ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

A Randomised Clinical Trial to Compare Prophylactic Phenylephrine Infusion with Ephedrine for the Prevention of Hypotension in Hysterectomies under Spinal Anaesthesia

Dr. Aratiprava Sahu[1], Dr Shyam Surat Sahoo[2], Dr Manoranjan Mahapatra[3], Dr Kalikinkar Senapati[4*]

[1]Assistant Professor, Department of Anaesthesiology, Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack, Odisha
[2]Assistant Professor, Department of Anaesthesiology, Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack, Odisha
[3]Associate Professor, Department of Oncogynaecology,Acharya Harihar Post Graduate Institute of Cancer (AHPGIC), Cuttack, Odisha
[4*]Consultant, Department Of Anaesthesiology,Kalinga Institute Of Medical Science (KIIMS) Pradyumna Bal Memorial Hospital, Bhubaneswar.Mail- drkalikinkars@gmail.com

4th Author and Corresponding Author
Dr Kalikinkar Senapati, Consultant, Department Of Anaesthesiology, Kalinga Institute Of Medical Science (KIIMS) Pradyumna Bal Memorial Hospital, Bhubaneswar.
Mail- drkalikinkars@gmail.com

Receiving date - 01/07/2023 Acceptance date - 05/07/2023 Publication date - 20/08/2023

Abstract
Aim: In order to maintain arterial pressure during hysterectomies under sub-arachnoid block, we aimed to evaluate and compare the efficacy of prophylactic infusions of ephedrine and phenylephrine.
Methods: The current study involved 80 patients who were having spinal anaesthesia for elective hysterectomies and who had physical statuses of Grade I and Grade II according to the American Society of Anaesthesiologists. Phenylephrine 15 micrograms/min, Group P. Group E: 1.5 mg/min of ephedrine. Blood pressure measurements were taken in both groups, and the results are shown as mean standard deviation.
Results: Phenylephrine and ephedrine prophylactic infusions were successful in keeping arterial pressure within 20% of the baseline. Ephedrine group required a larger additional bolus dosage than phenylephrine group. Phenylephrine caused a decrease in heart rate, whereas ephedrine caused an increase.
Conclusion: Although both medications were successful in keeping arterial blood pressure within a normal range, phenylephrine is more effective than ephedrine and requires less of an extra bolus dosage.
Keyword: spinal anaesthesia, ephedrine, hysterectomies, and phenylephrine.

INTRODUCTION

The most significant issue that might arise after spinal anaesthesia is hypotension. It is believed that prompt, effective therapy is crucial.1Spinal-induced hypotension is treated using a variety of strategies. Preloading the patient with crystalloids or colloids is one of these, as is the use of vasopressors2.Ephedrine has often been suggested as a vasopressor3. Due to the risks of consequences such foetal acidosis, tachyphylaxis, and supraventricular tachycardia, its status has been contested4.Due to the fact that it acts indirectly, it is challenging to titrate and can potentially cause tachyphylaxis.[5] Consequently, a medicine that treats hypotension but doesn't have the aforementioned negative effects is needed. The use of phenylephrine to alleviate hypotension after hysterectomies under spinal anaesthesia has recently attracted fresh attention6. A directly acting sympathomimetic drug with specific alpha 1 adrenergic action is phenylephrine. It is simple to titrate and keeps maternal blood pressure stable without excessively causing tachycardia.A improved foetal acid-base state has been linked to -agonists such phenylephrine, according to comparative studies7. When compared to ephedrine, phenylephrine has a faster peak effect and lowers heart rate. In order to compare the effects of preventive phenylephrine and ephedrine infusions as a vasopressor treatment in patients receiving spinal anaesthesia.

METHODS

A total sample size of 80 cases were included,40 cases in each group. The sample size was calculated by assuming the power of the study to be 80 percent, Alpha value of 0.05 and difference of mean of 9.
Sample size calculation was based on parent studyN $=[(Z\alpha + Z(1-\square)]^2 \times \sigma^2 \times 2]$
d^2
$Z\alpha = 1.96$ $Z\square=0.84$
σ = pooled variance
d = difference in mean

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

Inclusion Criteria

1. Age: 350-70yrs, Height: 140-170cms.
2. ASA Grade I and II.

Exclusion Criteria

1. Patient refusal for the procedure.
2. Diabetes mellitus.
3. Patients with history of significant systemic disorders (cardiovascular, cerebrovascular, respiratory, renal, metabolic or psychiatric disorder).
4. Patients with significant coagulopathies and other contra-indications for spinalAnaesthesia.

According to IEC/IRB No. 513, approval from the institutional ethics committee was obtained. All patients received a thorough explanation of the procedure in their native language, and their signed informed permission to participate in the trial was acquired. The study involved 80 singleton full-term pregnant patients having hysterectomies under subarachnoid block (SAB). Using a computer-generated randomization table, they were randomly split into two groups of 40 each: Group P (Phenylephrine group) and Group E (Ephedrine group). Infusion pumps were used to prepare and administer study medicines, as well as 5ml syringes for bolus doses, According to a non-study anaesthesiologist, the medication is referred to as "Study Vasopressor."The preparation of phenylephrine involved adding 750 mcg (15 mcg/ml) to 50 ml of NS. Ephedrine was made by mixing 75 mg in 50 ml of NS, or 1.5 milligrammes per ml. Bolus dosage included 5mg/ml of ephedrine and 50mcg/ml of phenylephrine. All patients underwent thorough preoperative evaluations that included full history, physical examinations that included height, weight, any signs of spinal deformity, and the patient's mental state. For 6 to 8 hours, all of the patients were kept on an oral diet. The position of the patients during transportation to the surgical room was left lateral. Two 18 G IV cannulas were used in the operating room to get access to the intravenous line. The patient was fitted with a non-invasive blood pressure monitor, ECG, and pulse oximeter. Three baseline blood pressure readings were collected to determine the baseline heart rate, systolic, diastolic, and mean blood pressures. Ringer lactate solution, 10ml/kg, was administered intravenously over the course of 30 minutes. Patients were placed in the lateral position while spinal anaesthesia was produced under stringent aseptic guidelines. Using a 25-gauge Quincke needle, 0.5% hyperbaric bupivacaine was administered intrathecally at the L3–4 vertebral interspace following lidocaine skin infiltration. The patients were then immediately made supine while receiving 4 litres of oxygen per minute using a face mask. Five minutes after SAB, the degree of sensory block was evaluated using the pinprick technique. Surgery was allowed to begin when the sensory level of block reached T6 dermatome.Infusion of study drug was started immediately after giving spinal anaesthesia. Group P received phenylephrine 1ml/min (15 microgram/min) and Group E received ephedrine 1ml/min. (1.5 mg/min)After spinal anaesthesia, systolic, diastolic and mean arterial pressures were recorded every 2 minutes for 20 minutes and thereafter every 5 minutes for 1 hour .Whenever further episodes of hypotension (fall in SBP> 20% from baseline or less than 90 mm of Hg) occurred, the study drug was given bolus iv. Group P received Phenylephrine 1ml (50 mcg) and Group E received 1ml (5 mg) Ephedrine as intravenous rescue bolus. Whenever any episodes of hypertension occurred (rise in SBP>30% from baseline), infusion of study drug was stopped until the SBP was restored to baseline. Bradycardia was defined as heart rate <60 bpm and was treated with 0.6 mg of intravenous atropine. The patients were monitored for any bradycardia, reactive hypertension, nausea, vomiting. Number of rescue boluses administered were also noted.

Statistical Analysis

Data entered in Microsoft Excel Statistical analyisis was done using SPSS Ver.17. Quantitative variables described by mean, sd, minimum and maximum. Qualitative variables described by percentage distribution. Between group comparison of quantitative variables were done by independent sample t test and that of the qualitative variables by Chi-square test. A p valueof 0.05 is taken as the level of significance

Results

The present study was conducted on 80 patients undergoing elective hysterectomies under spinal anaesthesia belonging to American society of Anaesthesiologists Grade I and Grade II physical status. Each group consisted of 40 patients and were divided as Group P (Phenylephrine group, n
= 40) and Group E (Ephedrine group, n =40) by a computer generated randomization table. Data was collected in both the groups and observations

of the analysed data are presented as mean ± standard deviation in the tabular form. The age, weight, height were comparable in both the groups.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

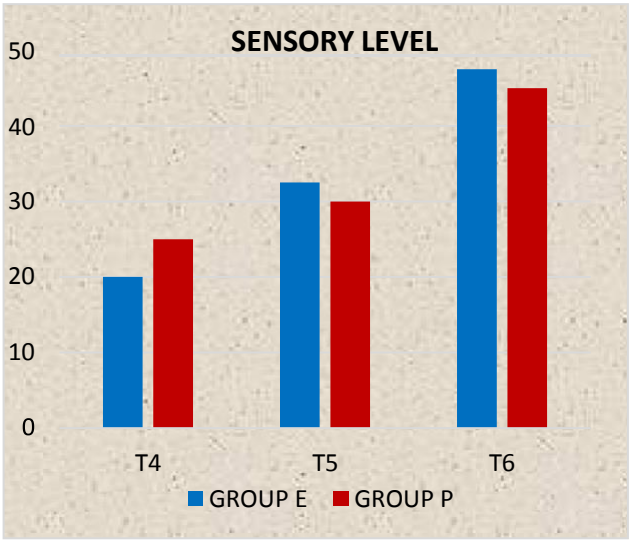

Figure 1: Comparison of sensory levels between two groups

Level of sensory blockade after 5min of SAB in both the groups were comparable. (fig-1)

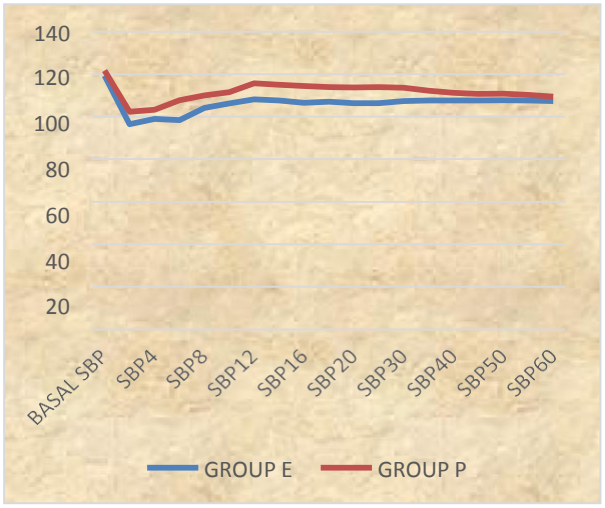

Figure 2: Changes in systolic pressures in both groups

Basal SBP in Phenylephrine group was 119.3±8.2 and that in Ephedrine group was 121.7 ± 8.8 mm of Hg. They are comparable statistically. (fig-2) But Systolic blood pressure remains high in Phenylephrine group compared to Ephedrine group throughout the observation period.

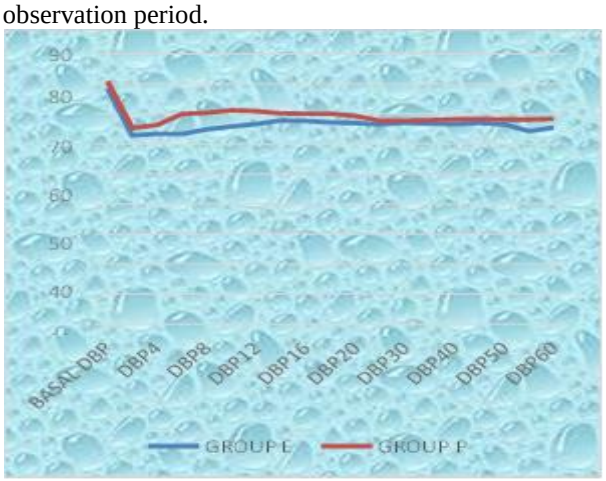

Figure 3: Intraoperative changes in diastolic blood pressure in Group P and E

Basal DBP were statistically comparable in both the groups. But diastolic blood pressure was well maintained with phenylephrine group than ephedrine group. (fig-3)

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

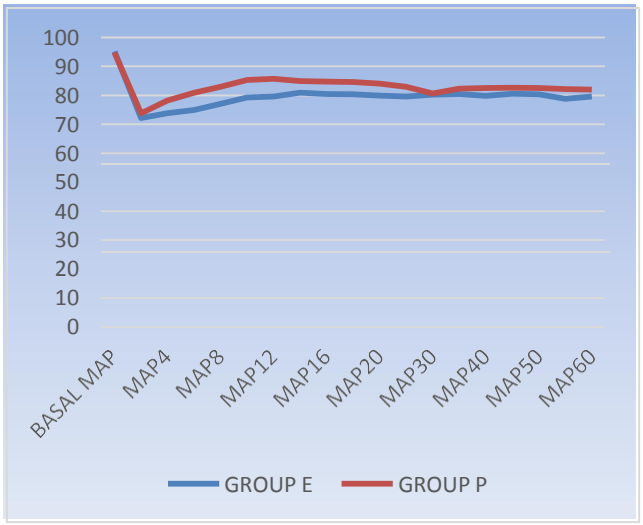

Figure 4: Intraoperative changes in Mean arterial pressure in Group P and E

Basal MAP and MAP intraoperatively were statistically comparable in both the groups. (fig-4)

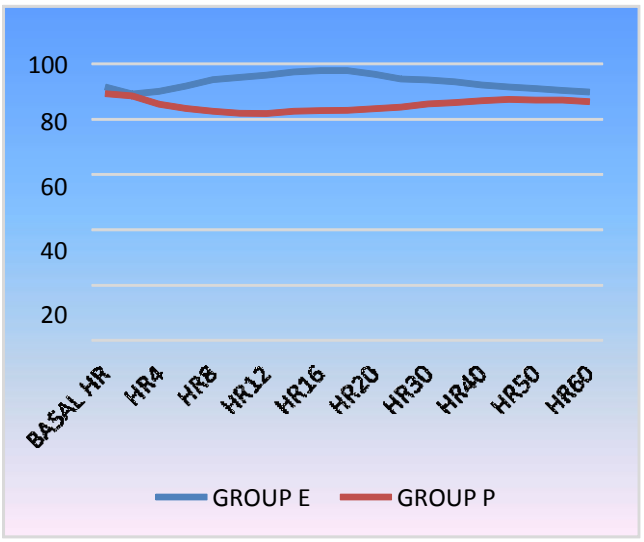

Figure 5: Changes in heart rate in both groups Phenylephrine group shows a significant fall in HR while in Ephedrine group there is a significantrise in the HR.(fig-5) 35 patients in both theroupsdeveloped hypotension and required additional vasopressor treatment. According to table 1, incidence of hypotension was more inephedrine group than phenylephrine group andadditional dose requirement (second, third andfourth) was higher in ephedrine group ($p<0.0001$). Out of 9 patients requiring 3 rescue bolus doses, 6 patients were from ephedrine group(66.6%) and 3 patients from phenylephrine group ($p <0.001$). (table 1)

Table 1: Number of additional vassopressorrequirement for treatment of hypotension

Additional vasopressor	**Total**	**Group E (N=40)**	**Group P (N=40)**	**P value**
Without additional vasopressor	35	9(25.7%)	26(74.28%)	0.0001
1 Dose	16	10(62.5%)	6(37.5%)	0.003
2 Doses	17	12(70.5%)	5(29.5%)	0.001
3 Doses	9	6(66.66%)	3(33.33%)	0.001
4 Doses	3	3(100%)	0	0.049

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

In the present study, none of the patients had nausea or vomiting in both groups.

DISCUSSION

Hypotension is the most frequent adverse outcome following spinal anesthesia7. There is still disagreement over the best management strategy for the prevention and treatment of hypotension. A common practise for preventing hypotension is fluid preloading using intravenous crystalloid or colloid solutions; however, when done alone without concurrent vasopressor medication, it has been proven to be ineffective. Finding the best treatment for hypotension has been attempted on several occasions. The use of vasopressors in concert with fluid preloading appears to be a more sensible way to restore arterial pressure as sympathetic blocking leading to vasodilatation is the major cause of the reduction in arterial pressure. In the majority of research, hypotension has been defined as a 20–30% drop from the baseline systolic arterial pressure or mean arterial pressure8. Hypotension was defined in our study as a 20% reduction in systolic arterial pressure from the initial systolic pressure. A bradycardia is a heart rate that is fewer than 60 beats per minute. Vassopressors administered intravenously have a well-established role in treating postspinal hypotension. Alpha and beta adrenergic receptors are affected by ephedrine both directly and indirectly. Because of its specific alpha adrenergic action, phenylephrine was thought to reduce uterine blood flow. But according to a study by Ngan *et al*9, phenylephrine induces less foetal acidosis than ephedrine9.Although Phenylephrine maintained a better blood pressure than Ephedrine in our investigation, both vasopressors kept arterial blood pressure within 80% of the baseline value's upper limit. These findings are consistent with a prior research by Sahu *et al*.14 Both medications kept systolic, diastolic, and mean arterial pressure stable, although the ephedrine group required more extra bolus doses than the phenylephrine group, according to our study. 0.001 (P value) These results were likely caused by tachyphylaxis brought on by repeated dosages or continuous infusion of ephedrine.In our research, The positive inotropic and negative chronotropic effects of phenylephrine may be responsible for the heart rate drop that was seen following phenylephrine infusion. This impact has also been consistent across investigations. There was a considerable bradycardia that was addressed with atropine in the trial by Moran DH *et al*. Similarly, Thomas DG *et al*11 demonstrated a 58% incidence of bradycardia (defined as a heart rate below 60 beats per minute) following the administration of a 100 mcg intravenous bolus of phenylephrine.Although there was a decrease in heart rate in our trial following phenylephrine administration, it was not sufficient to justify therapy. This is due to the medicine being supplied in a lower dosage. We discovered statistical significance in the ephedrine group's heart rate rise following the infusion compared to pre-drug administration values, and the findings was comparable with Sahu *et al*.14 The beta adrenergic action of ephedrine, which phenylephrine lacks, may be responsible for this tachycardia.

Since the 1970s, -agonist usage has been largely discouraged due to worries about their possible negative impact on uterine blood flow. However, Lee and colleagues12 found no difference in effectiveness between phenylephrine and ephedrine in a quantitative, comprehensive analysis of randomised controlled trials comparing the two drugs for the treatment of hypotension during spinal anaesthesia for caesarean birth. However, they discovered that neonates born to phenylephrine-treated mothers had greater pH levels in their umbilical cord blood than those born to ephedrine-treated women., Despite the fact that both groups had a comparable probability of genuine foetal acidosis (umbilical pH = 7.20). The authors came to the conclusion that their data provided indirect evidence that uterine blood flow may be better with phenylephrine than with ephedrine because acidotic variations in the umbilical artery pH are sensitive markers of impaired uteroplacental perfusion. Furthermore, a meta-analysis by Reynolds *et al*. 13 demonstrated that spinal anaesthesia for caesarean birth is connected to a lower cord pH than general or epidural anaesthesia. They hypothesised that these results were mostly explained by the administration of higher dosages of ephedrine in individuals who had spinal anaesthesia. Phenylephrine may be associated with a superior foetal acid-base state than ephedrine for two reasons. Ephedrine has been demonstrated to raise foetal heart rate and to easily pass the placenta. In addition to having a direct -adrenergic action and boosting the endogenous release of foetal catecholamines, ephedrine may also increase foetal metabolism. Therefore, a direct metabolic impact on the foetus is a possible cause of the acidosis linked to ephedrine consumption. The sympathectomy caused by regional anaesthesia shunts blood into the mesenteric bed, and -agonists like phenylephrine have a greater selective vasoconstrictive effect on the mesenteric bed than on the uteroplacental vasculature. This is the second explanation for the improved foetal acid-base status with phenylephrine compared to ephedrine. Improved uteroplacental perfusion is made possible by vasoconstriction in the mesenteric bed, which raises cardiac preload.Because of its alpha action, which causes placental vasoconstriction, the use of phenylephrine in pregnant patients has always been a subject of discussion and controversy.Phenylephrine was recommended as the best treatment for spinal anesthesia-related hypotension in a recent metanalysis by Ngan *et al*. Other research employing phenylephrine in pregnant people discovered that while it does produce foetal acidosis, it does so less than ephedrine and has no negative effects on the result of the newborn.

CONCLUSION

Following spinal anaesthesia for hysterectomies, prophylactic Phenylephrine at a dose of 15 micrograms per minute is more effective in maintaining arterial blood pressure than Ephedrine at a dose of 1.5 milligrammes per minute, according to the results of our study. Ephedrine requires a larger additional bolus dosage than phenylephrine.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

REFERENCES

1. Mercier FJ, Riley ET, Fredericson WL, Roger- Christoph S, Benhamou D, Cohen SE. Phenylephrine added to prophylactic ephedrine infusion during spinal anaesthesia forelective Caesarean section. Anaesthesiology 2001; 95: 668–74.
2. NganKee WD, Lee A. Multivariate analysis of factors associated with umbilicalarterial pH and standard base excess after Caesarean section under spinalanaesthesia. Anaesthesia. 2003 Feb;58(2):125-30.
3. NganKee WD, Khaw KS, Ng FF. Comparison of Phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia forCaesarean section.Br JAnaesth. 2004 Apr;92(4):469-74.
4. NganKee WD, Khaw KS, Ng FF: Prevention of hypotension during spinal anaesthesiafor caesarean delivery: An effective technique using combination phenylephrineinfusion and crystalloid cohydration. Anaesthesiology, 2005; 103: 744–50.
5. Sarvanan, MKocarev R. C. Wilson E. Watkins *et al*. Equivalent dose ofephedrine and phenylephrine in the prevention of post-spinal hypotension incaesarean section. British J. of Anaesthesia 2006(1):95-9.
6. NganKee WD, Khaw KS. Vasopressors in obstetrics: what should we be using? Curr Opin Anaesthesiol. 2006 Jun;19(3):238-43.
7. NganKee WD, Lee A, Khaw KS**,** Ng F, Karmakar MK, Gin T. A RandomizedDouble- Blinded Comparison of phenylephrine and ephedrine Infusion Combinationsto maintain blood pressure during spinal anaesthesia for caesarean delivery: The effectson foetal acid- base status and hemodynamic control. AnesthAnalg2008;107:1295-1302
8. Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Foetaland maternal effects of Phenylephrine and ephedrine during spinal anaesthesia for caesarean delivery. Anaesthesiology. 2002 Dec;97(6):1582-90.
9. Ngan Kee WD, Khaw KS, Lee BB, *et al*: A dose-response study of prophylactic ephedrine for the prevention of hypotension duringspinal anesthesia for cesarean delivery. AnesthAnalg 2000; 90:1390-1395.
10. Moran D. H, Perillo M, LaPorta R F, Bader AM, Datta S. Phenylephrine in theprevention of hypotension following spinal anaesthesia for caesarean delivery. JClinAnesth. 1991 jul- Aug; 3(4):301-5.
11. Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ. Randomized trial ofbolus Phenylephrine or ephedrine for maintenanceof arterial pressure duringspinalanesthesia for Caesarean section. Br J Anaesth. 1996 Jan;76(1):61-5
12. Lee A, NganKee WD, Gin T. A quantitative, systematic review of randomizedcontrolled trials of ephedrine versus Phenylephrine for the management ofhypotension during spinal anaesthesia for caesarean delivery. AnesthAnalg. 2002 Apr;94(4):920-926.
13. Reynolds F, Seed PT: Anesthesia for caesarean section and neonatal acid-base status: A meta-analysis. Anesthesia 2005;60:636-653.
14. Sahu D, Kothari D, Mehrotra A. Comparison of bolus Phenylephrine, ephedrine,and Mephentermine for maintenance of arterial pressure during spinal anaesthesiain caesarean section- a clinical study. Indian J Anaesthesia. 2003;47(2): 125-128.
15. NganKee W. D, Khaw K. S, Lau T. K, F. F. Ng, K. Chui, K.L. Ng. Randomizeddouble blinded comparison of Phenylephrine Vs Ephedrine for maintaining bloodpressure during spinal anaesthesia for non- elective caesarean section. Anaesthesia, 2008,63:1319-13263.