

AN UPDATE IN OBSTETRIC ANAESTHESIA

Clin A/Prof Nolan McDonnell

Department of Anaesthesia and Pain Medicine, King Edward Memorial Hospital for Women, Western Australia
School of Women's and Infants' Health, University of Western Australia, Crawley, Western Australia
School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia

This talk aims to highlight recent developments and research in obstetric anaesthesia that may have an impact on our day to day care of women in the birthing suite, the operating theatre and the post operative environment.

Maternal Mortality

There is generally good news on the subject of maternal mortality. Worldwide there has been a 34% decrease in the number of women dying in pregnancy and childbirth since 1990, with haemorrhage remaining the leading cause of death worldwide.¹ In developed countries, key reports have emerged from both the UK and NZ. The 2006-2008 UK CMACE report documents a decreased number of maternal deaths, mainly due to a fall in deaths related to thromboembolism after vaginal birth and from haemorrhage.² Of note is that sepsis became the leading direct cause of maternal death and the report highlighted the need for modified early warning charts and prompt recognition with aggressive, skilled management of these women in a multidisciplinary environment. Also, the CMACE report highlighted the important position of anaesthetists in the management of unwell women, with close to 50% of deaths receiving care from anaesthetists.

New Zealand is to be commended on the development of its own perinatal and maternal mortality reporting system, the Perinatal and Maternal Mortality Review Committee (PMMRC). The sixth report of the PMMRC was released in June 2012 and documented a total of 57 deaths over 5 years.³ New Zealand's Maternal Mortality Ratio was reported as 17.8 per 100,000 maternities, a rate higher than the UK (11.4 per 100,000). Whilst this may be of concern, the case ascertainment in New Zealand is likely to be close to 100%, meaning that almost all maternal deaths are captured, so the results should be interpreted within this context. Similar to other worldwide reports, older mothers and those from disadvantaged social or ethnic settings had a higher risk of dying. Eighteen deaths were thought to be potentially avoidable. Suicide was the leading cause of maternal death over this five year period, being responsible for nearly a quarter of all maternal deaths. The H1N1 pandemic was responsible for four maternal deaths in New Zealand in 2009.

How does Australia compare? Well, superficially the most recent MMR in Australia is better than New Zealand and the UK, at 8.4 per 100,000 maternities.⁴ However this data is now dated, being from between 2003-2005. Reporting in Australia is hindered by there being over 300 sites for maternity care, and many deaths may occur in ICUs without obstetric services on site. In addition, the numerous states and territories have different reporting obligations, making the true MMR difficult to deduce at present. The next report will likely be a 5-year summary published in late 2012 or early 2013.

Analgesia for Labour and Delivery

Neuraxial Analgesia

Delivery Method – Infusions, bolus and mandatory bolus techniques

Patient controlled or midwife administered bolus techniques appear to be superior to continuous infusion techniques, most likely due to the better spread of the solution in the epidural space. Patient controlled techniques (PCEA) have a number of advantages over midwife-administered top ups, particularly in regards to the decreased staff workload and improved maternal satisfaction. A background infusion is often used in conjunction with a patient administered bolus, the optimal combination of background and bolus dose volume and concentration is open to debate. To further improve on the PCEA technique, device manufacturers have been adding "mandatory



intermittent bolus” or “programmed intermittent bolus” modes to their infusion pumps. These deliver a bolus of a set volume at a set interval, generally in addition to the patient’s own demands. These new modes have been associated with less overall local anaesthetic use and less motor block.^{5,6}

Ultrasound Assisted Placement

Ultrasound assisted neuraxial techniques have now been well described. The potential benefits include more accurate identification of the level of insertion, with one study noting that in over 40% of cases the level of insertion was at least one space higher than initially thought (which is really only of major importance with combined spinal-epidural techniques).⁷ From our own departmental experience and research ultrasound is useful in the morbidly obese parturient who does not have clearly defined anatomical landmarks, as well as in women with difficult insertions. In these situations the ultrasound can identify not only space but also the angle and potential depth of insertion. Routine use is difficult to recommend at present and like most techniques a learning curve is present and practice on less complicated cases is recommended.

Addition of Clonidine and Neostigmine

A number of options have been investigated to enhance neuraxial labour analgesia. These options may seek to prolong the initial duration of analgesia (and hence decrease supplementation needs), decrease motor blockade and decrease the incidence of hypotension. A number of additives to traditional neuraxial opioids and local anaesthetic have been examined with clonidine and neostigmine receiving recent attention. Clonidine has been extensively investigated and is a commonly used neuraxial adjunct.⁸ Neostigmine has undergone less investigation but appears safe. Interestingly, neostigmine causes severe nausea and vomiting if administered intrathecally but this does not appear to be an issue with epidural administration.⁹ In labour analgesia, Van de Velde et al administered neostigmine (500 mcg) and clonidine (75 mcg) epidurally after performing combined spinal-epidural analgesia in labour.¹⁰ The duration of initial analgesia was extended from 95 to 144 minutes and overall local anaesthetic consumption was less. Interestingly, nearly a quarter of the women in the neostigmine / clonidine group delivered before additional analgesia was required. This may serve to be a useful technique in the future but caution is advised on a number of levels: the mixing and dilution of drugs at the bedside raises sterility and error issues and this technique has a number of ethical and medico-legal implications.¹¹

Remifentanil

Not all women in labour will be able to have an epidural or will want an epidural. Remifentanil provides a viable option and has been shown to be better than pethidine.¹² Uptake has been considerable in some institutions where it has become the primary method of labour analgesia.¹³ However it requires very close monitoring with 1:1 midwifery care and continuous SpO₂ monitoring¹³ and significant respiratory complications have been reported.¹⁴ Maternal satisfaction is high even though pain relief is not as effective as neuraxial analgesia.¹⁵ Neonatal metabolism is rapid, even in premature neonates.¹⁶ Bolus and infusion regimens vary, although a 40 mcg bolus with no background infusion has been recommended.¹⁷

Caesarean Delivery

General Anaesthesia

Mortality – Regional versus General Anaesthesia

General anaesthesia has traditionally been associated with an increased maternal mortality and the most recent CMACE report highlights continued deaths associated with the management of general anaesthesia.² Of concern, one woman died despite the presence of a functioning epidural catheter. Continued attempts at intubation were made despite oxygenation initially being achieved from an ILMA. Long acting muscle relaxants were then given, she died without a surgical airway being attempted.

Hawkins published one of the most widely quoted papers highlighting the discrepancy in deaths between general versus regional anaesthesia.¹⁸ This data led to the common quote of a mortality difference 16-17 times higher for general anaesthesia over regional anaesthesia. However, this data is now relatively dated and looked at cases prior to 1990. In the intervening period there have been a number of advances in monitoring and equipment as



well as education and protocols for the management of the difficult airway. It is perhaps not that surprising that when Hawkins looked at more recent data (1997-2002), there was no significant difference in mortality between general and regional anaesthesia.¹⁹ Of note, deaths secondary to regional anaesthesia had increased whilst those secondary to general anaesthesia had decreased.

Head-up Position

Placing the pregnant women in a 30-degree head-up tilt has been shown to increase the FRC. Although the mean increase is only approximately 190 ml this may be of benefit in a difficult airway.²⁰ Unfortunately an increasing BMI seems to decrease the benefits from the head-up position. Despite this, it seems difficult not to recommend the adoption of a 30-degree head-up position prior to general anaesthesia in pregnancy.

Neonatal Outcomes

Traditionally it has been suggested that the effects of general anaesthesia on the neonate would be transient and of little concern when skilled resuscitation staff are present. Data from Brisbane has suggested, when controlled for confounders, that general anaesthesia for fetal distress is associated with lower Apgar scores at 5 min and with at least twice the risk of a NICU admission.²¹ This data is in keeping with data from Sydney published in 2009 which showed markedly increased early neonatal morbidity with general anaesthesia, with the greatest impact being on already compromised babies.²² Whilst failure to provide general anaesthesia may lead to poorer outcomes, it does highlight the need for close communication between all team members in the setting of fetal distress.

Prevention of Hypotension

Research into the prevention of hypotension under spinal anaesthesia has been focused on three main directions – vasopressors, fluid pre- or co-load and the use of lower concentrations of local anaesthetics (“low dose” spinals).

Vasopressors

Phenylephrine is now firmly established in obstetric anaesthesia with well documented benefits for neonatal acid base status and maternal blood pressure control.²³ Metaraminol has not received as much attention and comparative studies with phenylephrine are lacking. Metaraminol has some potential advantages, particularly with respect to some effect at beta receptors, which may maintain cardiac output better. Of importance is that the majority of studies to date are in the elective caesarean situation with an uncompromised utero-placental unit. It is unclear whether the stress fetus may respond differently to these medications.

Fluids

The take home message is that fluids alone have an unpredictable efficacy and there is a high likelihood that vasopressors will be required.²⁴ Preload is partly effective when a colloid is used but not when a crystalloid is used. Co-loading with either solution can be effective but again is unreliable.

Low Dose Spinals

A significant amount of research has been directed at lowering the dose of intrathecal local anaesthetic. Whilst it is clear that this decreases maternal hypotension and nausea, the incidence of intraoperative pain is unacceptable.²⁵ The ED95 of hyperbaric bupivacaine is approximately 11 mg, but many studies define “low” dose as < 8mg. When used in this fashion, hypotension is reduced by approximately 20% but there is nearly a 4-fold increase in the requirement for intraoperative analgesic supplementation.²⁵ Hypotension can readily be managed with vasopressors but intraoperative pain will often require conversion to general anaesthesia. In the future it is difficult to see the place of low dose spinals except in selected situations.

Post-Caesarean Pain Relief

The combinations and permutations of options for post caesar pain relief continue to grow dramatically. What should be emphasised is that institutions should use what works best in their unique setting, rather than trying to



aspire to what may appear to be a new “gold standard”.⁹ Recent research has been concentrated around the TAP block and the incidence of chronic post-caesarean pain. The place of the TAP block has now been relatively well defined and appears to be useful when long acting neuraxial opioids are not used (eg GA caesarean).²⁶ There is little benefit to adding a TAP block to epidural or intrathecal morphine. Chronic post-caesar pain is an emerging issue, with recent studies documenting an incidence of between 10-20%.^{27, 28} Whilst much lower than other high risk surgical populations, given the comparatively large number of caesareans being performed (over 90,000 per annum in Australia), the potential burden is high. A recent study has shown that gabapentin 600 mg pre-caesarean, when combined with intrathecal morphine 100 mcg, decreased pain post operatively.²⁹ Whilst the study was not powered to look at chronic pain, the incidence in the placebo group was 20% and there was a trend to a lower incidence in the gabapentin group. It is too early to make widespread recommendations in regards to gabapentin as the neonatal effects when administered pre-delivery have not been well assessed, but it may be a useful adjunct post-delivery in high risk women, with sedation the major side effect.

Complications

Haemorrhage

rVIIa, Tranexamic Acid and Fibrinogen Concentrate

The use of rVIIa has anecdotally appeared to decrease in obstetric haemorrhage, most likely secondary to the lack of positive outcome data and the closure of the ANZ Haemostasis Registry. The Registry recently published the data on rVIIa in PPH which showed a “response” rate of 76%,³⁰ but this is a poor outcome measure and the reported response rate is similar to that reported in the placebo arm of at least three RCTs investigating rVIIa. The World Health Organization (WHO) also suggests that there is not enough evidence to currently recommend its use.³¹ Antifibrinolytics such as tranexamic acid have a robust evidence base for the reduction of transfusion requirements outside of the obstetric setting.³² Evidence is currently lacking in obstetric haemorrhage although the WOMAN trial, a large international study, is underway to examine its potential role. Interestingly, despite the relative lack of evidence, the WHO do recommend tranexamic acid as a potential therapeutic agent in post partum haemorrhage. Commonly used doses are 1 g intravenously, followed by another 1 g if additional bleeding issues are present from between 30 minutes to 24 hours after administration.

Fibrinogen concentrate, presented as a powder for reconstitution, is a very attractive option in obstetric haemorrhage, especially in resource limited areas and given the correlation between fibrinogen levels and the degree of haemorrhage.³³ It is not widely available in Australia currently (although Perth did have a special supply during the CHOGM meeting). Case series are promising and clinical trials are currently underway.³⁴⁻³⁶

Massive Transfusion Protocols and Monitoring of Coagulation

It has been recommended that massive transfusion protocols be in place in all obstetric hospitals.³⁷ Protocols vary but most use a relatively aggressive ratio of red cells to coagulation factors. Fibrinogen levels appear to correlate well with increasing volumes / severity of haemorrhage.³³ It is important to note that baseline levels of fibrinogen in pregnancy are higher than normal and hence using standard laboratory cut offs may not reflect the overall degree of fibrinogen deficiency. Experience is growing with the use of TEG and ROTEM in obstetric haemorrhage and normal values for pregnancy have been defined. Our own experience with ROTEM would suggest that it is a valuable tool in major haemorrhage cases, allowing targeted coagulation factor replacement.

Interventional Radiology

Interventional radiology in the acute management of PPH has been shown to have excellent results.³⁸ More controversial is the use of interventional radiology in the elective situation, despite it being recommended in some guidelines.³⁹ A robust evidence base is not currently present, reported data varies from showing potential benefit to no benefit and there is a lack of common outcome measures and heterogeneity in the case selection. Data from a retrospective review from Auckland where catheters were used in 14 women documented that of the 11 where the balloons were inflated, 9 required a hysterectomy, no benefit from inflation was seen in 4 and the median blood loss was 4,600 ml.⁴⁰ In the same edition of the journal a case report of a women who suffered multiple vascular complications after the prophylactic insertion of balloon catheters.⁴¹



Post-dural Puncture Headache (PDPH) and its Management

Management options for PDPH that have been shown to be effective include ACTH, neuraxial opioids, epidural blood patch and the placement of intrathecal catheters. However, hydration, bed rest, caffeine and NSAIDs are not thought to have much of a role in management. Gabapentin may be a relatively novel agent in the management of PDPH.⁴² A blood patch performed within 24 hours is less likely to be effective. The optimal volume of blood for an epidural blood patch is still not clear. The most recent multi-centre study examined 15, 20 and 30 ml with partial relief being found in 61%, 73% and 67% respectively.⁴³ Complete relief was surprisingly low at just 32% in the 20 ml group. Just under half of the patients in the 30 ml group did not receive the allocated volume secondary to back pain. The authors recommend aiming for 20 ml when performing an epidural blood patch. Another study examined the optic nerve sheath diameter as a measure of intra-cranial pressure with epidural blood patching and found that successful relief of PDPH was associated with evidence of a raised intracranial pressure, suggesting this as a possible mechanism of action of an epidural blood patch.⁴⁴

Stroke

Anaesthetists should be fully aware of the differential diagnosis of headache in a pregnant or recently pregnant women, especially vascular causes and cerebral venous thrombosis.⁴⁵ The incidence of stroke in pregnancy has increased by at least 50% in recent times⁴⁶ with identified risk factors being hypertension, heart disease, obesity, diabetes and clotting disorders. Guidelines are now available for the management of cerebral venous thrombosis.⁴⁷

VTE Prophylaxis

Thromboembolism has traditionally been the leading cause of direct maternal mortality in the UK triennial reports but in the most recent report there was an over 50% decrease in the number of deaths.² The decrease is generally put down to the adherence to risk assessment and management guidelines, with those of the RCOG being the most widely used throughout the UK.⁴⁸ Interestingly, the reduction in deaths was primarily in antenatal women and those after a vaginal delivery, with little change in the number of women dying after caesarean delivery. Australasian consensus guidelines have now been published.^{49,50} The key take home messages are that pharmacological prophylaxis is recommended in most non elective caesareans and in elective caesareans with one additional risk factor. Important risk factors for the anaesthetist include post-partum haemorrhage, which dramatically increases the VTE risk. In addition, obesity appears to increase the risk with a higher risk with higher BMIs. Dosing guidelines for the obese obstetric patient are available but are based on expert opinion rather than evidence from clinical trials.⁴⁸

References

1. Paxton A, Wardlaw T. Are We Making Progress in Maternal Mortality? *New England Journal of Medicine*. 2011; 364: 1990-3.
2. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer: 2006-2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG : an international journal of obstetrics and gynaecology*. 2011; 118 Suppl 1: 1-203.
3. PMMRC. 2012. Sixth Annual Report of the Perinatal and Maternal Mortality Review Committee. Reporting mortality 2010. Wellington: Health Quality & Safety Commission 2012.
4. Sullivan, EA, Hall, B, King, JF. Maternal deaths in Australia 2003–2005. AIHW National Perinatal Statistics Unit 2007; Maternal deaths series no. 3. Cat. no. PER 42.
5. Leo S, Ocampo CE, Lim Y, Sia AT. A randomized comparison of automated intermittent mandatory boluses with a basal infusion in combination with patient-controlled epidural analgesia for labor and delivery. *International journal of obstetric anaesthesia*. 2010; 19: 357-64.
6. Capogna G, Camorcia M, Stirparo S, Farcomeni A. Programmed intermittent epidural bolus versus continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women. *Anesth Analg*. 2011; 113: 826-31.
7. Lee AJ, Ranasinghe JS, Chegade JM, et al. Ultrasound assessment of the vertebral level of the intercrystal line in pregnancy. *Anesth Analg*. 2011; 113: 559-64.



8. Paech MJ, Pavy TJ, Orlikowski CE, Evans SF. Patient-controlled epidural analgesia in labor: the addition of clonidine to bupivacaine-fentanyl. *Reg Anesth Pain Med.* 2000; 25: 34-40.
9. McDonnell NJ, Keating ML, Muchatuta NA, Pavy TJ, Paech MJ. Analgesia after caesarean delivery. *Anaesthesia and intensive care.* 2009; 37: 539-51.
10. Van de Velde M, Berends N, Kumar A, et al. Effects of epidural clonidine and neostigmine following intrathecal labour analgesia: a randomised, double-blind, placebo-controlled trial. *International journal of obstetric anaesthesia.* 2009; 18: 207-14.
11. Paech M, Pan P. New recipes for neuraxial labor analgesia: simple fare or gourmet combos? *International journal of obstetric anaesthesia.* 2009; 18: 201-3.
12. Schnabel A, Hahn N, Broscheit J, et al. Remifentanil for labour analgesia: a meta-analysis of randomised controlled trials. *European journal of anaesthesiology.* 2012; 29: 177-85.
13. Hill D. The use of remifentanil in obstetrics. *Anesthesiology clinics.* 2008; 26: 169-82, viii.
14. Bonner JC, McClymont W. Respiratory arrest in an obstetric patient using remifentanil patient-controlled analgesia*. *Anaesthesia.* 2012; 67: 538-40.
15. Ismail MT, Hassanin MZ. Neuraxial analgesia versus intravenous remifentanil for pain relief in early labor in nulliparous women. *Arch Gynecol Obstet.* 2012.
16. Welzing L, Ebenfeld S, Dlugay V, Wiesen MH, Roth B, Mueller C. Remifentanil degradation in umbilical cord blood of preterm infants. *Anesthesiology.* 2011; 114: 570-7.
17. Hinova A, Fernando R. Systemic remifentanil for labor analgesia. *Anesth Analg.* 2009; 109: 1925-9.
18. Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia-related deaths during obstetric delivery in the United States, 1979-1990. *Anesthesiology.* 1997; 86: 277-84.
19. Hawkins JL, Chang J, Palmer SK, Gibbs CP, Callaghan WM. Anesthesia-related maternal mortality in the United States: 1979-2002. *Obstetrics and gynecology.* 2011; 117: 69-74.
20. Hignett R, Fernando R, McGlennan A, et al. A randomized crossover study to determine the effect of a 30 degrees head-up versus a supine position on the functional residual capacity of term parturients. *Anesth Analg.* 2011; 113: 1098-102.
21. Beckmann M, Calderbank S. Mode of anaesthetic for category 1 caesarean sections and neonatal outcomes. *Aust N Z J Obstet Gynaecol.* 2012.
22. Algert CS, Bowen JR, Giles WB, Knoblanche GE, Lain SJ, Roberts CL. Regional block versus general anaesthesia for caesarean section and neonatal outcomes: a population-based study. *BMC Med.* 2009; 7: 20.
23. Ngan Kee WD. Prevention of maternal hypotension after regional anaesthesia for caesarean section. *Current opinion in anaesthesiology.* 2010; 23: 304-9.
24. Mercier FJ. Fluid loading for cesarean delivery under spinal anaesthesia: have we studied all the options? *Anesth Analg.* 2011; 113: 677-80.
25. Rucklidge MW, Paech MJ. Limiting the dose of local anaesthetic for caesarean section under spinal anaesthesia--has the limbo bar been set too low? *Anaesthesia.* 2012; 67: 347-51.
26. McDonnell NJ, Paech MJ. The transversus abdominis plane block and post-caesarean analgesia: are we any closer to defining its role? *International journal of obstetric anaesthesia.* 2012; 21: 109-11.
27. Kainu JP, Sarvela J, Tiippana E, Halmesmaki E, Korttila KT. Persistent pain after caesarean section and vaginal birth: a cohort study. *International journal of obstetric anaesthesia.* 2010; 19: 4-9.
28. Sng BL, Sia AT, Quek K, Woo D, Lim Y. Incidence and risk factors for chronic pain after caesarean section under spinal anaesthesia. *Anaesthesia and intensive care.* 2009; 37: 748-52.
29. Moore A, Costello J, Wiczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. *Anesth Analg.* 2011; 112: 167-73.
30. Phillips LE, McLintock C, Pollock W, et al. Recombinant activated factor VII in obstetric hemorrhage: experiences from the Australian and New Zealand Haemostasis Registry. *Anesth Analg.* 2009; 109: 1908-15.
31. World Health Organization, Department of Reproductive Health and Research. WHO guidelines for the management of postpartum haemorrhage and retained placenta 2009.
32. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *Bmj.* 2012; 344: e3054.
33. de Lloyd L, Bovington R, Kaye A, et al. Standard haemostatic tests following major obstetric haemorrhage. *International journal of obstetric anaesthesia.* 2011; 20: 135-41.
34. Glover NJ, Collis RE, Collins P. Fibrinogen concentrate use during major obstetric haemorrhage. *Anaesthesia.* 2010; 65: 1229-30.
35. Mercier FJ, Bonnet MP. Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. *Current opinion in anaesthesiology.* 2010; 23: 310-6.



36. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. *International journal of obstetric anaesthesia*. 2010; 19: 218-23.
37. Shields LE, Smalarz K, Reffigee L, Mugg S, Burdumy TJ, Propst M. Comprehensive maternal hemorrhage protocols improve patient safety and reduce utilization of blood products. *American journal of obstetrics and gynecology*. 2011; 205: 368 e1-8.
38. Royal College of Obstetricians and Gynaecologists. The role of emergency and elective interventional radiology in postpartum haemorrhage. *Royal College of Obstetricians and Gynaecologists Good Practice Guideline No. 6*; 2007.
39. Royal College of Obstetricians and Gynaecologists. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management. *Green Top Guideline No. 27*; January 2011.
40. Thon S, McLintic A, Wagner Y. Prophylactic endovascular placement of internal iliac occlusion balloon catheters in parturients with placenta accreta: a retrospective case series. *International journal of obstetric anaesthesia*. 2011; 20: 64-70.
41. Bishop S, Butler K, Monaghan S, Chan K, Murphy G, Edozien L. Multiple complications following the use of prophylactic internal iliac artery balloon catheterisation in a patient with placenta percreta. *International journal of obstetric anaesthesia*. 2011; 20: 70-3.
42. Wagner Y, Storr F, Cope S. Gabapentin in the treatment of post-dural puncture headache: a case series. *Anaesthesia and intensive care*. 2012; 40: 714-8.
43. Paech MJ, Doherty DA, Christmas T, Wong CA. The volume of blood for epidural blood patch in obstetrics: a randomized, blinded clinical trial. *Anesth Analg*. 2011; 113: 126-33.
44. Dubost C, Le Gouez A, Zetlaoui PJ, Benhamou D, Mercier FJ, Geeraerts T. Increase in optic nerve sheath diameter induced by epidural blood patch: a preliminary report. *British journal of anaesthesia*. 2011; 107: 627-30.
45. Klein AM, Loder E. Postpartum headache. *International journal of obstetric anaesthesia*. 2010; 19: 422-30.
46. Kuklina EV, Tong X, Bansil P, George MG, Callaghan WM. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: reasons for concern? *Stroke*. 2011; 42: 2564-70.
47. Saposnik G, Barinagarrementeria F, Brown RD, Jr., et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011; 42: 1158-92.
48. Nelson-Piercy C. Guideline No. 37. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. London: Royal College of Obstetricians and Gynaecologists, 2009.
49. McLintock C, Brighton T, Chunilal S, et al. Recommendations for the diagnosis and treatment of deep venous thrombosis and pulmonary embolism in pregnancy and the postpartum period. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2012; 52: 14-22.
50. McLintock C, Brighton T, Chunilal S, et al. Recommendations for the prevention of pregnancy-associated venous thromboembolism. *The Australian & New Zealand journal of obstetrics & gynaecology*. 2012; 52: 3-13.

