthesiologists (SASA) guidelines, consisting of 3 lead ECG, pulse oximeter and non-invasive blood pressure monitoring. An appropriate sized blood pressure (BP) cuff for noninvasive BP measurements will be applied. According to the American Heart Association, the width of the compression

bladder should be equal to 40% of the circumference or 1.2 times the diameter of the extremity.[5] The diameter or circumference of the extremity is measured at midpoint of the limb. For the arm, midpoint is measured at half the distance between the shoulder and the elbow joints. If the patient's limb measurement is on the borderline of two different cuff sizes the likelihood of an erroneous measurement is decreased if the larger of the two cuff sizes is used. Cuffs that are wrapped too loosely result in falsely elevated values. Cuffs will be applied snugly, allowing only enough room for one finger to be slipped between the cuff and the skin surface. Baseline mean arterial blood pressure will be recorded with the patient lying in the left lateral position. It will be the average of three readings, which are within 10% of each other, measured during the five minutes prior to sitting up for SA. SA will be administered using aseptic technique with the patient in the sitting position. After skin infiltration with lignocaine, a 25G Whitacre spinal needle or a 103 mm Braun Pencan needle will be inserted at the L3/4 intervertebral space. After the subarachnoid space has been identified, a rapid infusion of Ringers Lactate 20 mL/kg will be administered. Subarachnoid injection will consist of 2 mL of hyperbaric 0.5% bupivacaine and 10 µg of fentanyl. The patient will then be placed supine, and a wedge placed under the right flank to achieve a 15^0 left lateral tilt. Bilateral sensory block height will be monitored 5 minutes after induction of SA, using both the light touch and cold sensation modalities in response to ethyl chloride spray.[6] Surgery will commence on achieving a bilateral sensory block of cold sensation to the T_4 dermatome level. Block height will be assessed again at 25 minutes, by which time maximum block height would have been reached. This will be repeated on completion of surgery. Strength of hand-grip, as measured by dynamometry, will be used to ensure that high motor block has not occurred (C8-T1 or higher). A peak flow meter will be used to assess the effect of SA on respiratory function. Hand-grip strength and peak flow readings will be taken in the induction room in the supine/wedged position (baseline), and 30 minutes after induction of SA. Haemodynamic data including systolic, diastolic and mean arterial pressure and heart rate (HR) will be recorded every minute for the duration of surgery. Hypotension, defined as a 20% decrease from baseline mean arterial pressure (MAP), will be treated with intravenous phenylephrine 50 µg. A 30%

decrease in MAP, or failure to restore blood pressure to within 20% of baseline value within the first minute after the administration of 50 µg, will be treated with 100 µg of phenylephrine. If HR decreases to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), ephedrine 10 mg will be administered, followed by atropine 0.25-0.5 mg if bradycardia persists. Ephedrine may also be administered if there is a poor response to two consecutive doses of phenylephrine. Associated nausea and vomiting will be treated with IV metoclopramide 10mg. If a patient should report discomfort during surgery, 50% nitrous oxide/oxygen will be administered via facemask, and further analgesia can be provided if necessary with up to 4 boluses of 250 µg of alfentanil. Continued discomfort will necessitate conversion to a general anaesthetic. After delivery, 3 units of oxytocin will be administered IV during one minute.

Time intervals to be noted will be:

a. Time from arrival in theatre until induction of anaesthesia
b. Time to T4 sensory block level
c. Induction to skin incision time
d. Induction to uterine incision time
e. Uterine incision to delivery time
f. Skin incision to closure

Adequacy of SA will be scaled as follows:

Grade 1: No supplementation required.
Grade 2: Analgesic supplementation required as per protocol.
Grade 3: Conversion to general anaesthesia required.

Bloodloss will be estimated by measurement in a graded suction bottle, and by observation of swabs. In patients in whom blood loss is estimated at 1 litre, vasopressor requirements from that time onwards will not be used to estimate total vasopressor requirement in that patient. Time to regression to T6 of block height as assessed by cold sensation, and to T10 as assessed by touch, will be measured in recovery room.

Calculation of sample size

With regard to the primary outcome variable, namely total phenylephrine dose, a clinically relevant between-group difference in mean vasopressor requirement is 200 μg. Assuming a standard deviation of 200 μg in each group, using a two-tailed t-test for independent samples, group sizes of 21 per group will be required to detect such a difference with 80% power and assuming an alpha error of 0.051"/>†.

In addition, according to clinical experience, subarachnoid injection of hyperbaric bupivacaine 10 mg and fentanyl 10 μg as described above, usually produces sensory block up to the T_3 dermatome (range T_1 to T_5). A difference of one dermatome in block height in the obese group would be regarded as clinically important (for example up to T_2 dermatome (range C_8 to T_4)). Similar power and alpha as for vasopressor requirement would be obtained using 16 patients per group.‡ In order to reduce allow for greater than anticipated variability in vasopressor response, and for the possibility that the occasional cervical block may be missed if a small number of patients are recruited, it is therefore intended to study a total of 50 patients.

1"/>† Calculated using the method described by Columb and Stevens (2008).[25]
‡ Medcalc Statistical Software, version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

Data analysis

Numerical, between-group data will be compared using two-tailed t-tests for independent samples. Within-group data will be analysed using analysis of variance for repeated measures. If data do not meet the requirements for normal distribution and equivalence of variance, then nonparametic, distribution-free tests (e.g. Mann-Whitney, Freedman) will be employed. Nonparametric tests will also be employed for analysis of ordinal, categorical data. Proportional data will be analysed using Chi-squared or Fisher's exact tests. A p-value of 0.05 or less will be regarded as indicating statistical significance.

References

1. Langesæter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol*. 2011;24(3):242-248. doi:10.1097/ACO.0b013e32834588c5.
2. Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. *Br J Anaesth*. 2011;107(3):308-318. doi:10.1093/bja/aer200.
3. Carvalho B, Collins J, Drover DR, Atkinson Ralls L, Riley ET. ED(50) and ED(95) of intrathecal bupivacaine in morbidly obese patients undergoing cesarean delivery. *Anesthesiology*. 2011;114(3):529-35. doi:10.1097/ALN.0b013e318209a92d.
4. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. *Anesthesiology*. 1993;79(6):1210-8.
5. Pickering, T.G., Hall, J.E., Appel, L.J., Falker, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S., Rocella, E.J.Kurtz TW.

American Heart Association Council on High Blood Pressure Research Professionals From the Subcommittee of Professional and Public Education of the Animals: Part 2: Blood Pressure Measurement in Experimental Animals: A Statement for Recommendations for Blo. *Circulation*. 2005;111:697-716. doi:10.1161/01.HYP.0000150857.39919.cb.

6. Ousley R, Egan C, Dowling K, Cyna a. M. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. *Anaesthesia*. 2012;67(12):1356-1363. doi:10.1111/anae.12034.
7. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11234459.
8. Milligan KR, Carp H. Continuous spinal anaesthesia for caesarean section in the morbidly obese. *Int J Obstet Anesth*. 1992;1(2):111-113. doi:10.1016/0959-289X(92)90009-S.
9. Palmer CM. Continuous spinal anesthesia and analgesia in obstetrics. *Anesth Analg*. 2010;111(6):1476-1479. doi:10.1213/ANE.0b013e3181f7e3f4.
10. McKeen DM, George RB, O'Connell CM, et al. Difficult and failed intubation: Incident rates and maternal, obstetrical, and anesthetic predictors. *Can J Anesth*. 2011;58(6):514-524. doi:10.1007/s12630-011-9491-9.
11. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft tissue anatomy within the vertebral canal in pregnant women. *Br J Anaesth*.

1996;77(2):153-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8881616.

12. Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L. Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure. *Anesthesiology*. 1996;84(6):1341-9. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2443094&tool=pmcentrez&rendertype=abstract\nhttp://www.ncbi.nlm.nih.gov/pubmed/8669675.
13. Pitkänen MT. Body mass and spread of spinal anesthesia with bupivacaine. *Anesth Analg*. 1987;66(2):127-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3813056.
14. Norris MC. Spinal Anesthesia - Bupivicaine Distribution. *Anesth Analg*. 1988;67:555-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3377210.
15. Norris MC. Patient Variables and the spread of Subarachnoid hyperbaric bupicavacaine in the term parturient. *Anesthesiology*. 1990;72:478-482.
16. Hodgkinson R, Husain FJ. Obesity and the Cephalad Spread of Analgesia following Epidural Administration of Bupivacaine for Cesarean Section. *Anesth Analg.* 1980;59(2):89-92. Available at: http://www.anesthesia-analgesia.org/content/59/2/89.short.
17. Hartwell BL, Aglio LS, Hauch M a, Datta S. Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. *Reg Anesth*. 1991;16(1):17-9. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/2007099.

18. Harten JM, Boyne I, Hannah P, Varveris D, Brown a. Effects of a height and weight adjusted dose of local anaesthetic for spinal anaesthesia for elective Caesarean section. *Anaesthesia*. 2005;60(4):348-353. doi:10.1111/j.1365-2044.2005.04113.x.
19. Ben-David B, Miller G, Gavriel R, Gurevitch a. Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med*. 2000;25(3):235-239. doi:10.1053/xr.2000.5654.
20. Choi DH, Ph D, Ahn HJ, Kim MH. in Spinal Anesthesia Effect of Fentanyl for Cesarean Delivery. 2000;25:240-245.
21. Dyer RA, Joubert IA. Low-dose spinal anaesthesia for Caesarean section. *Curr Opin Anaesthesiol*. 2004;17(4):301-308. doi:10.1097/01.aco.0000137088.29861.64.
22. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology*. 2004;100(3):676-682. doi:10.1097/01.sa.0000151214.68591.de.
23. Lee Y, Balki M, Parkes R, Carvalho JC a. Dose requirement of intrathecal bupivacaine for cesarean delivery is similar in obese and normal weight women. *Rev Bras Anestesiol*. 2009;59(6):674-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20011857.
24. Einhorn L, Akushevich I, Habib AS, Bch MB. Evaluation of the risk of exaggerated cephalad spinal block in obese parturients. :27710.
25. Columb MO, Stevens a. Power analysis and sample size calculations. *Curr Anaesth Crit Care*. 2008;19(1):12-14.

Part B: Descriptive Literature review

Dose regimen for spinal anaesthesia for caesarean section in morbidly obese patients

1. Objectives

This literature review aims to assess current literature on the influence of body mass index on bupivacaine dosing for single shot spinal anaesthesia (SA) for caesarean section (CS). The correct dose regimen for SA in morbidly obese parturients remains controversial amongst obstetric anaesthetists, since some practitioners perceive block height and concomitant hypotension as unpredictable in these patients.

2. Literature Search Strategy

The full text of relevant publications was obtained online, from the University of Cape Town Health Science Library search facility, which accesses 17 medical digital archive databases worldwide. Literature published in the English language before and including the year 2014 was included.

3. Quality criteria

The following keywords in various combinations were used for the search: spinal anaesthesia, pregnancy, body mass index, obesity, caesarean section, subarachnoid spread, block height assessment, hypotension, bupivacaine, and fetal outcome. The reference list was also used to identify further appropriate papers.

4. Review and critical appraisal of the literature

4.1 Introduction

Obesity is defined simply as a condition of abnormal or excessive fat accumulation in adipose tissue to the extent that health may be impaired. The WHO characterises obesity as a pandemic with the prevalence higher in women than men.[7] Consequently the obstetric anaesthetist is increasingly

confronted with the problem of anaesthetising obese parturients. Spinal anaesthesia (SA), using bupivacaine and opiates is the preferred technique to provide anaesthesia for elective and emergency CS. Maternal hypotension due to sympathetic blockade is a common and feared consequence of SA,[1] which often leads to maternal dizziness, nausea/ vomiting, and placental hypoperfusion, thus compromising maternal and fetal outcome. Combined spinal epidural (CSE) anaesthesia, which allows for reduction of the initial spinal dose and subsequent epidural top-up, is an attractive option commonly practiced in highly resourced units. However, CSE is not feasible in resource-limited peripheral hospitals in South Africa and for emergency caesarean section. The epidural catheter also remains "unproven" during the duration of SA, which poses a risk for failure of anaesthesia when SA regresses. Continuous spinal anaesthesia (CSA) has also been postulated to be an option for CS in the morbidly obese, but is technically difficult and may be associated with post-dural puncture headache and infection.[8,9] For this reason single shot SA is the preferred technique in most cases. Maternal weight may be a significant variable in predicting block height and consequent hypotension and the need for vasopressors/inotropes. Many obstetric anaesthetists adjust their dose regimen in morbidly obese patients, with a view to achieving adequate surgical anaesthesia while minimising haemodynamic side effects. Conversion to general anaesthesia for caesarean section in morbidly obese patients is associated with a significantly increased risk of difficult intubation,[10] which may result in poor maternal and neonatal outcome. Current practice at our institution is to use an identical dose of local anaesthetic and opiate for CS in both non-obese and morbidly obese parturients, since prolonged surgical time in obese patients is an important consideration, and a reduction in dose could compromise surgical anaesthesia.

4.2 Anatomical considerations within the vertebral canal during pregnancy

The effective capacity of the extradural and subarachnoid spaces is reduced in supine parturients as a result of the engorged extradural venous plexus.[11]

This reduced capacity results in a compensatory reduction in cerebrospinal fluid (CSF) volume. Hogan et al.[12] in a magnetic resonance imaging (MRI) study also suggested further reduction of the CSF volume in patients with a high body mass index (BMI). Various mechanisms that exert external pressure on the dural sac have been proposed for the lower CSF volume: increased intra-abdominal pressure from abdominal fat; epidural venous plexus engorgement secondary to inferior vena cava compression and diversion of venous return; and the inward movement of soft tissue in the intervertebral foramen displacing CSF. These changes in addition to possible enhanced neural susceptibility to local anaesthetics in pregnant women result in a 25% reduction in dose requirement for spinal and epidural anaesthesia compared to the non-pregnant state.

4.3 Relationship between block height and body mass index

An early investigation showed a tendency towards higher cephalad spread of local anaesthetic, more rapid onset and more rapid recovery from anaesthesia in obese non- pregnant patients receiving isobaric intrathecal bupivacaine, compared with patients with a normal BMI.[13] However, these observations are of limited clinical relevance in predicting subarachnoid spread of hyperbaric local anaesthesia in morbidly obese parturients. The studies investigating the relationship between patient variables (weight and height) and block height are limited and show conflicting results.[7-11] Norris *et al.*[14,15] showed no correlation between the height of sensory block and patient BMI. In these studies, morbidly obese patients were not included, and a fixed dose of up to 15 mg hyperbaric bupivacaine with morphine 150 µg was used. Hodgkinson *et al.*[16] showed a positive correlation between obesity and the cephalad spread of epidural bupivacaine in parturients undergoing either elective or emergency caesarean section. However, this study did not include morbidly obese patients and despite sensory blocks up to C5 dermatome level in some obese patients, no respiratory embarrassment was demonstrated. Vertebral column length was also suggested as an important variable with regard to local anaesthetic spread within the subarachnoid space, but no correlation has been shown.[17] In their randomized control trial Harten et al. suggest that

adjusting the SA dose regimen for cesarean section according to the patient's weight and height results in less hypotension and fewer blocks above T_1 dermatome level.[18] Patients were randomised to receive a fixed dose of 12 mg hyperbaric bupivacaine and 0,4 mg diamorphine, or an adjusted dose using a chart taking height and weight into account. The adjusted dose group received a median [IQR] dose of hyperbaric bupivacaine of 9.5 [9-10] mg. In the fixed dose group six patients experienced loss of sensation to pinprick above T_1 dermatome, and three patients to C_8 but no patients required ventilator support. On the other hand some patients in the adjusted dose group required supplementation of analgesia suggesting that adjusting the dose according to patient's weight might result in inadequate anaesthesia for caesarean section. The use of dose charts is not common practice at our institution and clinical experience is that 12 mg is too high a subarachnoid dose for our patient population while 9 mg increases the possibility of maternal discomfort requiring analgesia supplementation.

4.4 Evidence for spinal bupivacaine dose/response

The proposed advantages of minimising the intrathecal dose of hyperbaric bupivacaine include: reduced incidence of maternal hypotension, reduced vasopressor requirement, reduced incidence of nausea/vomiting and shorter discharge times from post anaesthesia care unit.[19,20] However, a recent review cautions against the use of low dose SA for CS, in view of the risk of inadequate anaesthesia.[21] A recent meta-analysis suggests that any reduction of the bupivacaine dose during single shot SA in the non-obese population to less than 8 mg, results in significantly increased requirement for analgesic supplementation and possibly conversion to general anaesthesia.[2] The authors reviewed low dose (LD) bupivacaine group (≤ 8 mg) and conventional dose (CD) bupivacaine group (> 8 mg) for elective or semi-urgent caesarean section. With regards to their primary outcome namely anaesthetic efficacy as measured by intraoperative anaesthetic/analgesic supplementation, the risk was three times higher in the LD bupivacaine group (RR=3.76, 95% CI= 2.38- 5.98, P< 0.00001) than the CD bupivacaine group. The dermatomal block height ranged between T_2 – T_6, however, there was

heterogeneity in the assessment methods used. Despite the proposed lower risk of maternal side effects in LD than CD (22% reduction in hypotension and 29% reduction in nausea and vomiting) [15], low dose spinal anaesthesia may not be the optimal technique for all patients especially if surgical time is likely to be prolonged and conversion to general anaesthesia poses a much higher maternal and neonatal risk. The potency of local anaesthetics is expressed in terms of the minimum effective concentration or dose (EC_{50} or ED_{50} and ED_{95}). In non-obese parturients the ED_{50} and ED_{95} for hyperbaric bupivacaine with opiate has been shown to be 7.6 mg and 11.2 mg respectively.[22] The authors also caution against dose reduction for hyperbaric bupivacaine doses for SA. Doses less than the ED_{95} and ED_{50} showed a 5% and 50% failure rate, respectively. In a further recent publication Lee *et al*[23] suggested the ED_{95} for intrathecal hyperbaric bupivacaine in obese patients (BMI more than 30 kg/m^2) to be 12.92 mg (95% CI: 11.49 – 34.77) which is similar to that in non-obese patients. This study is limited by use of historical control and the design was different to that used in the original study for the control group. A recent investigation, which is also limited by the use of historical controls, suggests that the ED_{95} for spinal bupivacaine with opiates in morbidly obese patients is 15 mg (CI 10.0 – 20.0), which is similar to that in non-obese patients.[3] Morbidly obese patients in the study (BMI ≥ 40 kg/m^2) undergoing elective CS under combined spinal epidural were randomly assigned to receive up to 11 mg intrathecal hyperbaric bupivacaine with 200 µg morphine and 10 µg fentanyl. The primary outcome was success or failure of the intrathecal block. A block was regarded as successful if a T_6 sensory level to pinprick was obtained within ten minutes of induction of SA with no epidural supplementation required during the operation. The adequacy of analgesia was assessed using a visual analogue scale and epidural supplementation was provided with score of 20mm and above as well as on patient request. Even with this modest dose of hyperbaric bupivacaine for SA, greater incidence or severity of hypotension or significant differences in the incidence of nausea and vomiting was not demonstrated. However, this study was not adequately powered to detect differences in the incidence or severity of hypotension or incidence of nausea and vomiting with doses above 10 mg. The authors conclude that morbidly obese and non-obese patients show a

similar response to modest doses of intrathecal hyperbaric bupivacaine. However, the dose response in the obese population is variable, but doses less than 10 mg (*i.e.* doses < 95% CI value) are not recommended. These findings do however support our hypothesis that the dose requirement for spinal bupivacaine for caesarean delivery is similar in morbidly obese and non-obese patients. Finally, a retrospective analysis suggests that high cephalad spread of bupivacaine is unlikely unless the BMI is higher than 50 kg/m^2.[24]

4.4 Proposed study

To our knowledge there is no published prospective comparison of identical dose spinal bupivacaine for CS in morbidly obese versus normal BMI parturients. In addition, more than 1000 morbidly obese parturients have received SA for CS employing 10 mg hyperbaric bupivacaine with 10 µg fentanyl during the past 3 years at our institution. It was therefore decided to study 2 groups of patients, one in the low BMI range, and the other in the morbidly obese category, and assess block height, vasopressor requirement and surgical anaesthesia.

References

1. Langesæter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol*. 2011;24(3):242-248. doi:10.1097/ACO.0b013e32834588c5.
2. Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-

analysis. *Br J Anaesth*. 2011;107(3):308-318. doi:10.1093/bja/aer200.

3. Carvalho B, Collins J, Drover DR, Atkinson Ralls L, Riley ET. ED(50) and ED(95) of intrathecal bupivacaine in morbidly obese patients undergoing cesarean delivery. *Anesthesiology*. 2011;114(3):529-35. doi:10.1097/ALN.0b013e318209a92d.

4. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. *Anesthesiology*. 1993;79(6):1210-8. doi:10.1097/00000542-199312000-00011.

5. Pickering, T.G., Hall, J.E., Appel, L.J., Falker, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S., Rocella, E.J.Kurtz TW. American Heart Association Council on High Blood Pressure Research Professionals From the Subcommittee of Professional and Public Education of the Animals: Part 2: Blood Pressure Measurement in Experimental Animals: A Statement for Recommendations for Blo. *Circulation*. 2005;111:697-716. doi:10.1161/01.HYP.0000150857.39919.cb.

6. Ousley R, Egan C, Dowling K, Cyna a. M. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. *Anaesthesia*. 2012;67(12):1356-1363. doi:10.1111/anae.12034.

7. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11234459.

8. Milligan KR, Carp H. Continuous spinal anaesthesia for caesarean section in the morbidly obese. *Int J Obstet Anesth*. 1992;1(2):111-113. doi:10.1016/0959-289X(92)90009-S.

9. Palmer CM. Continuous spinal anesthesia and analgesia in obstetrics. *Anesth Analg*. 2010;111(6):1476-1479. doi:10.1213/ANE.0b013e3181f7e3f4.

10. McKeen DM, George RB, O'Connell CM, et al. Difficult and failed intubation: Incident rates and maternal, obstetrical, and anesthetic

predictors. *Can J Anesth*. 2011;58(6):514-524. doi:10.1007/s12630-011-9491-9.

11. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft tissue anatomy within the vertebral canal in pregnant women. *Br J Anaesth*. 1996;77(2):153-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8881616.

12. Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L. Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure. *Anesthesiology*. 1996;84(6):1341-9. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2443094&tool=pmcentrez&rendertype=abstract\nhttp://www.ncbi.nlm.nih.gov/pubmed/8669675.

13. Pitkänen MT. Body mass and spread of spinal anesthesia with bupivacaine. *Anesth Analg*. 1987;66(2):127-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3813056.

14. Norris MC. Spinal Anesthesia - Bupivicaine Distribution. *Anesth Analg*. 1988;67:555-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3377210.

15. Norris MC. Patient Variables and the spread of Subarachnoid hyperbaric bupicavacaine in the term parturient. *Anesthesiology*. 1990;72:478-482.

16. Hodgkinson R, Husain FJ. Obesity and the Cephalad Spread of Analgesia following Epidural Administration of Bupivacaine for Cesarean Section. *Anesth Analg*. 1980;59(2):89-92. Available at: http://www.anesthesia-analgesia.org/content/59/2/89.short.

17. Hartwell BL, Aglio LS, Hauch M a, Datta S. Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. *Reg Anesth*. 1991;16(1):17-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2007099.

18. Harten JM, Boyne I, Hannah P, Varveris D, Brown a. Effects of a height

and weight adjusted dose of local anaesthetic for spinal anaesthesia for elective Caesarean section. *Anaesthesia*. 2005;60(4):348-353. doi:10.1111/j.1365-2044.2005.04113.x.

19. Ben-David B, Miller G, Gavriel R, Gurevitch a. Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med*. 2000;25(3):235-239. doi:10.1053/xr.2000.5654.

20. Choi DH, Ph D, Ahn HJ, Kim MH. in Spinal Anesthesia Effect of Fentanyl for Cesarean Delivery. 2000;25:240-245.

21. Dyer RA, Joubert IA. Low-dose spinal anaesthesia for Caesarean section. *Curr Opin Anaesthesiol*. 2004;17(4):301-308. doi:10.1097/01.aco.0000137088.29861.64.

22. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology*. 2004;100(3):676-682. doi:10.1097/01.sa.0000151214.68591.de.

23. Lee Y, Balki M, Parkes R, Carvalho JC a. Dose requirement of intrathecal bupivacaine for cesarean delivery is similar in obese and normal weight women. *Rev Bras Anestesiol*. 2009;59(6):674-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20011857.

24. Einhorn L, Akushevich I, Habib AS, Bch MB. Evaluation of the risk of exaggerated cephalad spinal block in obese parturients. :27710.

25. Columb MO, Stevens a. Power analysis and sample size calculations. *Curr Anaesth Crit Care*. 2008;19(1):12-14. doi:10.1016/j.cacc.2007.03.011.

Part C: Manuscript

Title page

The influence of body mass index on sensorimotor block and vasopressor requirement during spinal anaesthesia for elective caesarean section

1. Author: TC Ngaka, (MBChB)

- Title: Dr.
- Affiliation: Department of Anaesthesia, University of Cape Town, Cape Town, South Africa
- Email: ngakatc@yahoo.com
- Contribution: study design, conduct of the study, data collection, data analysis, and manuscript preparation
  Attestation: Dr. TC Ngaka approved the final manuscript
- Conflicts of Interest: None

2. Author: JF Coetzee, FCA (SA), PhD

- Title: Emeritus Professor
- Affiliation: Department of Anaesthesia and Critical Care, University of Stellenbosch, Cape Town, South Africa
- Email: jfc@sun.ac.za
- Contribution: study design, data analysis, and manuscript preparation
- Attestation: Prof Coetzee approved the manuscript
- Conflicts of Interest: None

3. Author: RA Dyer, FCA (SA), PhD

- Title: Professor

- Affiliation: Department of Anaesthesia, University of Cape Town, Cape Town, South Africa
- Email: robert.dyer@uct.ac.za
- Contribution: Study design, conduct of study, data analysis, and manuscript preparation
- Attestation: Professor Dyer approved the manuscript
- Professor Dyer is the archival author
- Conflicts of Interest: None

Name of Department(s) and Institution(s):
Department of Anaesthesia, University of Cape Town

Short Title: Spinal anesthesia for cesarean section in the morbidly obese

Funding: N/A
Corresponding Author:
Name: Professor RA Dyer
Department: Anaesthesia
Institution: University of Cape Town
Mailing address: D23 Department of Anaesthesia, University of Cape Town and New Groote Schuur Hospital, Anzio Road, Observatory 7925, Cape Town, South Africa
Phone: +27836002095
Fax: +27214066589
Email: robert.dyer@uct.ac.za

Did a Section Editor solicit this submission? N/A

IRB:
University of Cape Town Health Sciences Faculty Human Research Ethics Committee.
Chairperson: Professor M Blockman
Email: Marc.blockman@uct.ac.za
Telephone: +27214066496

Background

It has been suggested that the dose requirement for spinal anesthesia (SA) is lower in obese patients for cesarean delivery. In this prospective, observational, non-inferiority study we tested the hypothesis that obesity would not have a clinically important effect on vasopressor requirements or block height.

Methods

Two groups of 25 parturients, Group O (BMI >40 kg/m^2) and Group N (BMI <32 kg/m^2) requiring elective cesarean delivery were recruited. All patients received 10 mg intrathecal hyperbaric bupivacaine co-administered with 10 μg fentanyl. Dermatomal levels were assessed at 5 and 25 minutes after SA, and at completion of surgery, using light touch and cold sensation in response to ethyl chloride. The primary outcomes were phenylephrine requirement in the first thirty minutes following spinal anesthesia, and maximum block height, measured by the sensation of touch and cold. Secondary outcomes were total phenylephrine dose required, changes in hand grip strength, and peak flow rate.

Results

There were no significant between-group differences in median block height as assessed by touch at 5 or 25 minutes, or by temperature at 5 minutes. At 25 minutes, there was a two-dermatome difference in median block height for loss of temperature sensation between Group O and Group N (T2 vs. T4, 95% confidence interval (CI) of the difference in medians 0-2 dermatomes). No blocks extended to cervical dermatomes. The median (range) phenylephrine dose for the first 30 minutes was 150 μg (0-900 μg), and 100 μg (0-1250 μg) in Group N and O respectively. The 95% CI for the difference between the two median doses was -150 μg to 100 μg. There were no differences in median percentage reductions in peak flow rate or median hand grip strength after SA. Mean surgical time was longer in Group O than in Group N (49.1 vs 39.4 minutes, 95% CI difference 1.7 to 17.7 minutes). The mean time for recovery of touch sensation to T10 was longer in Group O (152 vs 132 minutes, 95% CI difference 3.8 to 36.2 minutes). No analgesic supplementation was required.

Conclusion

Only a minor increase block height as assessed by temperature occurred in Group O at 25 minutes. Vasopressor requirements during the first 30 min of SA were equivalent. Time for regression of SA block level was longer in the Group O, which may be beneficial considering the longer surgical time. A dose of spinal bupivacaine 10 mg for single-shot SA should not be reduced in morbidly obese parturients.

Main text

Introduction

Regional anaesthesia using local anesthetics and opiates is the preferred anesthetic technique for elective and emergency caesarean section in both non-obese and morbidly obese parturients. Hypotension following induction of spinal anesthesia (SA) is a common event,[1] leading to maternal dizziness, nausea and vomiting, impaired placental perfusion and fetal acidaemia. Morbidly obese patients pose particular challenges to the anesthesiologist. In limited resource settings such as peripheral hospitals in South Africa, combined spinal – epidural anesthesia, which allows for a reduction of the initial spinal dose and subsequent epidural top-up, is not a feasible option, particularly in the emergency situation. Therefore single shot SA for morbidly obese parturients is favoured in most cases.

A recent meta-analysis suggests that any reduction of the bupivacaine dose during single shot SA in the non-obese population to less than 8 mg, results in a significantly increased requirement for analgesic supplementation.[2] Maternal weight may be a significant variable in predicting block height and consequent hypotension and the need for inotropes/vasopressors. Many obstetric anesthetists do adjust their dose regimen in morbidly obese patients, with a view to achieving adequate surgical anesthesia while minimising hemodynamic side effects. Current practice at our institution is to use the same standard dose of local anesthetic and opiate for SA for caesarean section in both non-obese and morbidly obese parturients, since prolonged surgical time in obese patients is an important consideration. In addition, two recent investigations suggest that the ED95 for spinal bupivacaine in obese patients is similar to that in non-obese patients.[3;4] Conversion to general anesthesia for caesarean section in morbidly obese patients is associated with a significantly increased maternal and fetal risk. Therefore this study compared an identical dose of spinal bupivacaine of 10 mg, plus 10 µg

fentanyl, our usual practice, in non-obese and morbidly obese patients. The primary outcome variables were mean vasopressor requirement (phenylephrine) in the first 30 minutes after induction of SA, and maximum block height as measured by the sensation of touch and cold. Secondary outcomes were surrogate measurements of the extent of motor block (hand grip strength and peak flow rate), pertinent time intervals relating to the procedure, including time to regression of block, adequacy of anesthesia, maternal side effects, and early neonatal outcome.

Methods

This was a stratified cohort study. Approval for the study was obtained from the Health Sciences Faculty Human Research Ethics Committee of the University of Cape Town (HREC/REF:031/2013). The study was performed at the Groote Schuur Hospital Maternity Centre and at Mowbray Maternity Hospital, Cape Town, South Africa. Written informed consent was obtained at the time of recruitment, at least 12 hours before SA for elective CS. Two groups of 25 patients were recruited with widely differing body mass indices, in order to examine the influence of body mass index (BMI) on the responses to a specific dose of spinal bupivacaine. One group comprised women with BMI < 32 $kg.m^{-2}$ (Group N), and the other group had a BMI of > 40 $kg.m^{-2}$ (Group O). For consistency, parturients were weighed at the time of recruitment, since the investigating team did not have access to the participants in early pregnancy.

Inclusion criteria were: ASA Class 1 and 2, gestational age > 37 completed weeks, singleton pregnancy, and elective caesarean section.

Exclusion criteria were: Patient refusal, pre-existing hypertension, or preeclampsia, any contraindication to SA, multiple pregnancy, urgent or emergency caesarean section, patients in whom obstetric haemorrhage was likely, i.e. more than 2 previous caesarean sections, placenta praevia, active labour, inability to understand the procedure for testing for dermatome height of the neuraxial block, or failed SA.

Prior to the surgical procedure, each patient was visited in the ward by the anesthesiologist, who familiarised her with the testing procedures to determine the dermatome level of the neuraxial block using the modalities touch and cold sensation.

On arrival in theatre, IV access was secured with an 18G cannula; 30 mL of 0.3 M Sodium Citrate was administered per os, and intravenous Cefazolin 1 or 2 g, depending on maternal weight below or above 80 kg. Standard monitoring was applied, consisting of 3 lead ECG, pulse oximeter and non-invasive blood pressure monitoring. An appropriate sized blood pressure (BP) cuff for noninvasive BP measurements was applied. According to the American Heart Association, the width of the compression bladder should be equal to 40% of the circumference or 1.2 times the diameter of the extremity.[5] The diameter or circumference of the extremity is measured at midpoint of the limb. For the arm, midpoint is measured at half the distance between the shoulder and the elbow joints. If the patient's limb measurement is on the borderline of two different cuff sizes the likelihood of an erroneous measurement is decreased if the larger of the two cuff sizes is used. Cuffs that are wrapped too loosely result in falsely elevated values. Cuffs were applied snugly, allowing only enough room for one finger to be slipped between the cuff and the skin surface. Baseline mean arterial blood pressure was recorded with the patient lying in the left lateral position. It was the average of three readings, within 10% of each other, measured during the five minutes prior to sitting up for SA. SA was administered using aseptic technique with the patient in the sitting position. After skin infiltration with lignocaine, a 90- or 103 mm 25G pencil-point spinal needle was inserted at the L3/4 intervertebral space. After the subarachnoid space had been identified, a rapid infusion of Ringers Lactate 20 mL/kg was commenced. Subarachnoid injection consisted of 2 mL (10 mg) of hyperbaric 0.5% bupivacaine and 10 µg of fentanyl. The patient was then placed supine, and a wedge placed under the right flank to achieve a 15^0 left lateral tilt. Bilateral sensory block height, in the mid-clavicular line, was monitored 5 minutes after induction of SA, using both the light touch and cold sensation modalities in response to ethyl chloride. For the assessment of block height for touch,

single drops of ethyl chloride were used, starting at blocked abdominal segments and progressively moving cephalad to unblocked segments. The patient was asked the question, “Can you tell me when you feel something touching your skin”. For block height for temperature sensation, single drops of ethyl chloride were again used, moving caudad from unblocked cervical segments to blocked segments. In this case the patient was first asked, “How does this feel?”, when a drop of ethyl chloride made contact with her neck. They were then asked the open-ended question, "Is there any difference here?", while working cephalad from the T8 dermatome until the patient volunteered that they felt the sensation of cold. Surgery was allowed to commence on achieving a bilateral sensory block of cold sensation to the T_4 dermatome level. Block height was assessed again at 25 minutes, by which time maximum block height should have been reached. This was repeated on completion of surgery. Strength of hand-grip, as measured by dynamometry (JAMAR®, Lafayette Instruments Co., Indiana, USA), was used to assess whether high motor block had occurred (T1-C8 or higher). A peak flow meter (Mini-Wright, Clement Clark International Ltd, UK) was used to assess the effect of SA on respiratory function. Hand-grip strength and peak flow readings were taken in the induction room in the supine/wedged position (baseline), and 30 minutes after induction of SA.

Haemodynamic data including systolic, diastolic and mean arterial pressure and heart rate (HR) were recorded every minute for the duration of surgery. Hypotension, defined as a 20% decrease from baseline mean arterial pressure (MAP), was treated with intravenous phenylephrine 50 µg. A 30% decrease in MAP, or failure to restore blood pressure to within 20% of baseline value within the first minute after the administration of 50 µg, was treated with 100 µg of phenylephrine. If HR were to decrease to less than 55 beats per minute in association with hypotension (MAP decrease by 30% from baseline), ephedrine 10 mg would be administered, followed by atropine 0.25-0.5 mg if bradycardia persisted. Ephedrine was also administered if there was poor response to two consecutive doses of phenylephrine. Associated nausea and vomiting was treated with IV metoclopramide 10 mg. If a patient reported discomfort during surgery, 50% nitrous oxide/oxygen was

administered via facemask, and further analgesia was provided if necessary with up to 4 boluses of 250 μg of alfentanil. Continued discomfort necessitated conversion to general anesthesia. After delivery, 3 units of oxytocin were administered IV during one minute.

Time intervals noted were: time from arrival in theatre until injection of bupivacaine, time to T4 sensory block level, bupivacaine injection to skin incision time, bupivacaine injection to uterine incision time, uterine incision to delivery time, and skin incision to closure time.

Blood loss was estimated by measurement in a graded suction bottle, and by observation of swabs. Time to regression to T6 of block height as assessed by cold sensation, and to T10 as assessed by touch, was measured in recovery room.

Calculation of sample size

The null hypothesis was that a subarachnoid injection of bupivacaine 10 mg and fentanyl 10 μg would exert similar haemodynamic effects as indicated by equivalent vasopressor requirements to maintain mean arterial pressure within the stated limits in the two groups. We assumed that a mean difference between the total phenylephrine doses at 30 minutes of less than 200 μg (standard deviation of 200 μg) would denote equivalent doses. In order to demonstrate equivalent phenylephrine doses, sample sizes of 21 per group would be required.[6] In addition, according to clinical experience, subarachnoid injection of hyperbaric bupivacaine 10 mg and fentanyl 10 μg as described above, usually produces sensory block up to the T3 dermatome (range T1 to T5). We regarded an increase of one dermatome in block height in the obese group as clinically important (for example up to the T2 dermatome [range C8 to T4]). For similar power and alpha as for vasopressor requirement, 16 patients per group were required[‡]. In order to allow for greater than anticipated variability in vasopressor requirement, 50 patients were studied.

‡ Medcalc Statistical Software, version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

Statistical analysis

Data were analysed using Medcalc Statistical Software (version 14.12.0, MedCalc Software, Ostend, Belgium). Preliminary analysis of interval data included testing for normal distributions (D'Agostino-Pearson test) and equality of variances between groups (F-tests). Two-tailed t-tests for independent samples were used to evaluate mean differences between groups. If the sample data did not meet the criteria for parametric tests (normal distribution and equivalent variances), Mann-Whitney-U-tests were performed. 95% Confidence intervals between medians were estimated using Confidence Interval Analysis software (version 22.0, build 57, Trevor Bryant, University of Southampton). Correlations were sought by calculating Pearson's product moment correlation coefficient for interval data and Spearman's rho for ordered categorical data. A P value ≤ 0.05 was regarded as indicating statistical significance.

Results

All of the 50 recruited patients completed the trial without any protocol violations. Demographic data are presented in Table 1. All participants in the Group O were morbidly obese (BMI range 41-61 $kg.m^{-2}$ vs 21-31 $kg.m^{-2}$ in Group N). The weights ranged between 111-160 kg vs 51-96 kg. The Group O patients were statistically significantly older (mean [SD] 30.4 [6.0] years, vs 27.1 [5.3]). No differences were found in baseline mean- and diastolic blood pressures. Group O patients had statistically significantly higher average systolic [SD] arterial blood pressures (130.5 [19] mm Hg, vs 121.2 [13] mm Hg).

Primary outcomes were as follows:

i. Vasopressor requirement:

There were no significant between-group differences in vasopressor use at 30 minutes (median [interquartile range]) (150 [0-400] vs 100 [50-600] µg for Group N and Group O respectively. There were also no differences in total phenylephrine dose (mean [SD]) (286 [314] vs 412 [469] µg respectively, or during the pre-or post-delivery periods (Table 2, Figure 1). In order to

determine whether there were confounding variables that influenced vasopressor requirements, a one-way analysis of covariance was conducted with total phenylephrine dose as the dependent variable. The factor was the groups and the dependent variables were age, blood loss, baseline systolic arterial pressure, time from uterine incision to delivery, and time from skin incision to skin closure. None of these variables influenced phenylephrine consumption significantly. There were only 3 patients in Group N and 4 in Group O who received ephedrine ($p = 1.0$), and the doses were similar. Blood pressure control was similar in the two Groups (Figure 2).

ii. Assessment of upper limits of sensory block:

A summary of block height changes appears in Table 3. There were no significant between-group differences in block height as assessed by touch at 5- or 25 minutes, or temperature at 5 minutes. At 25 minutes after spinal injection, the median [range] dermatome height for loss of temperature sensation was significantly higher in the Group O than in Group N (T2 [T1-T4]) vs T4 [T2-T4]); 95% CI of the difference between medians 0 to 2 dermatomes (Figure 3).

Secondary outcomes were as follows:

i Hand-grip strength:

No difference between groups could be demonstrated with regard to the median percentage changes in handgrip strength (Table 3). The data were widely scattered. Three patients had blocks extending to T1 for temperature, of whom two revealed no change in handgrip strength and the other a decrease of 30%.

ii Peak flow rate:

No difference between the groups could be demonstrated with regard to the median percent reductions in peak flow (Table 3). The data were widely scattered and there was no correlation between percent change in peak flow and dermatome height for either temperature or touch.

iii Block regression:

The mean time for regression of loss of touch sensation to T10 was significantly longer in Group O (152 vs 132 minutes, 95% CI of the difference between means 3.8 to 36.2 minutes) (Table 3).

iv Other pertinent time intervals:

There were no differences in the mean times taken from arrival in the operating theatre until induction of SA, the time from induction to skin incision, or induction to uterine incision. The uterine incision to delivery time was greater in Group O (62 s vs 45 s, 95% CI of the difference between means 3 s to 47 s), as was mean time taken from skin incision to skin closure (49 vs 39 minutes, 95% CI of the difference between means 2 to 18 min). Mean blood loss was greater in Group O (600 mL vs 450 mL, 95% CI of the difference between means 0 to 300 mL) (Table 4).

v Adequacy of analgesia:

No patients required analgesic supplementation or conversion to general anesthesia.

vi Neonatal outcome:

There were no differences in Apgar scores or neonatal cord gas values (Table 4).

Discussion

The dose of hyperbaric bupivacaine for SA for CS in obese patients remains controversial. Considering that the 95% confidence interval of the difference between the mean phenylephrine doses required to maintain stable blood pressures (-150 µg to 100 µg) was within the pre-defined exclusion interval of -200 µg to 200 µg (Figure 1), we can conclude that subarachnoid injection of bupivacaine 10 mg and fentanyl 10 µg exerted similar haemodynamic effects in patients with a BMI > 40 $kg.m^{-2}$ and those whose BMI is < 32 $kg.m^{-2}$.

Sensory testing, using the modalities of touch and temperature to indicate the extent of anesthesia, showed that at 25 minutes after induction of SA, the median dermatome height for loss of temperature sensation was statistically significantly higher in Group O than in Group N, with a 95% CI of the difference in medians of 0 to 2 dermatomes. However the clinical importance of this difference is uncertain, as there were no physiological consequences resulting from the generally higher temperature block, which is not surprising considering that the 95% confidence interval of the differences in block height (0-2) included both zero difference and a clinically important difference.

The decision to use two modalities to assess the onset and extent of anesthesia was influenced by a publication which showed that single modality assessment of block height for CS, in particular touch, may erroneously indicate inadequate anesthesia.[7] The Neuropen filament has been shown to be equivalent within one dermatome to ethyl chloride in the assessment of touch; hence ethyl chloride was used for the assessment of both modalities, after discussion with the senior author of this paper (IR).[8]

One review has cautioned against the use of low dose SA for CS in normal BMI patients, in view of the risk of inadequate anesthesia.[9] In non-obese parturients the ED_{50} and ED_{95} for hyperbaric bupivacaine with opiate has been shown to be 7.6 mg and 11.2 mg respectively.[10] The authors also caution against dose reduction for hyperbaric bupivacaine for SA. A recent meta-analysis suggests that any reduction of the bupivacaine dose to less than 8 mg with opiate, during single shot SA in the non-obese population, results in significantly increased requirement for analgesic supplementation (risk ratio = 3.76, 95% CI = 2.38 to 5.98, $P< 0.001$), and could result in conversion to general anesthesia.[2] The dermatomal block height ranged between $T_2 – T_6$; however, there was no uniformity in the assessment method used.

Studies investigating the relationship between patient BMI and block height in obstetrics are limited and show conflicting results. Norris et al. showed no correlation between the height of sensory block and patient BMI.[11] In this

study, morbidly obese patients were not included, and a fixed dose of hyperbaric bupivacaine was used. Harten et al. concluded that adjusting the SA dose regimen for caesarean section according to the patient weight and height, results in less hypotension and fewer blocks above the T_1 dermatome level.[12] They randomised patients with weights 50- to 110 kg, and heights 140- to 180 cm, to receive either a fixed dose of 12 mg hyperbaric bupivacaine and 0.4 mg diamorphine, or an adjusted dose using a chart taking height and weight into account. The adjusted dose group received a median [IQR] dose of hyperbaric bupivacaine of 9.5 [9-10] mg. In the fixed dose group, six patients experienced loss of sensation to pinprick above the T_1 dermatome, and three patients to C_7 and C_8, but no patients required ventilatory support. Some patients in the adjusted dose group required supplementation of analgesia, suggesting that adjusting the dose according to patient weight may result in inadequate anesthesia. The use of dose charts is not common practice at our institution and clinical experience involving approximately 10,000 spinal anesthetics for CS per annum, is that 12 mg is too high a subarachnoid dose for our patient population, while 9 mg increases the possibility of maternal discomfort requiring analgesia supplementation.

It has been postulated that there may be increased cephalad spread of local anesthetic in obese parturients, due to decreased cerebrospinal fluid volume.[13] This is possibly attributable to increased intra-abdominal pressure and/or raised epidural venous pressure and compression of the intrathecal space.[14] Vertebral column length has also been suggested as an important variable with regard to local anesthetic spread within the subarachnoid space, but no formal correlation has been shown.[15]

An early investigation showed a tendency towards higher cephalad spread, and more rapid onset and recovery from anesthesia, in obese non- pregnant patients receiving isobaric intrathecal bupivacaine, compared with patients with a normal BMI.[16] However, Lee et al. found the ED_{95} for intrathecal hyperbaric bupivacaine in obese parturients to be 12.9 mg (95% CI 11.5 – 34.8 mg), which was similar to that in non-obese patients.[4] This study is limited by use of historical controls in whom the study protocol was different to

that used in the control group. A further recent investigation, which is also limited by the use of historical controls, suggests that the ED_{95} for spinal bupivacaine with opiates in morbidly obese patients is 15 mg (95% CI 10.0 – 20.0 mg), which is similar to that in non-obese patients.[3] Morbidly obese patients (BMI ≥ 40 kg/m^2) undergoing elective CS were randomly assigned to receive up to 11 mg intrathecal hyperbaric bupivacaine with opiates, and the ED_{95} was calculated from a logistic regression plot. Even with this dose, which many would regard as considerable in obese patients, a similar incidence and severity of hypotension, and incidence of nausea and vomiting, was shown as in parturients with a normal BMI. The authors concluded that morbidly obese- and non-obese parturients exhibit a similar response to modest doses of intrathecal hyperbaric bupivacaine. They reported that the dose response in the obese population is variable, but recommended that doses less than 10 mg should not be used. These findings support our hypothesis that the dose requirement for spinal bupivacaine for caesarean delivery should be similar in morbidly obese and non-obese patients. Finally, a recent retrospective analysis suggests that high cephalad spread of bupivacaine is unlikely unless the BMI is greater than 50 kg.m^{-2}.[17] The mean (SD) BMI in our study was 51 (5.4) kg.m^{-2}.

In terms of secondary outcomes in the present investigation, it was not surprising that no between-group differences could be shown in hand grip strength after induction of SA, considering that no patient had a sensory block at or above the C8 dermatomal level. A previous study comparing the effects of SA for CS on respiratory function in patients with a BMI > 30 kg/m^2 and those with BMI < 25 kg/m^2 showed that the obese patients had a greater reduction in respiratory function due to SA. The median (IQR) values for vital capacity after SA were -24 (-16 to -21)%, versus -11 (-6 to -16)% respectively.[18] In our study, which is the first to examine the effects of SA for CS on respiratory function in morbidly obese parturients, the between-group difference in decrease in peak flow rate was not significant (18.8- vs 19.7%). There was considerable variability in the data, evidenced by a wide range in percentage changes in both groups (Table 3).

The median time for regression of loss of touch sensation to T10 was 20 minutes longer in Group O (Range 82-195 minutes in Group N vs 103-205 min in Group O). The increased mean duration of surgery in Group O (49 vs 39 minutes), strengthens the conclusion that the dose of intrathecal local anesthetic should not be reduced in obese patients.

Limitations of this study include the fact that it was not blinded, and that the sample size does not preclude possible outliers experiencing cervical dermatome blocks, that might be identified in a larger study. However it is noteworthy that more than 1000 morbidly obese patients have received SA for CS at the Groote Schuur Maternity Centre using the same dose as in this study, in the past 3 years, with no patient requiring tracheal intubation due to high motor block. Finally, our results do not apply to patients with extremely high BMI, in whom prolonged surgery is envisaged. In these cases, combined spinal epidural-, continuous spinal-, or general anesthesia is required.

In conclusion, despite the statistically significantly higher median dermatome height for loss of temperature sensation in Group O, we can conclude that an intrathecal dose of bupivacaine 10 mg and fentanyl 10 µg resulted in clinically equivalent effects in two groups of parturients with widely differing BMI, considering that there were no clinically important consequences. In particular, vasopressor requirements were similar, as were the decreases in mean peak flow rate. Notably the affected dermatomes did not extend to the innervation by the cervical nerve roots in either group. Therefore, also in view of the possibly increased time to regression of the block and the longer surgical time in Group O, we conclude that the dose of intrathecal local anesthetic for single shot SA for CS should not be reduced in morbidly obese patients. This is of special importance in low resource environments where combined spinal-epidural anesthesia is not routinely available, and the subsequent risks associated with conversion to general anesthesia are considerable.

References

1. Langesæter E, Dyer RA. Maternal haemodynamic changes during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol*. 2011;24(3):242-248. doi:10.1097/ACO.0b013e32834588c5.
2. Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. *Br J Anaesth*. 2011;107(3):308-318. doi:10.1093/bja/aer200.
3. Carvalho B, Collins J, Drover DR, Atkinson Ralls L, Riley ET. ED(50) and ED(95) of intrathecal bupivacaine in morbidly obese patients undergoing cesarean delivery. *Anesthesiology*. 2011;114(3):529-35. doi:10.1097/ALN.0b013e318209a92d.
4. Hood DD, Dewan DM. Anesthetic and obstetric outcome in morbidly obese parturients. *Anesthesiology*. 1993;79(6):1210-8. doi:10.1097/00000542-199312000-00011.
5. Pickering, T.G., Hall, J.E., Appel, L.J., Falker, B.E., Graves, J., Hill, M.N., Jones, D.W., Kurtz, T., Sheps, S., Rocella, E.J.Kurtz TW. American Heart Association Council on High Blood Pressure Research Professionals From the Subcommittee of Professional and Public Education of the Animals: Part 2: Blood Pressure Measurement in Experimental Animals: A Statement for Recommendations for Blo. *Circulation*. 2005;111:697-716. doi:10.1161/01.HYP.0000150857.39919.cb.
6. Ousley R, Egan C, Dowling K, Cyna a. M. Assessment of block height for satisfactory spinal anaesthesia for caesarean section. *Anaesthesia*. 2012;67(12):1356-1363. doi:10.1111/anae.12034.
7. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11234459.
8. Milligan KR, Carp H. Continuous spinal anaesthesia for caesarean section in the morbidly obese. *Int J Obstet Anesth*. 1992;1(2):111-113. doi:10.1016/0959-289X(92)90009-S.

9. Palmer CM. Continuous spinal anesthesia and analgesia in obstetrics. *Anesth Analg*. 2010;111(6):1476-1479. doi:10.1213/ANE.0b013e3181f7e3f4.
10. McKeen DM, George RB, O'Connell CM, et al. Difficult and failed intubation: Incident rates and maternal, obstetrical, and anesthetic predictors. *Can J Anesth*. 2011;58(6):514-524. doi:10.1007/s12630-011-9491-9.
11. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Igarashi T. Soft tissue anatomy within the vertebral canal in pregnant women. *Br J Anaesth*. 1996;77(2):153-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8881616.
12. Hogan QH, Prost R, Kulier A, Taylor ML, Liu S, Mark L. Magnetic resonance imaging of cerebrospinal fluid volume and the influence of body habitus and abdominal pressure. *Anesthesiology*. 1996;84(6):1341-9. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2443094&tool=pmcentrez&rendertype=abstract\nhttp://www.ncbi.nlm.nih.gov/pubmed/8669675.
13. Pitkänen MT. Body mass and spread of spinal anesthesia with bupivacaine. *Anesth Analg*. 1987;66(2):127-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3813056.
14. Norris MC. Spinal Anesthesia - Bupivicaine Distribution. *Anesth Analg*. 1988;67:555-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3377210.
15. Norris MC. Patient Variables and the spread of Subarachnoid hyperbaric bupicavacaine in the term parturient. *Anesthesiology*. 1990;72:478-482.
16. Hodgkinson R, Husain FJ. Obesity and the Cephalad Spread of Analgesia following Epidural Administration of Bupivacaine for Cesarean Section. *Anesth Analg*. 1980;59(2):89-92. Available at: http://www.anesthesia-analgesia.org/content/59/2/89.short.
17. Hartwell BL, Aglio LS, Hauch M a, Datta S. Vertebral column length and spread of hyperbaric subarachnoid bupivacaine in the term parturient. *Reg Anesth*. 1991;16(1):17-9. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/2007099.

18. Harten JM, Boyne I, Hannah P, Varveris D, Brown a. Effects of a height and weight adjusted dose of local anaesthetic for spinal anaesthesia for elective Caesarean section. *Anaesthesia*. 2005;60(4):348-353. doi:10.1111/j.1365-2044.2005.04113.x.
19. Ben-David B, Miller G, Gavriel R, Gurevitch a. Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med*. 2000;25(3):235-239. doi:10.1053/xr.2000.5654.
20. Choi DH, Ph D, Ahn HJ, Kim MH. in Spinal Anesthesia Effect of Fentanyl for Cesarean Delivery. 2000;25:240-245.
21. Dyer RA, Joubert IA. Low-dose spinal anaesthesia for Caesarean section. *Curr Opin Anaesthesiol*. 2004;17(4):301-308. doi:10.1097/01.aco.0000137088.29861.64.
22. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology*. 2004;100(3):676-682. doi:10.1097/01.sa.0000151214.68591.de.
23. Lee Y, Balki M, Parkes R, Carvalho JC a. Dose requirement of intrathecal bupivacaine for cesarean delivery is similar in obese and normal weight women. *Rev Bras Anestesiol*. 2009;59(6):674-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20011857.
24. Einhorn L, Akushevich I, Habib AS, Bch MB. Evaluation of the risk of exaggerated cephalad spinal block in obese parturients. :27710.
25. Columb MO, Stevens a. Power analysis and sample size calculations. *Curr Anaesth Crit Care*. 2008;19(1):12-14. doi:10.1016/j.cacc.2007.03.011.

Figures and Tables

Table 1: Demographic data

	Group					
	Normal BMI		Morbidly Obese			
	Mean or median	SD or percentiles	Mean or median	SD or percentiles	p	95% CI Diff
Age (years)	27.1	5.3	30.4	6.0	0.0437	0.1 to 6.5
Weight (kg)	73.2	8.5	130.4	12.8	< 0.0001	51.1 to 63.4
Height (cm)	162.8	6.8	160.1	5.0	0.1263	-6.1 to 0.8
BMI ($kg.cm^{-2}$)	27.5	2.6	51.1	5.4	< 0.0001	21.2 to 26.0
Baseline peak flow ($L.s^{-1}$)	360	60	341	48	0.225	-50 to 12
Baseline handgrip (kg)	27.3	4.7	28.0	4.8	0.6146	-2.0 to 3.4
Gestational age (weeks)	39	39 to 40	39	39 to 39	0.2379	0.0 to 1.0
SAP (mmHg)	121.2	13.0	130.5	19.0	0.0497	0.01 to 18.5
MAP (mmHg)	89.4	13.0	92.2	13.3	0.4496	-4.7 to 10.3
DAP (mmHg)	68.6	13.3	69.3	12.1	0.8504	-6.5 to 7.9

SD = standard deviation; 95% CI Diff = 95% confidence interval of the difference between the means or the medians; Percentiles = 25^{th} to 75^{th} percentile; SAP = baseline systolic arterial pressure; MAP = baseline mean arterial pressure; DAP = baseline diastolic arterial pressure; p = p-value for t-test or Mann-Whitney-U-test.

Table 2: Vasopressor usage at various intraoperative stages

	Group							
	Group N			Group O				
	Median or mean	SD or percentiles	Range	Median or mean	SD or percentiles	Range	p	95% CI Diff
Phenylephrine pre-delivery (µg)	100	0 to 213	0 to 900	50	0 to 600	0 to 1050	0.4007	-100 to 50
Phenylephrine post-delivery (µg)	100	0 to 263	0 to 550	50	0 to 250	0 to 750	0.8417	0 to 0
Total phenylephrine at 30 minutes (µg)	150	0 to 400	0 to 900	100	50 to 600	0 to 1250	0.4442	-150 to 100
Total phenylephrine dose (µg)	286	314	0 to 1000	412	469	0 to 1450	0.2702	-101 to 353
Ephedrine pre-delivery (mg)	0	0.0 to 0.0	0 to 12.5	0	0.0 to 0.0	0 to 20	0.9703	0 to 0
Ephedrine post-delivery (mg)	0	0.0 to 0.0	0 to 17.5	0	0.0 to 0.0	0 to 20	0.4693	0 to 0
Total ephedrine at 30 min (mg)	0	0.0 to 0.0	0 to 30	0	0.0 to 0.0	0 to 20	0.9193	0 to 0
Total ephedrine dose (mg)	0	0.0 to 0.0	0 to 30	0	0.0 to 0.0	0 to 20	0.8350	0 to 0

Percentiles = 25^{th} to 75^{th} percentiles; 95% CI Diff = 95% confidence interval of the difference between the medians; p = p-value for Mann-Whitney-U-test or for t-test for independent sample.

Group N: BMI 21-31 $kg.m^{-2}$, Group O: BMI 41-61 $kg.m^{-2}$

Table 3: Data pertaining to assessment of sensory and motor block

		Group						Differences between groups	
		Normal			Obese				
		Mean or median	SD or percentiles	Range	Mean or median	SD or percentiles	Range	p	95% CI Diff
Dermatomes	Temperature (at 5 min)	T4	T2 to T5	T2 to T7	T3	T3 to T4	T1 to T5	0.6070	-1 to1
	Temperature (at 25 min)	T4	T3 to T4	T2 to T4	T2	T2 to T3	T1 to T4	0.0022	0 to 2
	Touch (at 5 min)	T4	T4 to T9	T2 to T10	T4	T4 to T6	T2 to T10	0.3311	0 to 2
	Touch (at 25 min)	T4	T3 to T4	T2 to T6	T3	T3 to T4	T2 to T5	0.0765	0 to 1
Physiological changes (%)	Peak flow rate Change (%)	-18.8	11.6	-42.9 to 0	-19.7	12.2	-50 to 0	0.8071	-7.6 to 6.0
	Hand grip strength Change (%)	0	0 to 0	-31.0 to 3.2	0	-16.3 to 0.0	-36.7 to 31.8	0.3400	0.0 to 14.3
Times to regression (min)	Temperature (to T6)	102.9	20.5	60 to 135	106.8	19.0	72 to 138	0.4862	-7.3 to 15.1
	Touch (to T10)	132.1	30.1	82 to 195	152.1	26.6	103 to 205	0.0164	3.8 to 36.2

SD = standard deviation; 95% CI Diff = 95% confidence interval of the difference between the means or the medians; Percentiles = 25^{th} to 75^{th} percentile; p = p-value for t-test or Mann-Whitney-U-test.

Table 4: Pertinent time intervals and neonatal outcome

	Group					
	N		O			
	Mean or median	SD or percentiles	Mean or median	SD or percentiles	p	95% CI Diff
Arrival to induction of SA (min)	15	13.8 to 15.3	17	10.8 to 25.0	0.0831	-10 to 0.0
Insertion to skin incision (min)	16.6	6.2	14.2	4.3	0.1316	-5.4 to 0.7
Insertion to uterine incision (min)	21.7	6.9	23.5	8.1	0.4020	-2.5 to 6.1
Skin incision to skin closure (min)	39.4	11.9	49.1	15.9	0.0180	1.7 to 17.7
Uterine incision to delivery (s)	45	30 to 95	62	45.0 to 142.5	0.0217	-47 to -3
Blood loss (mL)	450	400 to 563	600	450 to 850	0.0195	-300 to 0
APGAR (at 1 minute)	9	8 to 9	9	8 to 9	0.7108	0 to 0
APGAR (at 5 minutes)	10	9 to 10	10	9.8 to 10.0	0.4982	0 to 0
UV pH	7.34	7.3 to 7.4	7.34	7.30 to 7.35	0.3706	-0.02 to 0.04
UVPCO_2 (kPa)	5.75	5.3 to 6.4	5.85	5.2 to 6.3	0.8690	-0.45 to 0.40
UV PO2 (kPa)	3.1	0.8	3.4	0.8	0.2272	-0.2 to 0.8
UV bicarbonate (mmol/L)	22.1	19.9 to 23.6	21.8	20.6 to 22.6	0.5220	-0.7 to 1.5
UV BE	-1.3	-2.2 to 0.4	-1.5	-2.9 to -0.6	0.2483	-0.4 to 1.7

SD = standard deviation; 95% CI Diff = 95% confidence interval of the difference between the means or the medians; Percentiles = 25^{th} to 75^{th} percentile; p = p-value for t-test or Mann-Whitney-U-test; insertion = insertion of spinal needle into subarachnoid space; APGAR = APGAR score; BE = base excess; UV = Umbilical venous

Figure 1:

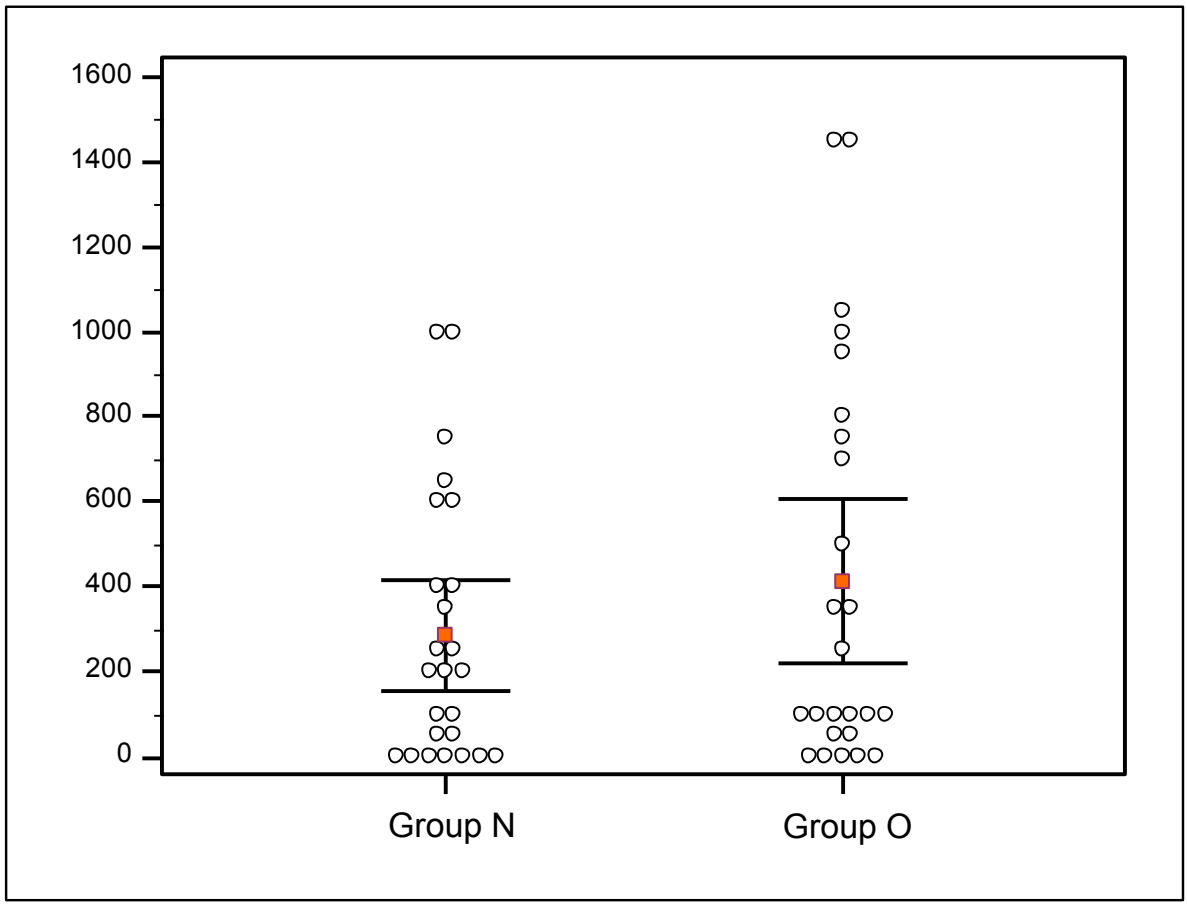


Figure 2:

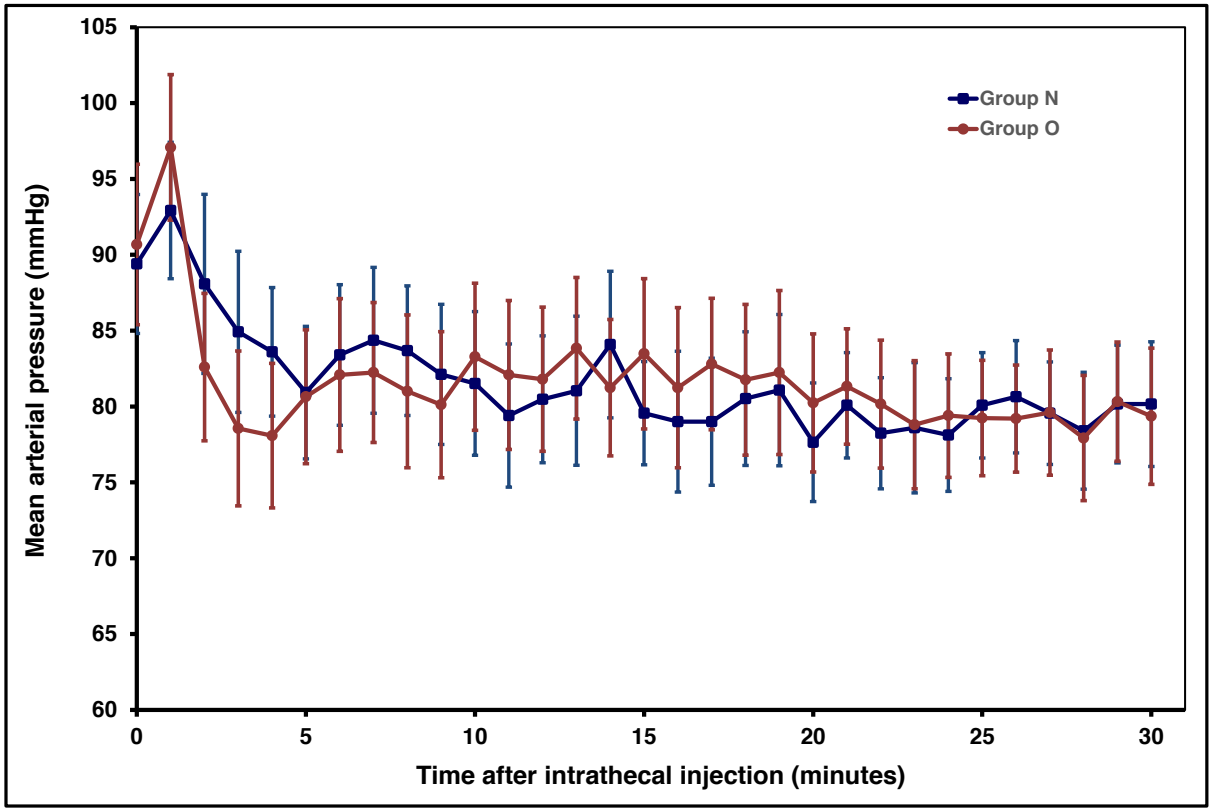
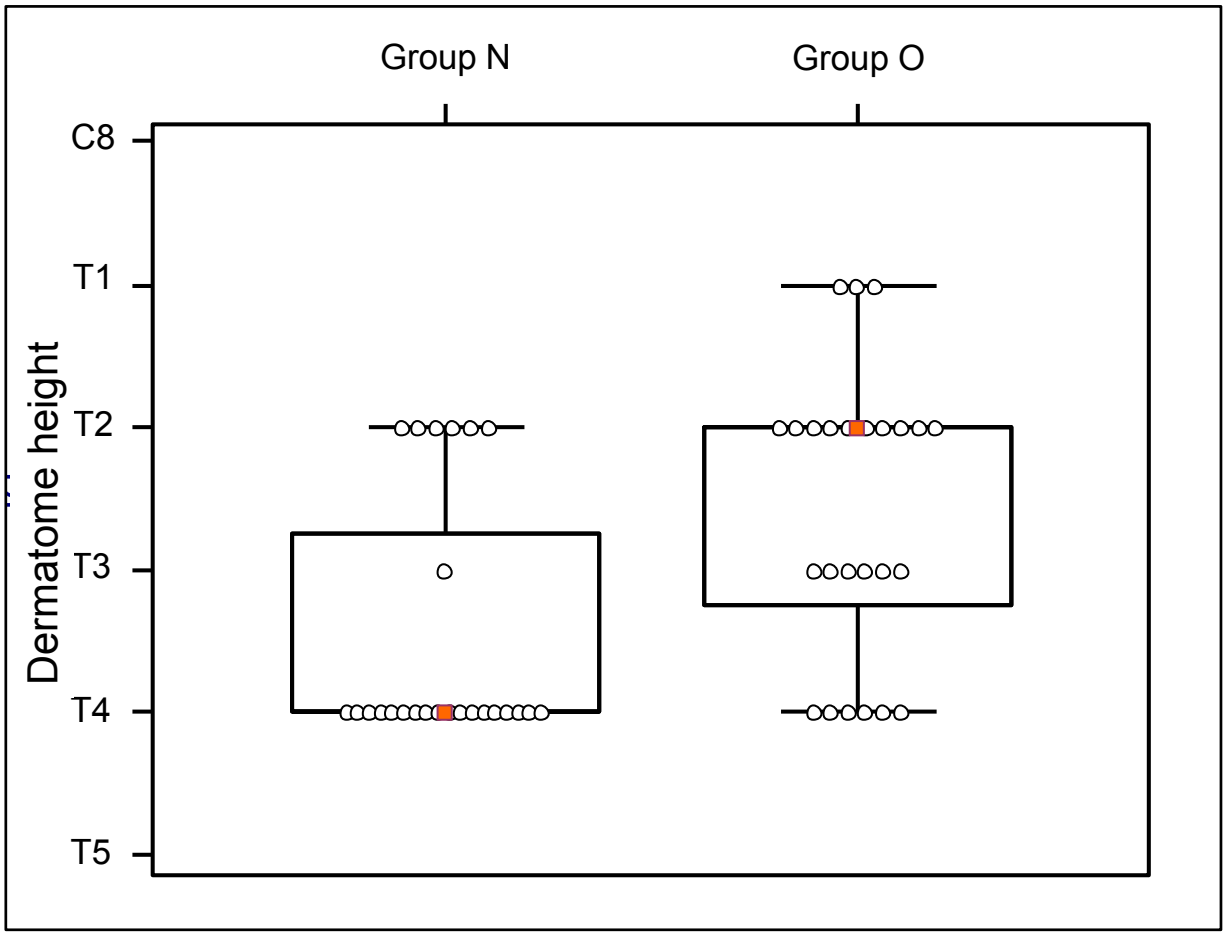

105
100
95
90
85
80
75
70
65
60
Mean arterial pressure (mmHg)
0
5
10
15
20
25
30
Time after intrathecal injection (minutes)
Group N
Group O

Figure 3:



Legends to figures:

Figure 1: Total phenylephrine dose for the two groups. The square markers depict mean values, the error bars, 95% confidence intervals of the mean values. Group N: BMI 21-31 $kg.m^{-2}$ Group O: BMI 41-61 $kg.m^{-2}$

Figure 2: Graph of mean arterial pressures of the two groups during the first 30 minutes of spinal anesthesia. The markers depict mean values and the error bars indicate the 95% confidence intervals of the mean values. Group N: BMI 21-31 $kg.m^{-2}$, Group O: BMI 41-61 $kg.m^{-2}$

Figure 3: Box and Whisker plot of block height for temperature sensation for the two groups. The square markers depict the median values. Group N: BMI 21-31 $kg.m^{-2}$, Group O: BMI 41-61 $kg.m^{-2}$

Part D: Supporting documents

Patient information sheet

Spinal anaesthesia is a technique for injection of medication into the fluid around your spinal cord for the purpose of making the lower part of your torso and legs numb to make it possible to do your caesarean section.

It is the preferred mode of anaesthesia for caesarean section and is safer than general anaesthesia, which involves putting you into a deep sleep.

Prior to the injection, an intravenous line will be inserted in your arm. We would like to assess the height of the numbness following the injection, using the same dose of local anaesthetic, 10 mg, regardless of your weight. Also, one of the possible side effects of spinal anaesthesia is a temporary drop in your blood pressure with associated dizziness, nausea and vomiting. We would like to monitor your blood pressure so as to detect any changes, and we can treat a decrease in your blood pressure by injecting some medication via your intravenous line to restore your blood pressure. We will record the total dose of medication used.

Should you decide not to enter the study, your treatment will be of the same high quality that you would receive if you entered the study. You can withdraw from the study at any time, and the doctors will continue your management in the usual way.

Informed Consent

Prospective Research Subject: Read this consent form carefully and ask as many questions as you like before you decide whether you want to participate in this research study. You are free to ask questions at any time before, during, or after your participation in this research.

Project Information

The influence of body mass index on sensorimotor block and vasopressor requirement during spinal anaesthesia for elective caesarean section

Project Number:
HREC/REF: 031/2013
Principal Investigator: Dr. C. Ngaka
Department: Anaesthesia
Location: D23 NGSH
Phone: 02104045003

You are being asked to participate in a study designed to compare the effect of using the same dose of spinal bupivacaine 10mg, plus fentanyl 10µg regardless of your weight.

Spinal anaesthesia is a technique for injection of medication into the fluid around your spinal cord for the purpose of making the lower part of your torso and legs numb to make it possible to do your caesarean section. It is the preferred mode of anaesthesia for caesarean section and is safer than general anaesthesia, which involves putting you into a deep sleep. Prior to the injection, an intravenous line will be inserted in your arm. We would like to assess the height of the numbness following the injection, using the same dose of local anaesthetic, 10 mg, regardless of your weight. We will again assess the height of the numbness at completion of the operation. Your participation in the study will end when you are discharged from the post anaesthesia recovery room and you will not be expected to take any extra time off work.

One of the possible side effects of spinal anaesthesia is a temporary drop in your blood pressure with associated dizziness, nausea and vomiting. We would like to monitor your blood pressure so as to detect any changes, and we can treat a decrease in your blood pressure by injecting some medication via your intravenous line to restore your blood pressure. We will record the total dose of medication used.

Your participation in this study will not provide any added benefit as it is standard of care for patients undergoing caesarean section. It will,

however, help improve the current practice in ensuring the safe management of anaesthesia to mothers regardless of their weight.

Your identity in this study will be treated as confidential. The results of the study, including laboratory or any other data, may be published for scientific purposes but will not give your name or include any identifiable references to you.

Should you decide not to enter the study, your treatment will be of the same high quality that you would receive if you entered the study. You can withdraw from the study at any time, and the doctors will continue your management in the usual way.

The Principal Investigator will answer any further questions you have about this study:

Name: Dr. Christian Ngaka
Phone Number: 076 468 7134

Any questions you may have about your rights, as a research subject will be answered by:

Name: Professor M. Blockman
Phone Number: (021) 406 6411

In case of a research-related emergency, call:

076 468 7134 (day or night)

I…….. have read and understand this consent form, and I volunteer to participate in this research study. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

Participant signature:……..

Name of person obtaining consent:…….

Signature: …….

Witness: (1)…….

(2)……

At…… Date……. ….

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za
www.health.uct.ac.za/research/humanethics/forms

25 February 2013

HREC REF: 031/2013

Dr C Ngaka
Anaesthesia
D-23
NGSH

Dear Dr C Ngaka

PROJECT TITLE: A COMPARISON OF IDENTICAL DOSES OF SPINAL BUPIVACAINE FOR ELECTIVE CAESAREAN SECTION IN MORBIDLY OBESE PATIENTS AND PATIENTS WITH A NORMAL BODAY MASS INDEX

Thank you for addressing the issues raised Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above mentioned sub- study.

Approval is granted for one year till the 28 February 2014.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

Please address the typographical error on the final page of the consent document.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

sAriefdien

ANESTHESIA & ANALGESIA
GUIDE FOR AUTHORS

Updated October 2015

INTRODUCTION

Anesthesia & Analgesia publishes articles that are novel, definitive, and improve clinical care or guide future research. This Guide for Authors was written for authors preparing manuscripts for submission to *Anesthesia & Analgesia*. It explains the Editorial Board's expectations for submitted manuscripts and Journal policies on manuscript handling. The Guide contains extensive information on manuscript preparation that may be helpful regardless of where the authors submit their manuscript.
Please contact our Editorial Office with any questions:

Anesthesia & Analgesia
44 Montgomery
Suite 1605
San Francisco, CA 94104-4703
E-mail: editor@anesthesia-analgesia.org Phone: (415) 777-2750
Fax: (415) 777-2803

ABOUT *ANESTHESIA & ANALGESIA*

Anesthesia & Analgesia, the oldest publication for the specialty of anesthesiology, is the official scientific journal of the following societies and foundations:

 International Anesthesia Research Society (IARS)
 Society of Cardiovascular Anesthesiologists (SCA)
 Society for Pediatric Anesthesia (SPA)
 Society for Ambulatory Anesthesia (SAMBA)
 International Society for Anaesthetic Pharmacology (ISAP)
 Society for Technology in Anesthesia (STA)
 Anesthesia Patient Safety Foundation (APSF)
 Society of Critical Care Anesthesiologists (SOCCA)
 Society for Obstetric Anesthesia and Perinatology (SOAP)
 Society of Anesthesia and Sleep Medicine (SASM)
 World Federation of Societies of Anaesthesiologists (WFSA)
 Trauma Anesthesiology Society (TAS)

Anesthesia & Analgesia is divided into the following sections:
 Editorials
 Cardiovascular Anesthesiology, which includes Hemostasis and Transfusion Medicine
 Pediatric Anesthesiology
 Pediatric Neuroscience
 Ambulatory Anesthesiology

 Anesthetic Pharmacology, which includes Pre-Clinical Pharmacology and Clinical
Pharmacology
 Technology, Computing, and Simulation
 Patient Safety
 Economics, Education, and Policy
 Critical Care, Trauma, and Resuscitation
 Neuroscience in Anesthesiology and Perioperative Medicine
 Obstetric Anesthesiology
 General (otherwise unspecified)
 Analgesia, consisting of
- Pain and Analgesic Mechanisms ○ Pain Medicine
- Regional Anesthesia

 Cochrane Corner
 Correspondence
 Book, Multimedia, and Meeting Reviews
 The Open Mind

We assign all manuscripts to one of these sections. Most sections have one or more designated Section Editors responsible for maintaining editorial control of manuscripts through the peer review process. Authors may request a journal section at the time of manuscript submission. These requests are considered by the Editor-in-Chief when the manuscript is assigned to a Section Editor.

AUTHORSHIP

Authorship is a profound responsibility. Authors enter into an implied contract with the Journal, our Editorial Board, our reviewers, our readers, patients, the scientific community, and the public assuring that the manuscript is a complete and honest account of the reported scholarly endeavor. Authorship lasts forever. Authorship permanently records the contribution of individuals who have advanced human knowledge.

The responsibilities of authorship must be taken seriously by *every* author. As stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, updated in 2010 (http://www.icmje.org) "*Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.*"

Attributing authorship to those who have not contributed intellectually is not acceptable. It is ***unacceptable*** to include senior members of a research group, chairs of academic departments, or representatives of the commercial sponsor, if they do not meet the stated requirements for authorship.

It is similarly ***unacceptable*** to exclude individuals meeting the requirements for authorship. For example, scientists from a sponsoring company who meet the stated requirements should be coauthors, with proper disclosure of conflict of interest.

Although we strongly endorse the ICMJE authorship requirements, the Editorial Board of *Anesthesia & Analgesia* cannot enforce these requirements. Similarly, the Journal cannot adjudicate authorship disputes. These must be resolved by the authors, or by the institution responsible for the research. The Committee on Publication Ethics has prepared excellent guidance on resolving authorship disputes.[a]

All authors reap the benefits that the society affords to those who contribute to human knowledge and share the burden for assuring that a submitted manuscript is a complete and honest account of the reported scholarly endeavor. All authors are therefore held accountable in the event that a manuscript is found to be a less than complete and honest account of the reported scholarly endeavor.

[a] http://publicationethics.org/files/u2/2003pdf12.pdf, last accessed May 28, 2012 5

ETHICAL CONDUCT OF RESEARCH

The following pages describe the standards set by the Editorial Board of *Anesthesia & Analgesia* for ethical conduct of research. The Editorial Board will not consider any manuscript that does not follow these rules.

The name of the institutional research ethical review and oversight committee varies with country and local custom. In the United States the committee is called the Institutional Review Board. Other countries may use other terms for their research ethical review committee, such as "Research Ethics Committee." Some institutions refer to the board that reviews animal studies as the "Animal Care and Use Committee." In this document, "Institutional Review Board" is used generically to refer to the local board that reviews the ethical treatment of human or animal experimental subjects and grants institutional approval for the study.

Human Subjects

Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at http://www.wma.net/en/30publications/10policies/b3/. Clinical studies not meeting the Declaration of Helsinki criteria will not be considered for publication. If published research is subsequently found to be noncompliant, it will be retracted.

Studies that do not involve human or animal subjects do not require IRB approval.

On the basis of the Declaration of Helsinki, *Anesthesia & Analgesia* requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

1. The study was approved by the appropriate Institutional Review Board, and
2. Written informed consent was obtained from all subjects, a legal surrogate, the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the Institutional Review Board.

Anesthesia & Analgesia's considers audits and some case reports to be clinical research requiring IRB approval for publication. As explained in a policy editorial:[1]

1. Research is a systematic investigation for the creation of generalizable knowledge. Any investigation submitted for publication demonstrates intent to create generalizable knowledge, and thus constitutes research.
2. Audits submitted for publication constitute human research, regardless of the original purpose of the audit.
3. Case reports involving experimental drugs or devices constitute human

research.

4. Human research requires IRB approval. There are no exceptions, including retrospective reviews of medical records.
5. The IRB is responsible for determining the requirement for informed consent. *Anesthesia & Analgesia* only recognizes written informed consent, or an IRB-approved waiver of written informed consent when written informed consent is impossible (e.g., audits).

6. The Editorial Board of *Anesthesia & Analgesia* reserves the right to reject a manuscript if the research is perceived as unethical, even if it has local IRB approval.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth, or other protected health care information. Retain copies of your Institutional Review Board approval and documentation of written informed consent from each study subject. The editor or reviewers may request copies of these documents to address questions about Institutional Review Board approval and study conduct.

Anesthesia & Analgesia fully supports the Guidelines for Personal Patient Information set forth by Lippincott, Williams, and Wilkins (LWW). The LWW guidelines can be downloaded from http://journals.lww.com/nsca-jscr/Documents/New Guidelines for Personal Patient Information 2.pdf

Key elements of this policy include:

 Photographs with bars placed over eyes of patients should not be used. If they are submitted, permission from the patient must be documented.
 Only specific details about the subject that are essential for understanding and interpreting the results of a study, a specific case report, or case series should be provided.
 Authors and editors should not alter or falsify details in case descriptions to provide anonymity because doing so may introduce false or inaccurate data into the medical literature.
 Previous publication of patient information or news coverage of a case does not eliminate a patient's right to privacy and does not negate the need for patient consent for use of any patient identifying information.
 If "deidentification" is not possible, the editors will ask the author to obtain consent from the patient. If the patient cannot be located or refuses to consent to publication of the identifying information, the manuscript will not be published. Should this situation arise, the corresponding author and the Section Editor should discuss the possibility of deleting the identifying information prior to peer review.
 In the event that the patient cannot provide consent due to death or legal

incompetency (this includes photos of cadavers), permission from the power of attorney is needed as well as proof of power of attorney.
 If the patient is a minor, a legal guardian must provide consent.

Investigational Drugs
The Editorial Board of *Anesthesia & Analgesia* may exercise judgment about the ethics of a clinical trial involving investigational drugs that differs from the view of the investigator's Institutional Review Board. This situation most frequently occurs in studies
involving neuraxial or perineural drug administration, drug studies in children, and nonconformity in dose, route, or indication ("off-label" use).

Neuraxial or Perineural Drug Administration
Studies using drugs injected into the neuraxial (caudal, intrathecal, or epidural) or perineural space must meet at least one of three criteria:
1. The drug is approved for neuraxial or perineural administration by the United States Food and Drug Administration (FDA) or the equivalent regulatory agency for the country in which the study took place.
2. The drug is not approved for neuraxial or perineural use, but it is widely used and accepted for neuraxial (e.g., fentanyl) or perineural administration. The publication of dosing guidelines in multiple textbooks represents a reasonable demonstration that a drug is widely used and accepted for neuraxial or perineural administration.
3. The study is performed under an Investigational New Drug (IND) or Biologics License Application (BLA) application approved by the FDA or the equivalent agency in the investigator's country. Investigators in the United States are directed to the FDA website for further information on obtaining an investigator IND.[b] To obtain an investigator IND, the investigator must complete forms 1571 and 1572 which are mailed to the FDA along with the investigator's curriculum vitae. Should the investigator's country not have an equivalent process, the investigator must submit a statement from the Institutional Review Board that the preclinical toxicity data were reviewed for safety by a qualified expert before approval of the human trial.

The status of drugs for neuraxial or perineural administration can be found at http://www.aaeditor.org/Neuraxial.Perineural.Drugs.xls. Questions about this list, or about proposed studies of neuraxial or perineural drugs, should be addressed to the Editorial Office at editor@anesthesia-analgesia.org. *Anesthesia & Analgesia* will not publish a retrospective paper involving neuraxial or perineural drug administration if the treatment would be considered inappropriate or unethical in a prospective trial.

Drug Studies in Children

Anesthesia & Analgesia is committed to expanding knowledge of the clinical pharmacology of drugs in children. However, studying drugs in children when there is no pediatric indication poses ethical concerns.[2] Therefore, studies of drugs in children must meet at least one of three criteria:

Updated October 2015

1. The drug is approved for pediatric administration by the FDA or an equivalent regulatory agency.
2. The drug is not approved for use in children but is widely used and accepted for pediatric administration. A reasonable demonstration that the drug is clinically accepted for use in children is when the administration in the study is consistent with the route, dose, and indication reported in multiple textbooks.
3. The study is done under an IND application approved by the FDA or the equivalent agency in the investigator's country, as described by Schultheis et al.[3] Investigators in the United States are directed to the FDA website for further information on obtaining an investigator IND.[b]

Anesthesia & Analgesia will not publish a paper describing retrospective assessment involving pediatric drug administration if the treatment would be considered inappropriate or unethical in a prospective trial.

Nonconformity in Dose, Route, or Indication ("Off-Label" Use)

In the United States, FDA regulations state that drug use conforms to the package insert ("on-label") when the dose, route of administration, and indication match the guidelines in the package insert. If the dose, route, or indication does not match the package insert, then the drug use is "off-label." Drugs are commonly used off-label in clinical trials, and the practice is generally acceptable. However, the Editorial Board of *Anesthesia & Analgesia* reserves the right not to review a manuscript describing off-label administration of a drug if the Editorial Board believes the study posed unacceptable risk to subjects. To preclude such a determination, investigators are encouraged to obtain an Investigator IND from the FDA[b] or an equivalent agency in their country before initiating studies involving off-label drug administration.

[b] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalN ewDrugINDApplication/ucm071098.htm, last accessed April 9, 2010

Animal Subjects

Manuscripts describing investigations performed in vertebrate animals must explicitly state that the study was approved by the authors' Institutional Review Board for animal research (e.g., the Institutional Animal Care and Use Committee). The Journal expects humane and ethical treatment of all experimental animals, and requires that the study has been conducted in a manner that does not inflict unnecessary pain or discomfort upon the animals, as outlined by the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals (1996), prepared by the National Academy of Sciences' Institute for Laboratory Animal Research. A statement to this effect should appear at the beginning of the Methods section.

Registration of Clinical Trials

All clinical trials involving assignment of patients to treatment groups must be registered prior to patient enrollment. The registry, registration number, principal investigator's name, and date of registration must be stated in the first paragraph of the Methods section of the manuscript. A number of registries have been approved by the International Committee of Medical Journal Editors (http://www.icmje.org/faq_clinical.html)including http://www.clinicaltrials.gov (the most commonly used registry in the United States), http://isrctn.org, http://www.umin.ac.jp/ctr/index/htm,http://www.anzctr.org.au,and http://www.trialregister.nl. Submissions that have registered with the European Clinical Trials Database, EudraCT (https://eudract.ema.europa.eu/) meet this requirement.

CONFLICT OF INTEREST

A conflict of interest exists when an author's judgment about a manuscript may be influenced by secondary gain. Secondary gain typically involves personal, financial, academic, or political advancement. Examples of financial gain are easiest to identify and include direct monetary benefits, such as investments, stocks, honoraria, etc. When study results (as differentiated from publication *per se*) may affect an author's bonus, incentive payment (e.g., from likely changes in clinical workload), or salary (e.g., research about academic appointments and salary), this is also considered a conflict of interest. Academic recognition and advancement resulting from publishing high quality papers are the appropriate reward for good work and do not represent a conflict of interest.

Potential conflicts of interest in addition to actual conflicts of interest also commonly occur and must be considered. In some disciplines they may be unavoidable. Authors of scientific studies sponsored by industry possess a conflict of interest. Authors employed by a company with a commercial interest in the outcome of a study also possess a conflict of interest. Although these conflicts are understood and accepted, they must be disclosed. Investigators may have consulting or lecturing relationships with companies sponsoring their research. These relationships may be entirely appropriate, but they must be disclosed. Conflicts of interest must be disclosed on initial submission for every author. Disclosure is required for every manuscript, including Editorials and Letters to the Editor. Disclosures are reviewed by the handling editor so that a

decision can be made on whether competing interests may have influenced the manuscript in any manner. A manuscript will not be rejected solely because of conflicts of interest. Disclosures are available to reviewers during peer review, and are included when the manuscript is published.

Conflicts of interest must be disclosed on every title page whether created through the Title Page Generator (http://www.aaauthor.org) or our Title Page template (http://edmgr.ovid.com/aa/accounts/ifauth.htm). This title page must appear at the beginning of the manuscript.

Anesthesia & Analgesia does not have a threshold monetary value to determine "relevant" or "significant" conflicts of interest. The Journal does not have a threshold period of time after which a potential conflict of interest ceases to exist. All relevant potential conflicts of interest should be declared regardless of monetary value or the date of the relationship. Conversely, extensive disclosures of irrelevant or ancient relationships may unintentionally obfuscate relevant conflicts.

Authors are encouraged to err on the side of full disclosure. Full disclosure at the time of submission has fewer repercussions than subsequent exposure of a real or potential conflict. Authors are encouraged to contact the Editorial Office at editor@anesthesia-analgesia.org if they have questions about whether specific conflicts of interest should be disclosed.

PREPARING YOUR MANUSCRIPT

The following pages describe the types of manuscripts published by *Anesthesia & Analgesia*. The guidelines offer general rules on length, format, and content. These guidelines are intended to help authors write manuscripts meeting the expectations of reviewers and editors, improving chances that a manuscript will be accepted for publication. If a manuscript must deviate from these guidelines in any significant manner, please contact the Editorial Office at editor@anesthesia-analgesia.org before submitting the manuscript to be certain that the Journal will consider publication. Additionally, please explain any significant deviations from the expected format in the "Enter Comments" section when submitting your manuscript via Editorial Manager.

Submissions to *Anesthesia & Analgesia* should use grammatically accurate English with American spellings. Authors not fluent in English are encouraged to write their submissions in their native language. After fully vetting the manuscript in their native language, authors can hire a professional service to translate the manuscript into scientific English prior to submission. Professional translation services should be acknowledged in the manuscript. Individual translators should be named either as an acknowledgment or, in exceptional circumstances, as coauthors. All accepted submissions will be edited for syntax, grammar, and spelling.

Manuscript Types and Word Count

Please review the following descriptions of manuscript types and recommended word counts. *Word counts are included for guidance. They are not strictly enforced.* Manuscripts should be as succinct as possible. All submissions must include a title page created either through the Title Page Generator (http://www.aaauthor.org) or the appropriate manuscript template (http://edmgr.ovid.com/aa/accounts/ifauth.htm).

Research Reports
Research Reports describe original clinical or laboratory investigations. A meta-analysis of a series of research papers is also a Research Report. Research Reports include a structured Abstract typically less than 400 words, an Introduction (typically less than 500 words, e.g., 1 page), Methods, Results, and Discussion (typically less than 1500 words, e.g., 3 pages). Research Reports are typically less than 3000 words (excluding supplementary online data).
A meta-analysis is a formal statistical analysis of an existing body of literature with the intention of producing new knowledge. A meta-analysis should be written and submitted as a Research Report, not as a Review Article.
Anesthesia & Analgesia is among the most selective journals in our discipline. Accepted Research Reports use state-of-the art tools in study design, data collection, and statistical analysis. Accepted reports typically provide novel information to improve patient care or increase our understanding of fundamental mechanisms.

Research Reports may be rejected without peer review if the question is not interesting, the results are inconclusive, the results could be predicted as logical extrapolations of existing knowledge, the methodology is inappropriate to the research question, or *Anesthesia & Analgesia* is the wrong journal for the material.

Case Reports
As of November 15, 2012, *Anesthesia & Analgesia* will no longer accept Case Report submissions. Case Reports will be reviewed and published in the online journal *A&A Case Reports*. For more information please visit http://journals.lww.com/aacr/Pages/default.aspx.

Echo Rounds
Echo Rounds are brief reports providing a focused discussion of one or more unique or interesting perioperative echocardiographic image (transesophageal, precordial, epicardial, or epiaortic) from a clinical situation in which echocardiography was central to clinical management. Submissions should provide succinct points on echocardiographic views, techniques, or calculations. Only relevant clinical details should be presented. Echo Rounds are not "Mini Case Reports" because they include far less clinical detail than Case Reports.
The suggested format is to present clinical details and specific echo findings in the first third of the report and didactic discussion of the echo topic(s) in the subsequent two-thirds followed by no more than 7 references. The report should be accompanied by no more than 3 echocardiographic still images and 3 video clip(s), with legends, which will be available online. The still images should usually, but not always, correspond to the respective video clip(s). Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) of figures and video clips (if possible) and may elect to consolidate consecutive time segments into one clip (although adequate viewing time for each segment must be provided to clearly illustrate the primary findings being discussed in the text). Selected reports may benefit from the addition of a brief table or schematic figure. Authors are advised to examine previously

published Echo Rounds (either via the Table of Contents or via the online Echo Rounds database at http://www.scahq.org or via www.anesthesia-analgesia.org) to avoid submission of topics previously published in this series. See page 29 for video formatting details. Echo Rounds do not include an Abstract and are typically less than 1100 words in length.

Consent

Echo Rounds about one or more patients must include a statement that the patient and/or the patient's family reviewed the report and gave written permission for the authors to publish the report. At least one author must have participated in the care of the patient described in the case report. Please include your consent statement at the beginning of your report.

In cases where neither the patient nor any family member can be contacted due to certain circumstances (e.g., patient death), and the local IRB has determined that review and written approval are unnecessary, a statement by the author explaining this circumstance may be acceptable if:

1. The reported event(s) occurred more 3 years prior to submission of the report. In this circumstance, the year of the event(s), as well as a detailed explanation regarding why attempts to obtain written consent were unsuccessful, should be included in the cover letter.
2. The patient(s) can be de-identified by removing obvious demographic information without compromising the scientific value of the report. The editors reserve the right to further delete or request additional information considered essential for complete understanding of the report.

These standards will apply to both adult and minor patients.

Retain copies of your documentation of written informed consent from each patient

and /or the IRB approval and reasons for obtaining it. The editors or reviewers for *Anesthesia & Analgesia* may request copies of these documents at any time. Please DO NOT submit a copy of the written consent form unless it is specifically requested by the editors or reviewers.

Checklist

All Echo Rounds must also include a completed Echo Rounds Checklist. This checklist is available at http://edmgr.ovid.com/aa/accounts/ifauth.htm#Before.

Echo Didactics

Echo Didactics are solicited submissions presenting a practical clinical review of a particular echocardiographic topic (e.g., important measurements, specific anatomic evaluation, current or emerging technologies). Echo Didactics do not include an Abstract but should include a discussion of the relevant background, the "nuts and bolts" of assessment and measurement, and new concepts. Echo Didactics should include 1 to 3 figures or short tables, 1 to 3 video clips (composite videos, as described for Echo Rounds) and appropriate references (not to exceed 10). The author should provide 3 to 4 bulleted teaching points summarizing the most important teaching points. Echo Didactics are typically less than 1000 words.

Brief Reports

Brief Reports are intended to report clinical or laboratory research observations.

Brief reports are not appropriate for hypothesis-based research which should be reported as a Research Report. Brief Reports may be appropriate for studies reporting observations without formally testing a hypothesis. Brief Reports can also be used to provide initial reports of new technologies, or describe a novel pilot study.
Brief Reports require an Abstract typically less than 100 words, which may be structured or unstructured depending on the topic. Brief Reports contain an Introduction, Methods, Results, and a very brief (1 paragraph) Discussion. Brief Reports are typically less than 1000 words.

Technical Communications
Technical Communications describe instrumentation and analytic techniques. Technical Communications include an unstructured Abstract, typically less than 400 words, and the text of the communication, typically less than 1500 words.

Review Articles
Review Articles synthesize previously published material into an integrated presentation of current understanding of a topic. Review Articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review Articles are expected to be comprehensive in scope. If the author used a formal strategy to search the medical literature, this strategy should be described. Review Articles should include an unstructured Abstract typically less than 400 words. Review Articles are typically less than 5000 words.

Medical Intelligence Articles
Medical Intelligence Articles collate and evaluate previously published material to aid in evaluating new concepts or updating old concepts germane to anesthesiology. Medical Intelligence Articles are expected to be highly focused in scope. They should include an unstructured Abstract typically less than 100 words, and the text of the review, which is typically less than 2000 words.

Special Articles
Special Articles are manuscripts not described by any of the above categories. They are typically invited by the Editorial Board to examine a particular topic. There are no word limits or rules for the structure of Special Articles. They may have a structured or unstructured abstract typically less than 400 words, or no abstract.
Statements issued by organizations to guide clinical care (e.g., guidelines, practice parameters, recommendations, consensus statements, position papers) are published as Special Articles. Societies interested in publishing such statements in *Anesthesia & Analgesia* should contact the Editor-in-Chief at editor@anesthesia-analgesia.org to discuss the process of publishing guidelines in the Journal. Affiliate Societies should contact the appropriate Section Editor to discuss the role of the Journal in the process of publishing the guideline. The submission must describe the clinical problem to be addressed, the mechanism by which the statement was generated, a review of the evidence for the statement, if available, and the statement on practice itself.
Occasionally more than one group or society will issue guidelines on the same

topic, resulting in confusion among clinicians.[4] To minimize confusion and enhance transparency, guidelines published in *Anesthesia & Analgesia* should begin with the following 4 bulleted phrases, followed by brief comments addressing each phrase:

- What other guidelines are available on this topic?
- Why was this guideline developed?
- How does this guideline differ from existing guidelines?
- Why does this guideline differ from existing guidelines?

Editorials

Editorials provide perspective on articles published in the Journal or express the general policies or opinions of the Editorial Board. Editorials are solicited by the Editorial Board. Editorials do not have Abstracts and are typically less than 1500 words.

Pro/Con Editorials

Pro/Con Editorials are scholarly discussions of clinically relevant topics providing opposing, well-founded viewpoints. They are solicited by the Editorial Board. Pro/Con Editorials do not have Abstracts and are typically less than 1500 words.

Pro/Con/Core Reviews

Pro/Con/Core Reviews present a focused Review Article accompanied by expert commentary for and against a specific clinical topic or technique. The Core Review Article includes an Abstract typically less than 100 words, and the text of the review which is typically less than 2500 words. It may be accompanied by figures or a video supplement. Pro/Con/Core Reviews are solicited by the Editorial Board.

Book and Multimedia Reviews

Book and Multimedia Reviews report current literature and apps in perioperative medicine, critical care, and pain management, as well as general scientific topics of interest to anesthesiologists. Publishers interested in having their book or multimedia material reviewed by the Journal should first contact our Media Reviews editor at bookreviews@anesthesia-analgesia.org before sending the material. Book Reviews, App Reviews, website or blog reviews (all encouraged) are typically less than 750 words.

All contributors to *Anesthesia & Analgesia* are encouraged write reviews about books that our readership might find interesting. Authors interested in submitting a book review should contact our Media Reviews editor at bookreviews@anesthesia-analgesia.org to see if the editor believes the review would be of interest to readers of the Journal.

Meeting Reports

Meeting Reports are scholarly outlines of the program and content of a scientific meeting. They may be organized temporally (day by day) or thematically (topic by topic). Authors interested in submitting meeting reports should first contact our Media Reviews editor at bookreviews@anesthesia-analgesia.org to confirm that the meeting is of general interest to the readership. Meeting reports do not

have Abstracts and are typically less than 1500 words.

Focused Reviews
Focused Reviews summarize recent advances in a particular field with direct application to clinical practice. They are intended to efficiently communicate new knowledge to make clinical practice safer, more efficient, and up-to-date. They are solicited by the Editorial Board. Focused Reviews contain an unstructured abstract, text, and references. They are typically less than 1500 words.

Commentaries
Commentaries provide expert perspective on articles or topics published in the Journal. They are typically solicited from reviewers who provide unusually thoughtful insight during the peer review process that should be shared with the *Anesthesia & Analgesia* readership. They are solicited by the Editorial Board. Commentaries contain a title page, text and references and do not have an Abstract. They are typically less than 1500 words.

The Open Mind
The Open Mind is a forum for thoughtful, scholarly, and well-referenced reader perspectives. The Open Mind is intended to stimulate discussion. Submissions to The Open Mind must be intellectually rigorous. The Open Mind is not a forum for rants, tirades, or complaints about being overworked and underpaid.[5] Submissions to The Open Mind do not have an Abstract and are typically less than 1500 words.

Letters to the Editor
Letters to the Editor are submitted using Editorial Manager (http://aa.edmgr.com). Authors should consider the following points when composing a Letter to the Editor:[6]
Consent
Letters to the Editor about one or more patients must include a statement that the patient, the patient's family, or the local IRB reviewed the Letter to the Editor and gave written permission for the authors to publish the letter. If such permission has not been obtained, this must be disclosed in the letter as well as the reason for not obtaining patient permission. A Letter to the Editor becomes a research study if the authors *intended* to publish the outcome at the time they provided treatment for the patient. The authors should obtain Institutional Review Board approval and written informed consent before treating the patient. If that is not possible then the author should obtain Institutional Review Board approval and patient consent to pursue publication shortly after providing treatment and in advance of submission to *Anesthesia & Analgesia*.

Brevity
Letters that respond to a published paper are typically less than 300 words. Long critiques are difficult to follow and will likely generate a response that is also too lengthy. Letters describing an interesting or uncommon clinical experience should be limited to relevant clinical details. Unlike Case Reports, letters that describe clinical care should not delve into the background of diseases or

therapeutic interventions. A letter describing a new gadget or technique should not exceed 3-5 paragraphs. References should be limited to a few key articles.

Focus

A letter should address a single issue, not an entire subject. The first sentence should identify the reason for submission (e.g., a flaw in methodology, relevant observations, or alternative explanation). A letter should be of interest to more than the correspondent and the author of the article in question. Quibbles involving a complex and sophisticated subject or methodology should be settled privately rather than in the Correspondence Section of the Journal.

Scientific Accuracy

Letters do not necessarily have the imprimatur of external peer review. Nevertheless, scientific accuracy is crucial. If letters deal with complex or arcane issues they will be peer reviewed by members of our Editorial Board and outside reviewers, especially when letters propose a new idea or methodology.

Tone

Letters must be respectful. Letters that attack authors, the Journal, or our readership will not be published. Letters that are self-promoting will not be published. Just as we discourage authors of peer-reviewed articles from claiming to be the first to make an observation, we similarly are not interested in letters claiming prior publication of an observation. We will publish letters to correct the record if we believe that the claim is meritorious and important for the scientific record.

Timeliness

A letter written in response to a published paper should be submitted no later than 4 months after the paper has been published in print. A longer interval detracts from the interest, relevance, and impact. Letters responding to manuscripts published online are held, but not considered, until the manuscript appears in print.

Writing

All letters are edited, and occasionally completely rewritten, to be highly focused, readable, and succinct. Accepted letters may or may not be forwarded to the author to approve the edited text.

Conflict of Interest

Conflict of interest disclosure is required for all submissions to the Journal, including letters.

All Letters to the Editor must include a Title Page in the style of our journal. Please use our Title Page template at: http://edmgr.ovid.com/aa/accounts/ifauth.htm#Before.

GENERAL GUIDELINES AND SET-UP INSTRUCTIONS

Authors are encouraged to follow these guidelines carefully to improve the timeliness and quality of the review process. The Editors of *Anesthesia & Analgesia* may return manuscripts to authors without peer review if the manuscripts do not conform to these guidelines.

 Follow the specifications in Uniform Requirements for Manuscripts Submitted

to Biomedical Journals, as updated in 2010, available at http://www.icmje.org.
 Carefully think through the overall organization of the manuscript. Follow the guidance given in the subsections below to prepare each section.
 Write clearly. Be straightforward, unambiguous, and succinct. Strunk and White's The Elements of Style[7c] provides excellent guidance on clear writing.
 Follow the technical styles found in these texts:
o Scientific Style and Format: The CSE manual for Authors, Editors, and Publishers. 7th ed.[8]
o American Medical Association. Manual of Style, 10th ed.[9]
 First-time authors will benefit by reading the unpublished "A Step by Step Guide to Writing a Scientific Manuscript" by Wenzel, Dünser and Lindner, at http://www.aaeditor.org/StepByStepGuide.pdf
 Prospective randomized clinical trials should be presented in accordance with the CONSORT statement (http://www.consort-statement.org). The CONSORT statement includes general principles applicable to many types of investigations. Authors should complete and submit the CONSORT checklist when preparing their submission.
 Prospective and retrospective observational trials should be presented in accordance with the STROBE statement (http://www.strobe-statement.org). Authors should complete and submit the appropriate STROBE checklist when preparing their submission.
 Systematic reviews and meta-analyses should be presented in accordance with the PRISMA statement (http://www.prisma-statement.org). Authors should compete and submit the appropriate PRISMA checklist when preparing their submission.
 Follow these rules when composing your manuscript:
o Create your manuscript using Microsoft Word or a fully compatible program.
o Use "Standard US Paper" or "Letter" page format (width of 8.5 inches or 21.59 centimeters, length of 11 inches or 27.94 centimeters) for your manuscript before uploading the document to Editorial Manager.
o Double-space all text, including references and table and figure legends. o Begin each section (title page, abstract, introduction, methods, results, discussion, acknowledgments, references, tables, and legends) on a new page by inserting a page break before each part.
[c] See http://www.bartleby.com/141, last accessed May 28, 2012

o Number pages consecutively in the upper right corner beginning with the title page.
 Upon submission for all new submissions, we require each author to complete and sign a digital copyright assignment agreement uploaded into Editorial Manager (under "Attach Files") by the corresponding author. We do not accept copyright assignment forms by fax or email. For more information visit: http://edmgr.ovid.com/aa/accounts/ifauth.htm. Please direct questions about copyright transfer to the Editorial Office at editor@anesthesia-analgesia.org.
The Editorial Office has prepared templates in Microsoft Word format that should be downloaded and used for manuscript preparation (http://edmgr.ovid.com/aa/accounts/ifauth.htm). Each template includes the

appropriate formatting defaults, instructions for the type of manuscript being submitted, and a checklist for manuscript submission. The instructions and checklist should be deleted before submitting the manuscript electronically. Templates exist for the following types of submissions:

- Book/Multimedia Reviews
- Brief Reports
- Commentaries
- Echo Didactics
- Echo Rounds
- Editorials
- Focused Reviews
- Letters to the Editor
- Medical Intelligence Reports
- Meeting Reports
- Research Reports
- Review Articles
- Special Articles
- Statistical Grand Rounds
- Technical Communications
- The Open Mind

Please download our Case Reports template (http://edmgr.ovid.com/aacr/accounts/ifauth.htm#Before) before submitting your Case Report for consideration to *A&A Case Reports*. For more information on *A&A Case Reports* please visit http://journals.lww.com/aacr/Pages/default.aspx.

Title Page

All submissions require a title page. Please create the title page of your manuscript by either using the Title Page Generator (http://www.aaauthor.org) or our Title Page template (http://edmgr.ovid.com/aa/accounts/ifauth.htm). With the Title Page Generator, a complete title page will be generated (as an RTF file), which you must copy and paste into your manuscript (typically a Microsoft Word document). The Title Page Generator efficiently gathers the necessary information for the title page. If you use the Title Page Generator you do not need to prepare a separate title page.

Title pages must contain the following elements (Note: all elements are provided when using the Title Page Generator or Title Page template):

- **Title of the article**: Be concise but informative. Include species when appropriate.
- **Short Title**: An abbreviated title of no more than 60 characters including letters and spaces. The short title appears in the abbreviated table of contents in the Journal and
also appears in the footer of the published article.
- **List of Authors**: First name, middle initial, and last name of each author, with highest academic degree(s) (MD, PhD, etc) and an e-mail address for each author. Each author must:
  - Indicate his or her affiliation (Department, Institution/Company, City,

State/Country) at the time the work was performed. If the author has moved since the work was performed the current institution may appear in parentheses, e.g., (Current Affiliation: Department, Institution/Company, City, State, Country).

- Disclose his or her contribution to the manuscript. Identified contributions include study design, conduct of the study, data collection, data analysis, and manuscript preparation, e.g., "this author helped design the study and prepare the manuscript."
- Attest to having approved the final manuscript, e.g., "Dr. Smith approved the final manuscript."
- For research reports, brief reports, and technical communications involving more than one author, at least two authors must attest to having reviewed the original study data and data analysis e.g., "Dr. Smith attests to the integrity of the original data and the analysis reported in this manuscript."
- One author must be designated as the archival author who is responsible for maintaining the study records, e.g., "Dr. Smith is the archival author."
- Disclose all conflicts of interest or indicate that no conflict of interest exists. All relationships between authors and any company or organization with a vested interest in the outcome of the study should be disclosed including both current and previous relationships. More information on conflict of interest can be found on page 9.

 If two authors are to be considered "co-first authors" this should be identified as a footnote to each co-first author. The footnote will appear in the published paper, but does not appear in PubMed.

 Authors who wish to change the authorship line during peer review should be prepared to explain the rationale for the change. Following acceptance of the manuscript the authorship line can only be changed with a written request to the Editor-in-Chief at editor@anesthesia-analgesia.org.

 Name of Department(s) and Institution(s) to which the work should be attributed. Multiple institutions may be listed if appropriate. The National Library of Medicine (PubMed) determines institutional affiliation from the affiliation of the first author. *Anesthesia & Analgesia* has no control over this process.

 Corresponding Author: Name, department, institution, full address, telephone number, and e-mail address of author responsible for manuscript correspondence.

 Reprints: Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author.

 Funding Statement: The source(s) of funding, including foundations, institutions, pharmaceutical and device manufacturers, private companies, donors, or intramural departmental sources. Please also indicate if this work was funded by: National Institutes of Health (NIH), Howard Hughes Medical Institute (HHMI), Medical Research Council (MRC), and/or Wellcome Trust.

 IRB Contact Information: For all studies involving human research, include the name and full contact information (Contact Name, Institution, Address, Phone, Email) for the Institutional Review Board that approved the study.

Abstract

 The Abstract should appear after the title page(s).
 Structured abstracts include Background, Methods, Results, and Conclusions.
Structured abstracts should provide enough detail to permit the reader to quickly understand the study and findings.
o **Background**: State the context and purpose of the research, and the hypothesis being tested.
o **Methods**: Define the study subjects or experimental animals, study groups, controls, data collected, primary and secondary endpoint(s), and analytic and statistical methods.
o **Results**: State the number of subjects studied, key findings, and statistical significance including confidence intervals.
o **Conclusions**: State whether or not the hypothesis was proven, and the scientific and clinical conclusions drawn from the study.
 Unstructured Abstracts summarize the article, including salient observations and conclusions.
 Word Count: The table below suggests word limits for abstracts, based on manuscript type. Abstracts may modestly exceed the word limit if necessary.
Table 1: Word Counts
Updated October 2015
Manuscript Type
Abstract Type
Word Limit **(typically less than)**
Research Reports
Structured
400
Case Reports
Unstructured
100
Echo Rounds
None
1100
Echo Didactics
None
—
Brief Reports
Structured or unstructured
100
Technical Communications
Unstructured
400
Review Articles
Unstructured
400
Medical Intelligence Articles
Unstructured
100
Special Articles Structured, unstructured, or none 400
Editorials
None

—
Pro/Con Editorials
None
—
Pro/Con/Core Reviews
Unstructured
100
Book and Multimedia Reviews
None
—
Meeting Reports
None
—
Focused Reviews
Unstructured
100
Commentaries
None
—
The Open Mind
None
—
Letters to the Editor
None
—

Text

The text of Research Reports is usually, but not necessarily, divided into the following sections: Introduction, Methods, Results, and Discussion.

Introduction

 Summarize the background in one or two sentences.
 Offer only fundamental background information for the work.
 Succinctly state the purpose of the study.
 If the study tests specific hypotheses, state the hypotheses.
 Do not review the topic.
 The introduction is typically less than 500 words.

Methods

 Methods must be presented in sufficient detail that readers can understand how the results were obtained, and other investigators can replicate the study.[10]
 State the study's conformance with the Journal's requirements for human and animal trials, as described in Ethical Conduct of Research, page 5.
 If the study involves neuraxial or perineural drug administration, drug administration in children, or "off-label" use of drugs, please state how the study conforms to the Investigational Drugs guidelines on page 6. If the drug is used "off- label" and an investigator IND was not obtained, this should be stated. If an investigator IND was obtained please include the IND number.
 If the trial is registered (see page 8) state the clinical trial registry, registration number, and date of registration.
 Inclusion and exclusion criteria: describe how observational or experimental

subjects (patients or experimental animals, including controls) were selected.
 Describe methods, materials, devices (manufacturer's name and city, state, country in parentheses), computer software (including revision numbers), and procedures in sufficient detail so that the experiment can be reproduced by other investigators. If
22 the text and the references cannot succinctly provide adequate detail, include an
Appendix, or provide additional material as Supplemental Digital Content.
 Disclose molecular structures when describing novel compounds. Structural disclosure may be waived at the discretion of the Editorial Board when there is a compelling reason to publish a manuscript before the sponsor is ready to disclose the molecular structure.
 Provide references to established methods.
 Provide references and brief descriptions for published methods that are not well
known. The Methods section should be interpretable to a knowledgeable reader without requiring accessing another manuscript to understand to the methods used.
 Describe new or substantially modified methods, give reasons for using them, and
define their limitations.
 Identify all drugs and chemicals including generic name(s), dosage(s), and route(s)
of administration. Refer to the drugs throughout the text by their generic names unless the subject of the research is a comparison of branded formulations in which case the use of the brand name is more precise.
 If you use a methodology that you previously reported it is appropriate to use wording identical to your previous wording. If you are not the author of the previous description of the methodology, then the methodology must be rewritten with reference to the original description of the methodology, or placed in quotation marks with a citation to the original description.
 Present methodologies in the same order in which the results are presented.
Statistical Methodology
 Describe all data handling and statistical methods.
 Clearly state the exact statistical test used for the primary hypothesis and all secondary hypotheses.
 Conventional biostatistics, such as the T test, ANOVA, and Chi Square test, were developed more than 60 years ago. Statistical methodology has advanced since then. While these tests may still be appropriate, it is likely that additional statistical analysis will be required. *Anesthesia & Analgesia* has published a series of "Statistical Grand Rounds" and other statistically oriented papers to help authors understand our expectations of statistical methodology for different types of studies.

Table 2: Statistical Guidance in *Anesthesia & Analgesia*

If your study	**Then please review the statistical guidance in**
Includes learning curves	

Learning curves and mathematical models for interventional ultrasound basic skills. Anesth Analg. 2008;106:568-73[11]
Includes P-values but not confidence intervals
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Has an intervention variable that was not randomized, such as choice of drug dose, but does not include propensity scores
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Has a dependent variable that may differ among providers, such as physicians, but that dependent variable is not analyzed by stratification or mixed models
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Includes an intervention applied for the patients of some but not all providers, some but not all facilities, etc.
An introduction to multilevel modeling for anesthesiologists. Anesth Analg 2011;113:877-87[13]
Has multiple observations measured over time
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Uses meta-regression without complete study data
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Has a primary or secondary endpoint that is either cost or time, but the endpoint has not been analyzed using methods suitable to estimate the mean of skewed data
Checklist for statistical topics in *Anesthesia & Analgesia* Reviews. Anesth Analg 2011;113:216-9[12]

Has included time to complete a task
Analysis of variance of communication latencies in anesthesia: comparing means of multiple log- normal distributions. Anesth Analg 2011;113:888-96[14]
Includes patient waiting times
Analysis of interventions influencing or reducing patient waiting while stratifying by surgical procedure. Anesth Analg 2011;112:950-7[15]
If your study includes a survey
Inconsistent survey reporting in anesthesia journals. Anesth Analg 2011;113; 591-5[16]
Evaluates equivalence (inferiority), and is neither paired nor simply involves two groups
Equivalence and noninferiority testing in regression models and repeated-measures designs. Anesth Analg 2011;112:678-87[17]

Includes analgesic consumption (e.g., total morphine received during first 24 hours postoperatively)
The influence of age on sample size calculation in acute pain trials using

morphine consumption as an end point. Anesth Analg 2010;110:1186- 90[18]
If your study includes both analgesic consumption and visual analog scale for pain, or equivalents
Mixed effect modeling in analgesia trials. Anesth Analg. 2008;107:9-10,[19] and
Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesth Analg 2012;114:1304-17[20]
Includes a statistical power analysis but does not provide a 1 or 2 sentence summary of previous studies showing what is the minimum clinically important difference
Beyond effect size: consideration of the minimum effect size of interest in anesthesia trials. Anesth Analg 2012;114:471-5[21]
Assesses concordance (agreement) in trends of hemodynamic variables
A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg 2010;111:1180- 92[22]
Includes a composite endpoint
Design and analysis of studies with binary-event composite endpoints: Guidelines for anesthesia research. Anesth Analg 2011;112:1461-71[23]
Reports multiple uncorrected P-values as "P < 0.05"
Publication bias, retrospective bias, and reproducibility of significant results in observational studies. Anesth Analg 2012;114:931-2[24]
Includes binary operating room management data such as cancellation rates
Validation of statistical methods to compare cancellation rates on the day of surgery. Anesth Analg 2005;101: 465-73[25, 26]
Includes continuous operating room management data such as turnover times
Numbers of simultaneous turnovers calculated from anesthesia or operating room information management system data. Anesth Analg 2009;109:900-5[27]
Includes prediction probabilities
A program for computing the prediction probability and the related receiver operating characteristic graph. Anesth Analg 2010;111:1416-21[28]
Includes a Bland-Altman plot
Let's think clinically instead of mathematically about device accuracy. Anesth Analg 2011;113:89-91[29]
Includes logistic regression or propensity score analysis, and procedure or duration is used as an independent variable
Statistical Grand Rounds: Importance of appropriately modeling procedure and duration in logistic regression studies of perioperative morbidity and mortality. Anesth Analg 2011;113:1197-201[30]
25
 If the guidance in Table 2 is not clear, please consult a statistician for assistance with the statistical analysis.

Results

 The results are the most important part of the manuscript.
 The presentation must minimize the possibility of misinterpretation of the study
findings.[31]
 Present results in a logical sequence in the text, tables, and illustrations. To the

extent possible, the order of presentation in the Results should match the order of
presentation of the Methods.
 Account for all subjects, e.g., number enrolled but not randomized, number withdrawn and for what reasons, etc.
 Do not repeat large amounts of material in the text that are also presented in the
tables or figures. However, commenting on key data from tables or figures is necessary to highlight the main findings.
 Focus on the important results.
 In the text, tables, and illustrations, present P values as the actual value rounded to
the nearest one-hundredth if greater than 0.01 (e.g., P = 0.04) rather than as an inequality (e.g., P < 0.05). Inequality may be used in footnotes describing symbols that designate statistical significance in tables and figures (e.g., *P < 0.05) and when statistical software uses an inequality to report very small P values (e.g., P < 0.001).
 Use consistent rules for presenting numerical results. For example, if a numeric result appears in the abstract, the results, and a table, it must be reported with the same precision in each instance.
 In general, determining that the difference between two groups is greater than 0 at P < 0.05 is not an interesting result. Even the most trivial difference might be statistically significant if enough subjects were studied. The important questions are: 1) what are the confidence bounds for the difference between groups; and 2) is the difference large enough to matter scientifically or clinically?

Discussion

 Discussions should be focused and succinct.
 The Discussion is typically less than 1000 words.
 The Discussion should not be a comprehensive review of the literature.
 The Discussion need not cite every previous study in the field.
 The Discussion should not contain product advertisements, e.g., “this new product
is conveniently packaged and may transform anesthesia and perioperative medicine.”
 Do not claim to be the first to report something. This claim only invites angry Letters to the Editor. Claims of being the first to publish a finding are best made in
retrospect.
 Where possible, structure your Discussion in the same order in which the results
were presented in the Results section.
 Emphasize new and important aspects of the study and the conclusions that follow.
 Succinctly relate the observations to other relevant studies.
 Do not repeat data presented in the Results section, except as required for clarity.
 All claims must be fully supported by the data.
 Avoid claims that could be misinterpreted when taken out of context.[31]

 State the limitations of the study including the limitations of the materials and methods. State how the limitations temper the conclusions.
 In the last paragraph link the conclusions with the goals of the study. If the study
tested a hypothesis, state whether the hypothesis was proven, disproven, or the study was inconclusive.

Tables
 Preferably, tables should be embedded in the Word document although they can also be uploaded separately.
 Use a separate page for each table.
 Double-space each table's entries.
 Do not submit tables as photographs or pasted images.
 Number the tables consecutively, and cite them consecutively (on first instance) in
the text. Each table should have a brief title. Each column in a table should have a brief name.
 Use footnotes (not table titles or column headings) for explanatory matter and definitions of abbreviations. Abbreviations must be described with footnotes even if
they are defined in the text or in other tables.
 For footnotes, use lower-case italicized letters in alphabetical order.
 If you include a block of data, a table, or a figure from another source, whether published or unpublished, acknowledge the original source.

Figures and Illustrations
 Figures are preferred over tables for presenting data.
 Important research findings should be visually evident in the accompanying figures.
 For useful information on preparing digital art, please review the detailed instructions at http://art.cadmus.com/da/index.jsp.
 You are encouraged to read The Visual Display of Quantitative Information by Edward Tufte,[32] a superb treatise on statistical graphics, charts, and tables.
 Design figures and illustrations with their published size in mind, i.e., 1 or 2 columns wide. Large figures will be reduced.
 Anesthesia & Analgesia publishes in full color, and encourages authors to use color
to increase the clarity of figures. Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not grey. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable and printed in black.
 The default formatting provided with Microsoft Excel is not acceptable for scientific graphics. There are numerous programs for creating scientific graphics that are more suitable than Excel (e.g., R, Origin, Prism, SigmaPlot, StatGraphics, S+). If you decide to use Microsoft Excel to create figures, please use fonts that are clear and appropriately sized for all axis names and labels. In general sans

serif fonts (e.g., Arial or Helvetica) are better for figures than serif fonts (e.g., Times).
 Number figures consecutively. Supply a brief title for each. Cite figures in the text in consecutive, numerical order on first instance.
 If a figure has already been published, acknowledge the original source. You must obtain and submit written permission from the copyright holder to reproduce the material when you submit the manuscript for review. Unpublished figures require permission of the author. Permission is required to reproduce any previously published material except for documents or figures in the public domain.
 Define all abbreviations used in each figure. Repeat definitions of any abbreviations used in subsequent legends.

References
 All references must be generally available to readers. Cite references to articles only if they are published in peer-reviewed journals included in the Index Medicus. Unacceptable references include abstracts appearing only in meeting programs or abstracts more than 3 years old. These should be listed as footnotes. Number references consecutively in the order in which they are first mentioned in the text. Double-space between all lines of each reference and between references.
 Cite references in text, tables, and legends using superscripted numbers after the punctuation in the order in which the citations appear in the text, tables and figure legends (e.g., Wong et al.[1] described . . .).
 The titles of journals must be abbreviated according to the style used in Index Medicus.
 Verify all references against the original documents or Medline. (http://www.pubmed.gov)
 Upload copies of "in press" references to Editorial Manager when the manuscript is submitted.
 Check the citation list for duplicate entries.
 Use the formats of the example references shown in Table 1 above as guides for
formatting references.
Table 3. Reference Formats

Document type
Example format
Standard journal article (list all authors, do not use "et al")
Dalal PG, Murray D, Cox T, McAllister J, Snider R. Sedation and anesthesia protocols used for magnetic resonance imaging studies in infants: provider and pharmacologic considerations. Anesth Analg 2006;103:863–8
Books/monographs
Zar JH. Biostatistical Analysis. 3rd ed. Upper Saddle River, NJ: Prentice-Hall, 1996 28
Supplemental Digital Content
Supplemental digital content provides additional material too detailed for inclusion in the manuscript, or only accessible electronically (e.g., video,

simulation software). Supplemental digital content may include audio and video files, spreadsheets, additional figures and tables, appendices, data files, and statistical analysis programming code, simulations, and apps. Remove all patient identifiers from the supplemental digital content prior to uploading.
Supplemental digital content should be labeled as to whether the content is to be published in the print journal, as an online supplement, or not published and for reviewers only. Please cite the supplemental digital content in the text along with a very brief description, for example, "Supplemental Video 1, dilated right coronary artery..."
Because supplemental digital content is part of the overall submitted manuscript, make every effort to have the supplement clearly formatted and organized. More detailed instructions can be found online at http://sites.google.com/site/lwwsdcauthorchecklist.
Authors are urged to share raw data whenever possible. Raw data are invaluable to the community of investigators working to move a discipline forward. The submission of raw data as supplemental digital content also provides an external storage site for the authors' data, helping to ensure that the original research data are preserved. Lastly, including raw data as a supplemental digital content enhances the transparency of the published research and the peer review process.
Excel spreadsheets are commonly used to share raw data. ASCII "CSV" (comma separated values) files are also acceptable. All data shared as a web supplement should be appropriately de-identified to protect patient privacy.

Book chapter
Eger EI II. Uptake and distribution. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone, 2005:131–53
Published proceedings
DuPont B. Bone marrow transplantation in severe combined immunodeficiency with a paper unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974:44-6
Website
Do not use as a reference. May be used as a footnote listing the URL and the date it was last accessed by the author, e.g., NIH Request for Applications. Available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-005.html. Accessed May 6, 2010.
If authors are not comfortable sharing data online as supplemental digital content, they may indicate as a footnote on the title page which author (if any) can be contacted via e-mail for the raw data.

Video
Please follow the guidelines below for submitting supplemental video (including video for Echo Rounds and Echo Didactics) and audio files:
 The preferred video file formats are MPEG-4 (MP4), QuickTime (MOV), and Windows Media Video (WMV). Please preview video clips on both Windows and Macintosh platforms to be certain they play correctly. The review process will be delayed if the Editorial Office cannot play the video clip.

 Deliver still images from video clips in high-resolution JPEG or TIFF formats.
 Individual video clips should not exceed 15 MB.
 Use video-compression software to reduce video size if necessary. Optimal video
frame dimensions are 480 · 360 pixels and 640 · 480 pixels. Videos of 320 · 240 pixels have inadequate resolution for teaching purposes. Video clips are typically 15–25 seconds.
 Combinations of clips: If several video clips are combined, for example, several transesophageal echocardiographic loops, please provide adequate time for each segment and leave a suitable gap between the videos. Use appropriate labeling to ensure that the viewer can understand the timing of the pathology and events. Labeling can be added with video editing programs, such as Adobe Premiere or iMovie.
 Patient identifiers: All patient identifiers must be removed from video clips and still images, including the date of the study.
 For echocardiographic video, please consult Rokey and Vick. Masking Personal Health Information on Real-time Echocardiographic Images.[33]

Audio

 Submit audio files in WAV or MP3 formats.

Units of Measurement

Anesthesia & Analgesia serves an international audience. For this reason, Système International (SI) units are preferred.

We recognize that authors and readers unfamiliar with SI units have difficulty interpreting them. Authors unfamiliar with SI units may make undetected errors if they convert their measurements to SI units. To minimize the chance of conversion errors, authors should submit manuscripts using the units of measurement used in the study, or the units that are used clinically at the author's institution. These are the units that will appear in the published manuscript.

Readers may readily convert published units to units of their choice using commonly available conversion tables. *Anesthesia & Analgesia* provides a spreadsheet for unit conversion available at http://www.aaeditor.org/units.xls.

A more complete conversion table can be found in the American Medical Association Manual of Style, A Guide for Authors and Editors, Chapter 15: Units of Measure, Table 4: Conversions from Conventional Units to Système International (SI) Units, pp 486–503.[34]

Abbreviations

AAWP: Avoid Abbreviations Whenever Possible. Idiosyncratic abbreviations make text difficult to read. Abbreviations widely used within a narrow discipline can make a manuscript uninterpretable to the interested reader from outside that discipline.

Do not create new or unusual abbreviations. For example, if the paper refers to the paw pressure test, just call it the paw pressure test throughout the paper, not the PPT. The added length of spelling out words is more than compensated for by the increased readability of your manuscript when words are spelled out.

When it is necessary to use an abbreviation, at the first mention of an

abbreviated term in the abstract, text, each figure legend, and each table, write the unabbreviated term first, immediately followed by the abbreviation (within parentheses). For subsequent uses of the term in the same section use the abbreviation without parentheses.

Please do not use abbreviations to decrease the word count of a manuscript. Clarity is more important than brevity. If a term is used fewer than 3 times, an abbreviation is unnecessary.

Write as you speak. An electrocardiogram might be called an ECG, or EKG, so it is acceptable to abbreviate it as ECG (after it is spelled out on first use). However, spell out words if there is any possible ambiguity. This will help clarify the manuscript on *morphine sulfate* kinetics in *multiple sclerosis* patients with severe *mitral stenosis* undergoing *maxillary sinus* surgery and analyzed with *Microsoft* Excel.

Consult the following sources for abbreviations:

 Scientific Style and Format: The CSE manual for Authors, Editors, and Publishers.

7th ed.[8]

http://www.resourcenter.net/Scripts/4Disapi07.dll/4DCGI/store/item.html?Action= StoreItem&Item=13693&LoginPref=1

 American Medical Association. Manual of Style. 10th ed.[9]

Updated October 2015

31

SUBMITTING YOUR MANUSCRIPT

1. Go to Editorial Manager at http://aa.edmgr.com, or access the same site from either www.iars.org where the link can be found under "Journal Submit an Article" or www.anesthesia-analgesia.org where the link can be found under "For Authors."

2. If you have not previously submitted a manuscript to *Anesthesia & Analgesia* or reviewed for the Journal, then you must click "Register" to create a username and password and create a new account. We recommend that your username be your e- mail address, but this is not required.

What Happens After Submission?

Manuscripts are reviewed by the Editorial Office to make certain that the submission contains all required elements and is properly formatted. The Editorial Office will not forward manuscripts to the Editor-in-Chief if the manuscript is not complete. An e-mail will be sent to the author describing any changes necessary to conform to our submission guidelines.

Manuscripts are then forwarded to the Editor-in-Chief, who makes an initial assessment of the manuscript. This assessment includes screening for plagiarism, verifying compliance with the guidelines for ethical conduct of research described on page 5, and assessing scientific merit. If the manuscript does not appear meritorious or is not appropriate for *Anesthesia & Analgesia* the manuscript will be rejected with an explanation that it has not been forwarded for external peer review.

If the manuscript appears meritorious and appropriate for the Journal, the Editor-in-Chief assigns the manuscript to the appropriate Section Editor or serves as the handling editor if the manuscript falls within the "General" section of the Journal. Authors are encouraged to suggest the section of the Journal they believe is best suited for their manuscript. The Editor-in-Chief considers authors'

suggestions when assigning a manuscript to a section within *Anesthesia & Analgesia*.

Upon receiving the manuscript from the Editor-in-Chief, the Section Editor makes an initial assessment of the manuscript. The Section Editor determines whether the manuscript is meritorious and verifies that the assignment of the manuscript to his or her section is appropriate. If the manuscript meets these criteria it is sent for peer review.

Authors are encouraged to recommend specific reviewers with the necessary expertise to assess their paper. These recommendations are helpful to handling editors. Authors may also request that their work not be assessed by specific reviewers. Author recommendations regarding specific reviewers are always considered when assigning reviewers, but the handling editor may choose to not follow these suggestions.

Acceptance of manuscripts is based on importance, originality, scientific rigor, and clinical relevance. Reviewers submit their critiques of the manuscript to the Section Editor using Editorial Manager. The Section Editor drafts an initial decision letter weighing the assessments of the reviewers and his or her own evaluation of the manuscript. This decision letter is forwarded to the Editor-in-Chief, who reviews and may modify the decision. The decision letter is then forwarded by the Editor-in-Chief to the Editorial Office, where it undergoes final editing. The Editorial Office sends the final decision letter to the author by e-mail.

Anesthesia & Analgesia currently publishes less than one-quarter of the manuscripts submitted, making it among the most selective journals in the specialty. If a manuscript is rejected and the author believes that the reviewers' critiques can be addressed, the author may appeal the rejection by sending a letter to the Editor-in-Chief at editor@anesthesia- analgesia.org. Appeals are generally granted, provided the author makes a convincing argument that the issues can be addressed in the revision, and the dialog is respectful. Rejected manuscripts resubmitted without permission from the Editor-in-Chief will be rejected without further review.

Sometimes we recommend that a rejected manuscript be resubmitted to *Anesthesia & Analgesia* as a Letter to the Editor. This occurs when a rejected manuscript contains an interesting observation that our readers would value. If the manuscript is rejected with a recommendation to resubmit as a Letter to the Editor, the manuscript must be revised to meet the guidelines for Letters to the Editor described on page 14. The letter will be handled by the Correspondence Editor, and evaluated on its own merits. The Correspondence Editor is under no obligation to accept a Letter to the Editor submitted at the suggestion of a Section Editor.

Authors can expect an initial decision on submitted manuscripts or letters within 6 weeks. Nearly all accepted manuscripts undergo several rounds of revision and copyediting to produce the best possible published paper.

Once the Section Editor decides that a manuscript is ready for publication, a provisional acceptance letter is forwarded to the Editor-in-Chief. If the Editor-in-Chief accepts the recommendation, the manuscript is accepted. The corresponding author is notified by e- mail. Following acceptance the manuscript is reviewed by the Editorial Office for scientific English, clear writing, and conformance with Journal style. The Editorial Office may return the manuscript to the Section Editor or Editor-in-Chief if portions are incomprehensible. The

Editorial office frequently contacts authors for clarifications about specific text or references. Once the Editorial Office has completed its copyediting the manuscript is forwarded to the publisher.
The publisher further edits the manuscript and prepares a "galley proof" of the typeset manuscript. The author will receive galleys from the publisher via an e-mail link. It is essential that authors carefully review the galley proof. Manuscripts are in the publication queue when the galley proof is created, so any delay in reviewing the galley proof may delay publication of the manuscript. Authors are strongly encouraged to return the corrected galley proof within two working days to ensure that any corrections are detected before the Journal is printed. Errors in printed manuscripts are almost always present in the galley proof and would have been detected before publication had the author carefully reviewed the galley proof. For example, authors occasionally notify the Journal that an author's name has been misspelled. This is *always* a result of an author failing to carefully read the names of the authors in the galley proof.
The galley proof will include "author queries" which must be answered. These appear in the margin of the proof, and are summarized at the end of the galley proof.
Galley proofs are only for vetting the text, layout, and typesetting of the manuscript prior to publication. They should not be posted in a public forum, and distribution should be limited to coauthors.
The average time from acceptance to printed publication is 4–6 months, although this can be as short as 3 months for very brief communications to as long as 1 year for manuscripts included in a collection of related papers. Most research reports appear online approximately 12 weeks after acceptance.
The article is considered published when it appears online.
Authors are encouraged to contact the Editorial Office at editor@anesthesia-analgesia.org with any questions or concerns about the status of their manuscript throughout the submission, review, editing, and publication process. All communications must be civil, respectful, and collaborative. The Journal holds itself to this same standard in its dialog with authors.

OPEN ACCESS
LWW's hybrid open access option is offered to authors whose articles have been accepted for publication. With this choice, articles are made freely available online immediately upon publication. Authors may take advantage of the open access option at the point of acceptance to ensure that this choice has no influence on the peer review and acceptance process. These articles are subject to the journal's standard peer-review process and will be accepted or rejected based on their own merit.
Authors of accepted peer-reviewed articles have the choice to pay a fee to allow perpetual unrestricted online access to their published article to readers globally, immediately upon publication. The article processing charge for Anesthesia & Analgesia is $3,000 A&A Case Reports is $500. The article processing charge for authors funded by the Research Councils UK (RCUK) is $3,800. The publication fee is charged on acceptance of the article and should be paid within 30 days by credit card by the author, funding agency or institution. Payment must be received in full for the article to be published open access.

Authors retain copyright
Authors retain their copyright for all articles they opt to publish open access. Authors grant LWW a license to publish the article and identify itself as the original publisher.

Creative Commons license
Articles opting for open access will be freely available to read, download and share from the time of publication. Articles are published under the terms of the Creative Commons License Attribution-NonCommerical No Derivative 3.0 which allows readers to disseminate and reuse the article, as well as share and reuse of the scientific material. It does not permit commercial exploitation or the creation of derivative works without specific permission. To view a copy of this license visit: http://creativecommons.org/licenses/by-nc-nd/3.0.

Compliance with NIH, RCUK and other research funding agency accessibility requirements
A number of research funding agencies now require or request authors to submit the post- print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The revised Copyright Transfer Agreement provides the mechanism. LWW ensures that authors can fully comply with the public access requirements of major funding bodies worldwide. Additionally, all authors who choose the open access option will have their final published article deposited into PubMed Central.
RCUK funded authors can choose to publish their paper as open access with the payment of an article process charge, or opt for their accepted manuscript to be deposited (green route) into PMC with an embargo.
With both the gold and green open access options, the author will continue to sign the Copyright Transfer Agreement (CTA) as it provides the mechanism for LWW to ensure that the author is fully compliant with the requirements. After signature of the CTA, the author will then sign a License to Publish where they will then own the copyright.
It is the responsibility of the author to inform the Editorial Office and/or LWW that they have RCUK funding. LWW will not be held responsible for retroactive deposits to PMC if the author has not completed the proper forms.

FAQ for open access
http://links.lww.com/LWW-ES/A48

COPYRIGHT AND RETAINED RIGHTS

Copyright Assignment Agreement
Upon submission for all new submissions, we require each author to complete and sign a digital copyright assignment agreement which is then uploaded into Editorial Manager (under "Attach Files") by the corresponding author. Please note that we no longer accept forms by fax or email. For more information visit: http://edmgr.ovid.com/aa/accounts/ifauth.htm.
The copyright assignment agreement covers all submitted written material and supplementary digital content and assigns the copyright to the International

Anesthesia Research Society, owner of *Anesthesia & Analgesia*. If excerpts from copyrighted works are included in the submitted material, authors must obtain a written release before submission and provide credit to the original publication.
In the case of material written as part of the duties of an employee, an authorized representative of the employer must also sign. If the submitted material or a portion of it has been created in the course of any author's employment by the United States Government, it is called a "work of the U.S. Government" and is not subject to copyright.

Preprints

Upon acceptance of the article for publication, each author must remove any prior versions of this work (normally a preprint) that may have been posted to an electronic server.

Retained Rights, Institutional Postings

Except for copyright, other proprietary rights related to the submitted material (such as patent or other rights to any process or procedure, or reuse of the material for the personal noncommercial benefit of the author) are retained by the authors. *Anesthesia & Analgesia* will permit the author to deposit for display a "post-print" (the final manuscript after peer- review and acceptance for publication but before the publisher's copyediting, design, formatting, and other services) 12 months after publication of the final article on his/her personal website, university's institutional repository, or employer's intranet.
Compliance with NIH and Other Research Funding Agency Accessibility Requirements: A number of research funding agencies now require or request authors to submit the post- print to a repository that is accessible online by all without charge. As a service to our authors, based on your indication of funding on the copyright assignment agreement, the Journal will identify articles that require deposit and transmit the post-print of the articles to NIH Manuscript Submission System (NIHMS). Upon NIHMS request to the author, it remains the legal responsibility of the author(s) to validate the submission with the repository.

Fair Use

Authors can republish portions of their accepted manuscript, for personal noncommercial purposes, at their discretion. When this occurs, we ask that the article be attributed as published in the Journal. If an author wishes to reproduce an article in its entirety, exactly as published in the Journal, permission should be obtained through the "Request Permissions" link to the article on the journal's online website.

EXPECTATIONS OF AUTHORS

The Journal has an overriding interest in research integrity. To fulfill this obligation, all authors must fulfill the following expectations:
1. All authors must attest to having reviewed and approved the final manuscript.
2. For research reports, brief reports, and technical communications a single author
must be designated as the archival author. The archival author is responsible for maintaining the study records. The archival author will be contacted should questions about the data arise following publication.
3. For research reports, brief reports, and technical communications with more than one author, at least two authors must attest to:

a. Having seen the original study data.
b. Having reviewed the data analysis.
4. Authors are expected to participate in any external review assessing the integrity of
their research. Failure to fully cooperate with any inquiry into the integrity of their research may result in retraction of papers related to the research by *Anesthesia & Analgesia*.
5. Authors should be prepared to make the research protocol, original research records, informed consents, IRB approvals, spreadsheets, and analyses available for review by the Journal should questions arise during or after the peer review process about the integrity of the data or the ethical conduct of the research. Authors should redact protected healthcare information and proprietary business information from research records and protocols to protect patient and organizational confidentiality prior to making the records available.
6. *Anesthesia & Analgesia* recognizes that authors may have legitimate reasons for not providing raw data to the Journal. If such data are not provided, the Journal may elect not to consider the manuscript. Following publication, the Journal encourages authors to make data freely available to other investigators. The Journal acknowledges that the decision to share data rests with the authors and that there are legitimate reasons for authors declining such requests.
7. Senior authors must accept responsibility for misconduct by junior authors under their mentorship.
8. Authors understand that the Journal may make available to an author's institution any communications between the author and the Journal if requested to do so by a review panel investigating possible academic misconduct under the auspices of the institution.
9. Authors understand that journal editors may share information about academic misconduct with the editors of other journals, as misconduct frequently involves more than a single journal.
10. Academic misconduct discovered during peer review may be publicly disclosed if disclosure is required to insure the integrity of the scientific record.

RED FLAGS

Red flags are issues identified during peer review that raise suspicion of improper conduct. Most **red flags** are the result of simple misunderstandings. However, **red flags** typically require that the author explain an issue uncovered during peer review to the editor. **Red flags** delay manuscript review, and place authors in the uncomfortable position of defending the integrity of their submission.

Red flags are similar to conflict of interest concerns:
1. They arise because of something discovered during peer review,
2. Most are completely innocent, and
3. Can be prevented by careful attention to full disclosure at the time of submission.

This section reviews several common **red flags** to help authors anticipate concerns that might arise during peer review. The intent is to alert authors to potential issues so that they can provide clear explanations in their manuscript and cover letter, and thus avoid raising **red flags**.

Multiple Publications Derived from a Single Study

In the interest of minimizing risk to human and animal subjects, as well as promoting efficient use of scarce research funds, investigators may pose several questions and make multiple measurements in a single study with the intent of publishing multiple manuscripts. Large longitudinal multicenter outcome trials often generate dozens of high quality manuscripts.

The screening that manuscripts undergo to detect plagiarism is exquisitely sensitive to multiple submissions from a single study. Identification of undisclosed previous papers from a single study is a **red flag** for inappropriate data slicing into "minimum publishable units," or attempting to publish the same research multiple times. The lack of disclosure suggests an intent to conceal the previous publications.

To prevent this **red flag** from arising during peer review, the Journal has adopted the following three requirements when multiple papers arise from a single research study:

1. The cover letter for every paper derived from the study should explain the need for dividing the study into multiple manuscripts. This requirement applies even if only one of the submissions is to *Anesthesia & Analgesia*. The Journal will consider the appropriateness of the division as part of the review process.
2. In all manuscripts after the first published manuscript the investigator must disclose in the Methods section any data previously reported with appropriate citations to the earlier manuscripts. This practice is essential for scientific continuity. This disclosure requirement does not apply to previously published abstracts.
3. Measurements must not interfere with each other. Such interference may happen in ways not evident at the time of the study. For example, measurements of pain thresholds may make it impossible to measure sedative effects. The potential for interfering measurements may not be evident if the pain thresholds and sedation effects are reported in separate manuscripts that are not appropriately cross- referenced. If these requirements are met, then the submission is forwarded to peer review. However, if these requirements are not met, then authors are asked to explain the relationship of the new submission to their previous work prior to peer review. If the explanation is not satisfactory, then the matter may be referred to the author's institution for further review.

Multiple Publications Derived from a Single Database

Many important outcomes are identified by querying large databases, such as those used for billing purposes, derived from medical records, or registries of patients and outcomes. These databases are often used by multiple investigators at multiple institutions. There may be no way for investigators to know what queries are being analyzed by other investigators.

Investigators may pose a query to a database that is nearly identical to one previously posed to the same database. This raises a **red flag**, because of the very real possibility of duplicate publication. If an investigator is aware that a database has been used for similar queries, then the cover letter and manuscript should describe the similar queries made from the database and list the resulting manuscripts, regardless of whether they are published or merely under review.

Extending a Study

Occasionally authors will extend a previously published study by adding

additional subjects, groups, or years of follow-up assessment. This is typically entirely appropriate, provided it is fully explained in the study methodology. It is a **red flag** if it is discovered during peer review that the data in the manuscript represent new data added to previously published data.

Failure to Self-Reference Recent Publications

Authors typically reference their previous work when discussing new findings in an area of research. It is a **red flag** when authors fail to reference their own previous work, particularly if it is similar to the submitted manuscript. Failure to reference a recent paper suggests that the authors are attempting to hide it from peer reviewers.

Failure to Advise the Editor and Reviewers of Concurrent Publications

If the authors have submitted a similar manuscript to another journal for consideration, they should include it in the references as "submitted for publication." If the manuscript has extensive overlap, then the manuscript itself should be included with the submission to permit the reviewers to assess overlap. Failure to report concurrent submission of a similar publication is a **red flag**, because it prevents the reviewers from assessing the novelty of the submission to *Anesthesia & Analgesia*.

Changes in Research Methodology Identified During Peer Review

In many areas of research only a handful of experts regularly review manuscripts. If a paper has been rejected by one journal, and submitted to another journal, there is a high probability that the same reviewer will assess both submissions. It is a **red flag** when reviewers identify inexplicable changes in the paper. Reviewers have identified the introduction of new groups into a "prospective randomized trial," changes of inhaled anesthetics or intravenous drugs, changes in drug dose, and different outcomes for study groups in papers that they have previously reviewed for other journals.

Authors submitting a previously rejected manuscript should anticipate that the same reviewers will see the submission. Any significant change in the methodology or results should be explained in the cover letter, so that a **red flag** is not triggered when the reviewer spots the difference.

Request for Withdrawal

It is unusual for authors to withdraw their manuscript during the peer review process. This is a **red flag**. If an author wishes to withdraw a manuscript while it is undergoing peer review, the author must submit the request in writing to the Editor-in-Chief at editor@anesthesia-analgesia.org. The letter must explain the request for withdrawal. Until the withdrawal is granted authors are expected to fully cooperate with the Journal in the peer review process.

Misrepresentation

Any misrepresentation in the peer review process raises a **red flag**, even if not directly related to the manuscript content. For example, misrepresentation of an author's academic credentials, sources of funding, institutional affiliation, or registration of a clinical trial is not acceptable.

Most misrepresentations are simple mistakes and readily corrected. However, to

avoid raising **red flags**, authors should advise the journal as soon as possible of any errors they have discovered in their representations. This will preclude discovery of the error during peer review, raising the specter of intentional deceit. Errors discovered after publication may result in publication of an Erratum for a simple oversight, or a Statement of Concern if the Editorial Board is concerned about intentional misrepresentation, or retraction.

All communication between authors and the Journal must be honest. Occasionally the Journal discovers misrepresentations in authors' responses to the questions posed during peer review, or in correspondence with the Editorial Board or the Editorial Office. This raises a **red flag**. Authors must vet the integrity of every statement to the Journal during the peer review process.

Failure to Disclose Authors Affiliated with Industry

As discussed on page 4, authors sometimes fail to list as authors individuals associated with industry who meet the stated requirements for authorship. Ghostwriting is an example of this, where the contribution of the author of the text is not acknowledged, sometimes in an effort to hide the contribution of the study sponsor. This is a **red flag**, because it denies reviewers, and readers, access to disclosure of conflicts of interest that may have biased the manuscript. Additionally, it denies scientists from industry recognition of their work. All individuals meeting the requirements of authorship must be listed as coauthors, or an explanation provided for why these individuals are not authors.

Academic Misconduct

Anesthesia & Analgesia is a member of the Committee on Publications Ethics (COPE) Code of Conduct for Editors of Biomedical Journals, and adheres to COPE's Good Publication Practice (see http://publicationethics.org).

The US Public Health Service's Office of Research Integrity has devoted a considerable amount of effort to help institutions and authors understand responsible conduct of research. We strongly recommend that authors utilize this excellent resource, available at http://ori.dhhs.gov.

Plagiarism

Plagiarism is the use of previously published material without attribution. *Anesthesia & Analgesia's* policy on plagiarism is described in a 2011 editorial.[35] Prior to peer review all manuscripts are screened for plagiarisms by the Editor-in-Chief using iThenticate. The screening process identifies passages of text that have been previously published. Text copied from previously published work is interpreted using the following taxonomy:

- **Intellectual theft** is misrepresentation by an author that words and ideas previously published by another author represent the plagiarist's own scholarship. It is the most serious form of plagiarism. Intellectual theft identified during screening results in immediate rejection of the manuscript and a request for an explanation from the author.
- **Intellectual sloth** is the use of the words of another author to avoid the effort of writing new text. It commonly occurs when descriptions of research methodology are taken from prior publications. It is less serious than intellectual theft, because the text is generic and of no particular value. Submissions containing intellectual sloth are typically returned to the authors with a request

that the copied text either correctly cite the original author or be rewritten in the authors' own words.

 Plagiarism for scientific English occurs when authors uncomfortable using scientific English compose their manuscripts as a patchwork of previously published sentences and paragraphs. Papers constructed in such a manner are rejected outright, primarily because patchwork plagiarism suggests that the authors may not understand the text they have submitted for publication.

 Technical plagiarism is the use of verbatim text not identified as verbatim, but referenced to the original source. The offense is a technical one, and authors are simply asked to correct it prior to peer review.

 Self-"plagiarism" occurs when an author uses his or her verbatim words from a previous manuscript in a new submission. Provided the authors are not engaged in duplicate publication, the Journal does not view "self-plagiarism" as misconduct. Authors are permitted to reuse their own words, and are encouraged to do so when describing identical research methods in multiple papers.

Duplicate Publication

Duplicate publication is prior publication of a manuscript with considerable content overlap, particularly in the research results, by the same author or co-authors. Prior
publication may be in the same language or it may be a translation (usually from the author's native language to English). If a manuscript has been published previously, the submission to *Anesthesia & Analgesia* will be rejected unless it has already been published in which case it will be retracted.

We request that authors inform the Journal when results of a submitted manuscript have been previously published in *any* venue. Several websites aggregate posters from society meetings. If the online poster discloses all of the results in the submission, then the poster may be considered prior to publication.

The following forms of prior publication of research results are *not* considered prior publication of a submission:

1. Prior publication of an abstract at a scientific meeting.
2. Prior publication of study results in product labeling (e.g., the FDA Package Insert).
3. Prior publication of study results in a patent application.

There is sometimes value in publishing in English an important manuscript previously published in another language. *Anesthesia & Analgesia* will consider such submissions, however, they must be accompanied by a letter from the copyright holder of the original publication granting *Anesthesia & Analgesia* permission to publish the work.

There is sometimes value in publishing Editorials, Guidelines, or other articles in more than one journal. This is always planned in advance by the involved journals. One journal is designated the primary publication. In all other journals the paper is only published after receiving permission from the copyright holder, and the primary publication is explicitly acknowledged as the original publication.

Duplicate submission is concurrent submission of a nearly identical manuscript to two journals. Duplicate submissions identified during peer review will be

immediately rejected. Duplicate submissions that are discovered after publication will be retracted.

Data Falsification

Data falsification is any manipulation of data that is not disclosed in the publication. This can include editing data (removing outliers, altering values), fabricating data, taking data from a previous publication, or misrepresenting the data analysis. Data falsification is fraud.

Anesthesia & Analgesia has a zero tolerance policy on fraud.[36,37,38] If fraud is discovered during peer review the manuscript will be rejected. If fraud is discovered after publication the manuscript will be retracted.

Journal Policy on Misconduct

Anesthesia & Analgesia reviews all allegations of academic misconduct. The Journal follows the protocol recommended by the Committee on Publication Ethics.[d] When credible evidence of misconduct is brought to the Journal's attention, the Journal will bring the concerns to the author. If the author fails to respond, or responds but does not adequately address the concerns, the Journal will take the concerns to the institution. If the institution is unwilling to investigate the concerns, then the Journal will take the concerns to the appropriate government agencies.[38,39,40]

Anesthesia & Analgesia has a policy of full cooperation with any institutional inquiry into allegations of academic misconduct. The Journal will provide the institution with copies of all submissions and correspondence. In general *Anesthesia & Analgesia* will follow the recommendations of an institutional inquiry. However, the Journal is not bound by the finding of the inquiry, and may elect a different course of action if the objectivity of the inquiry is questioned.[41]

Although peer review is considered confidential, *Anesthesia & Analgesia* recognizes a responsibility to notify research institutions, other journals, and occasionally our readership when significant misconduct is discovered during peer review.[38]

When academic misconduct is identified the Journal may institute sanctions against an author, ranging from requesting a Letter to the Editor acknowledging the error and voluntarily retracting a manuscript, to a lifetime ban on publication in *Anesthesia & Analgesia*.

Updated October 2015

[d] http://publicationethics.org/resources/flowcharts. Last accessed May 28, 2012

45

CONCLUSION

Anesthesia & Analgesia exists for the benefit of current and future patients under the care of health care professionals engaged in the disciplines broadly related to anesthesiology: perioperative medicine, critical care, and pain management. The Journal furthers the care of these patients by reporting the fundamental advances in the sciences of these clinical disciplines, and by documenting the clinical, basic science, administrative, and educational advances that guide therapy. The Journal seeks a balance between outstanding basic scientific reports and definitive clinical and management investigations. The Journal welcomes original manuscripts reflecting rigorous analysis, even if unusual in style and focus.

Anesthesia & Analgesia accepts a limited number of the manuscripts submitted for publication. However, the Journal is genuinely honored by every submission. In exchange for authors following this Guide for Authors, the Journal promises to consider every manuscript thoughtfully. In addition, the Journal promises to treat all authors with the respect and dignity they have so thoroughly earned by their dedication to improving the health and well-being of patients.

ADDENDUM

Many members of the Editorial Board of *Anesthesia & Analgesia* serve on the editorial boards of other journals. *Anesthesia & Analgesia* acknowledges the contribution of these editorial boards to these guidelines through our overlapping editors. Neither *Anesthesia & Analgesia* nor the International Anesthesia Research Society (IARS) wishes to claim ownership of the principles or text in these guidelines. The IARS hereby grants societies, journals, and individuals the right to paraphrase or quote verbatim sections of any length from these guidelines without attribution.

REFERENCES

1. Shafer SL. Anesthesia & Analgesia Policy on Institutional Review Board Approval and Informed Consent for Research. Anesth Analg 2011;112:494-5
2. Tobin JR, Shafer SL, Davis PJ. Pediatric research and scholarship: another Gordian knot? Anesth Analg 2006;103:43–8
3. Schultheis LW, Mathis LL, Roca RA, Simone AF, Hertz SH, Rappaport BA. Pediatric drug development in anesthesiology: an FDA perspective. Anesth Analg 2006;103:49–51
4. Kahn R, Gale EAM. Gridlocked guidelines for diabetes. The Lancet 2010; 375:2203-4
5. Shafer SL. Changes for 2009. Anesth Analg 2009;108:1–2
6. Saidman LJ. Let us hear from you. Anesth Analg 2006; 103:1347– 8
7. Strunk W Jr, White EB. The Elements of Style. 4th ed. New York: Allyn & Bacon, 2000
8. Council of Science Editors, Style Manual Committee. Scientific Style and Format: the CSE manual for authors, editors, and publishers. 7th ed. Reston (VA): The council; 2006
9. JAMA and Archives Journals, Annette Flanagin (Editor), Stacy Christiansen (Editor) American Medical Association manual of style: a guide for authors and

editors. 10th ed. Oxford University Press USA, 2007
10. Zigmond MJ, Fischer BA. Beyond fabrication and plagiarism: the little murders of everyday science. Science and Engineer Sci Eng Ethics 2002;8:229-34

11. de Oliveira Filho GR, Helayel PE, da Conceição DB, Garzel IS, Pavei P, Ceccon MS. Learning curves and mathematical models for interventional ultrasound basic skills. Anesth Analg 2008;106:568-73
12. Dexter F. Checklist for Statistical Topics in Anesthesia & Analgesia Reviews. Anesth Analg 2011;113:216-219
13. Glaser D, Hastings RH. An introduction to multilevel modeling for anesthesiologists. Anesth Analg 2011;113:877-87
14. Ledolter J, Dexter F, Epstein RH. Analysis of variance of communication latencies in anesthesia: comparing means of multiple log-normal distributions. Anesth Analg 2011;113:888-96
15. Ledolter J, Dexter F. Analysis of interventions influencing or reducing patient waiting while stratifying by surgical procedure. Anesth Analg 2011;112:950-7
16. Story DA, Gin V, na Ranong V, Poustie S, Jones D; ANZCA Trials Group. Inconsistent survey reporting in anesthesia journals. Anesth Analg 2011;113:591-5
17. Mascha EJ, Sessler DI. Equivalence and noninferiority testing in regression models and repeated-measures designs. Anesth Analg 2011;112:678-87
18. Reeves M. The influence of age on sample size calculation in acute pain trials using morphine consumption as an end point. Anesth Analg 2010;110:1186-90
19. Shafer SL, Struys MM. Mixed effect modeling in analgesia trials. Anesth Analg 2008;107:9-10
20. Mascha EJ, Turan A. Statistical grand round: joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesth Analg 2012;114:1304-17

21. Gibbs NM, Weightman WM. Beyond effect size: consideration of the minimum effect size of interest in anesthesia trials. Anesth Analg 2012;114:471-5
22. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg 2010;111:1180- 9
23. Mascha EJ, Sessler DI. Statistical grand rounds: design and analysis of studies with binary- event composite endpoints: guidelines for anesthesia research. Anesth Analg. 2011;112:1461-71
24. Shafer SL, Dexter F. Publication bias, retrospective bias, and reproducibility of significant results in observational studies. Anesth Analg. 2012;114:931-2
25. Dexter F, Marcon E, Epstein RH, Ledolter J. Validation of statistical methods to compare cancellation rates on the day of surgery. Anesth Analg. 2005;101:465-73
26. Dexter F, Shafer SL. Validation of Statistical Methods to Compare Cancellation Rates on the Day of Surgery: Erratum Anesth Analg 2012;114:693
27. Dexter F, Marcon E, Aker J, Epstein RH. Numbers of simultaneous turnovers calculated from anesthesia or operating room information management system data. Anesth Analg 2009;109:900-5

28. Jordan D, Steiner M, Kochs EF, Schneider G. A program for computing the prediction probability and the related receiver operating characteristic graph. Anesth Analg 2010;111:1416-21
29. Morey TE, Gravenstein N, Rice MJ. Let's think clinically instead of mathematically about device accuracy. Anesth Analg 2011;113:89-91

30. Dexter F, Dexter EU, Ledolter J. Statistical grand rounds: Importance of appropriately modeling procedure and duration in logistic regression studies of perioperative morbidity and mortality. Anesth Analg 2011;113:1197-201
31. Gonon F, Bezard E, Boraud T. Misrepresentation of neuroscience data might give rise to misleading conclusions in the media: the case of attention deficit hyperactivity disorder. PLoS One 2011 Jan 31;6(1):e14618
32. Tufte ER. The Visual Display of Quantitative Information. 2nd ed. Cheshire: Graphics Press, 2001
33. Rokey R, Vick GW 3rd. Masking personal health information on real-time echocardiographic images. J Am Soc Echocardiogr 2005;18:970–8
34. Manual of Style, A Guide for Authors and Editors. 9th ed. Baltimore: Lippincott Williams & Wilkins, 1998
35. Shafer SL. You will be caught. Anesth Analg 2011;112:491-3
36. Shafer SL. Tattered threads. Anesth Analg 2009;108:1361-3
37. Shafer SL. Shadow of doubt. Anesth Analg 2011;112:498-500
38. Eldawlatly A, Shafer SL. Caveat Lector Anesth Analg 2012;114:1170-2
39. Hoffart J, Teichmann A, Wessler I. Biomedical research in Germany: the role of ethics committee and state medical association. Anesth Analg 2011;112:501-3
40. Förstermann U. Research Oversight in Germany: Safeguards and Shortcomings. Anesth Analg 2011;112:504-506
41. Bogod DG. The editor as umpire: clinical trial registration and dispute resolution. Anaesthesia 2006;61:1133-5