09 May 2014
No.13

NEURAXIAL ANALGESIA: EFFECTS ON THE PROGRESS AND OUTCOME OF LABOUR

P Reddy

Moderator: R Samuel

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

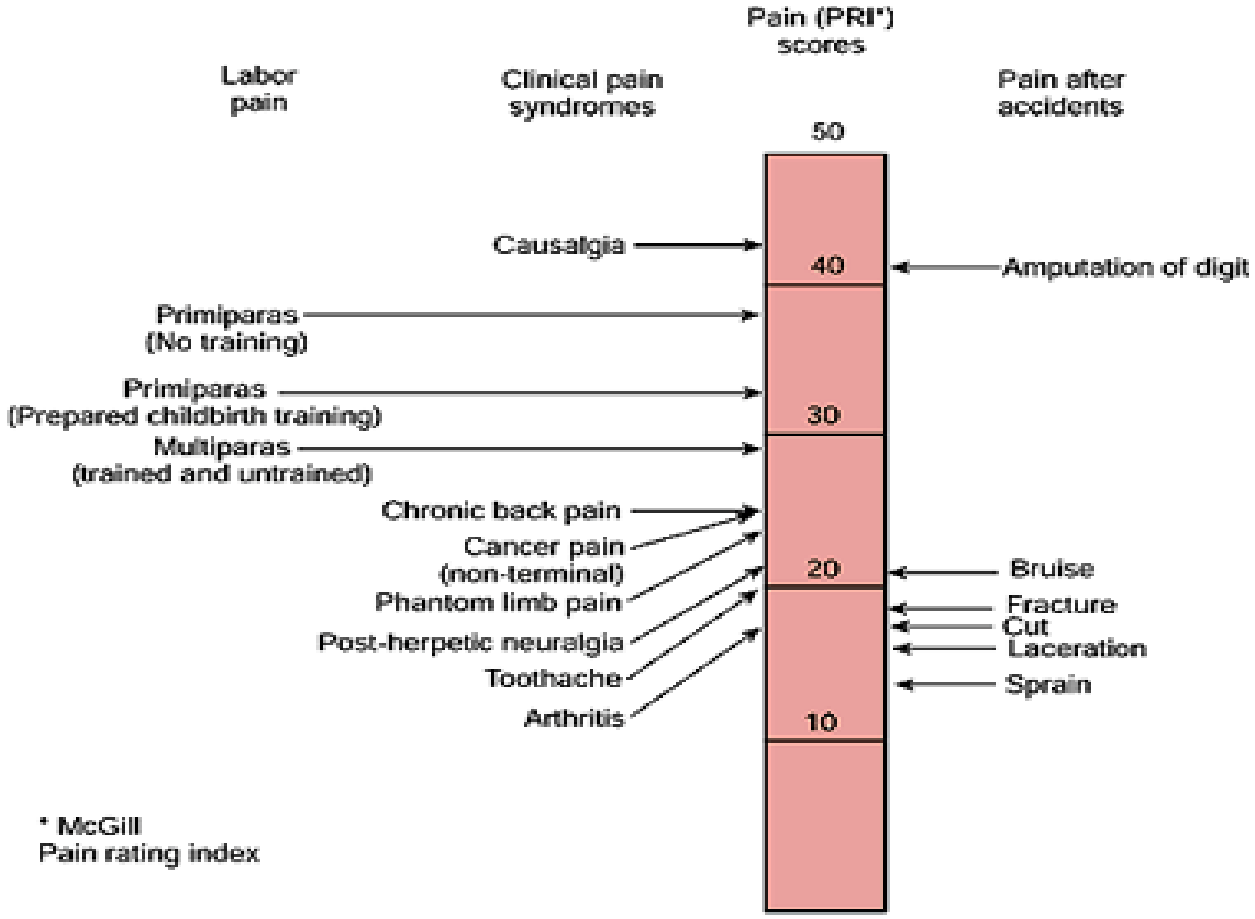
CONTENTS

NEURAXIAL ANALGESIA: EFFECTS ON THE PROGRESS AND OUTCOME OF LABOUR

INTRODUCTION

Labour is one of the most painful situations a person can experience. It was rated more painful than cancer pain and as painful as amputation of a digit without anaesthesia.

Figure 1: McGill Pain Questionare



Neuraxial techniques are the gold standard for intrapartum labour analgesia. There have been a number of trials that have compared neuraxial analgesia with systemic opioids, nitrous oxide or both. The results have shown lower maternal pain scores and higher maternal satisfaction with neuraxial analgesia.[2-5] Due to the advantages of excellent pain control, safety and the benefit improving the physiology of the mother and foetus [10-12], the use of neuraxial analgesia and increased tremendously over the past 30 years. In America it has increased from 21% to 77% and in the UK it has increased to 33%.

Table 1:

The Positives and Negatives of neuraxial labour analgesia

Advantages
Patient has the benefit of complete analgesia • There is no maternal sedation and the mother can there more fully participate and enjoy the birth and is better able to bond with baby • Decreases negative responses to pain • There is little or none neonatal sedation which decreases the risk and need for neonatal resuscitation • In the event of a need for surgical intervention, labour analgesia can easily be converted to surgical anaesthesia. This also decreases the risk of having to convert to a general anaesthetic, which carries its own risk in the obstetric patient.
Disadvantages
• The service needs to be provided by a skilled anaesthetist • There is the risk of the failed block • Neuraxial analgesia causes a sympathectomy which may lead to maternal hypotension. The consequence of which could lead to decreased utero-placental flow • There is the risk of prolonged 2nd stage of labour and possible increased risk of instrumental vaginal delivery or the need for surgical intervention • Neuraxial techniques are contraindicated in patients with coagulopathy or receiving anticoagulants

HISTORY

The “birth” of obstetric anaesthesia dates back to 19 January 1847. Sir James Simpson was an eminent Scottish obstetrician and Professor at the University of Edinburgh. He initially used ether for childbirth. He then began experimenting with chloroform. Labour analgesia became more recognised and accepted when it was used on Queen Victoria during the birth of her eighth child.[8-9] Unfortunately, it was not widely accepted by religious leaders as they believed childbirth was intended by God to be painful.

Most recently however, the American Society of College of Obstetricians and Gynaecologists put out the statement: “Labour results in severe pain for women. There is no other circumstance where it is considered acceptable for a person to experience severe pain amenable to safe intervention while under a physician’s care. Maternal request is sufficient justification for pain relief during labour.” Three Neuraxial techniques of regional anaesthesia for caesarean section have evolved to be most commonly utilized:

(1) Spinal anaesthesia,
(2) Epidural anaesthesia,
(3) Combined spinal-epidural anaesthesia

EFFECTS OF EFFECTIVE ANALGESIA ON MOTHER AND FOETUS

There are a number of studies that show that epidural analgesia in labour decreases or blocks the rises in stress hormones such as adrenaline, cortisol, ACTH, peptide hormones, and angiotensin II.[10-12]
This effect of epidural analgesia, plus the added benefit of decreasing harmful maternal hyperventilation, all help to account neonatal acid base benefits.

Maternal Benefits

Painful labour produces many negative changes in the physiology & biochemistry of the parturient.

- During the first stage of labour, the mother's respiration increases by 75-150%.
- Uterine contractions result in severe pain. This in turn causes an increase in minute volume and oxygen consumption, the consequence of which is a respiratory alkalosis and a shift to the left of the oxygen-haemoglobin dissociation curve.
- During labour the sympathetic system is activated due to pain. This results in an increase in the level of catecholamines. It also increases cardiac output and systemic vascular resistance. These may lead to a decrease in blood flow to the uterus. Neuraxial analgesia is beneficial because it decreases catecholamine surges.
- Uterine contractions cause auto-transfusion of blood from uterus into the circulation. While this is well tolerated in the normal population this, may be disastrous in parturients with limited cardiac reserve. The utero-placental unit is perfused only during uterine diastole. The decrease in uterine blood flow during contractions that occurs against a background of utero-placental insufficiency may not be tolerated by the foetus. Effective pain relief may contribute to better outcomes in these situations.
- A painful labour can interfere with maternal-neonatal bonding, affect future sexual relationships and cause postpartum depression.
- Pregnant patients are at increased risk of DVT. Epidural analgesia helps attenuate the hypercoagulable state of pregnancy

Table 2. Physiologic Changes In Pregnancy

Cardiovascular	Increased cardiac output Increased blood volume Increased resting heart rate Decreased peripheral resistance Decreased blood pressure (second trimester)
Pulmonary	Increased respiratory rate Decreased functional residual capacity Increased tidal volume Increased minute ventilation Respiratory alkalosis
Gastrointestinal	Decreased gastric motility Decreased esophageal sphincter tone
Musculoskeletal	Increased ligament laxity

Physiology of pain during labor

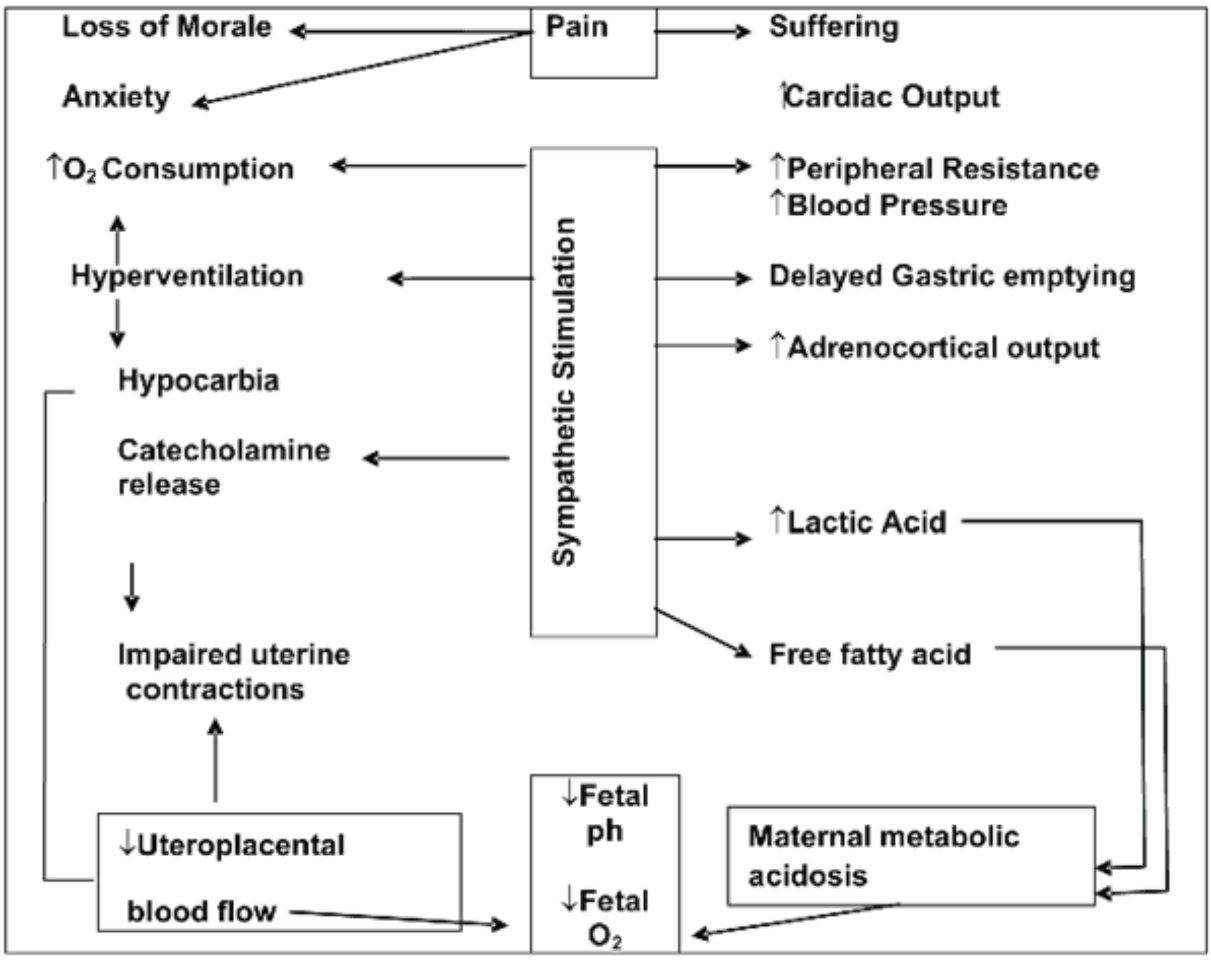
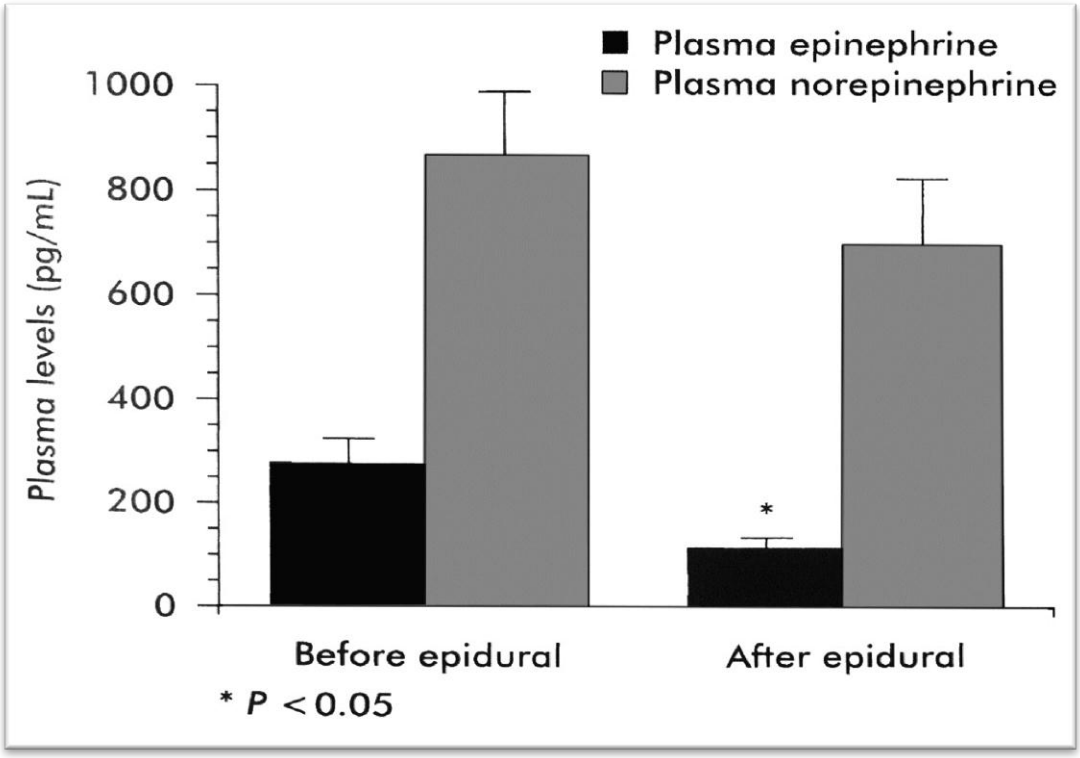


Figure 2: Influence of epidural analgesia on maternal plasma concentrations of catecholamines during labour. Modified from Shnider SM et al. Maternal catecholamines decrease during labour after lumbar epidural analgesia.Am J Obstet Gynecol 1983; 147:13-5



Foetal effects

The cause of foetal bradycardia after combined spinal epidural remains unclear. It may be related to a decrease in the circulating maternal catecholamine levels which results from the quick onset of analgesia. It appears also that the dose of intrathecal opioids affects the incidence of prolonged decelerations that require emergency caesarean section.[45, 47] When high doses of intrathecal opioids were used (50-75ug of fentanyl or 7.5-10ug of sufentanil), the incidence of prolonged decelerations were between 3.9-12%. When lower doses were used, CSE analgesia did not show any adverse outcome for the baby.

Table 3 Maternal changes produced by neuraxial analgesia that may affect the baby[20]

UNFAVOURABLE EFFECTS	**FAVOURABLE EFFECTS**
Decreased maternal blood pressure	No drug transfer across the placenta
Increased maternal temperature	Less episodes of desaturation
Increased need for oxytocin	Increased uterine blood flow due to the vasodilation from the block
Increased length of second stage of labour	Decreased maternal pain and therefore decreased maternal hyperventilation and stress
Risk of increased need for instrumental delivery	

NEURAXIAL ANALGESIA AND LABOUR OUTCOMES

Effects on Caesarean Rates

Wong et al. published a trial using 750 nulliparous women at term. These parturients were in spontaneous labour or had spontaneous rupture of membranes and had a cervical dilation of less than 4 cm. At random, these patients were to receive either intrathecal fentanyl or systemic hydromorphone at the first request for analgesia. At the second request for analgesia, epidural analgesia was initiated in the group that had received intrathecal fentanyl. In the group that had initially received only hydromorphone, epidural analgesia was initiated when cervical dilation was 4cm and greater or at the third request for analgesia.

The primary outcome was the rate of caesarean delivery.[40-45] Investigators looked at the rate of Caesarean deliveries which were shown to not be significantly different between the groups (17.8 % after intrathecal analgesia vs. 20.7 % after systemic analgesia; 95% confidence interval for the difference, -9.0 to 3.0 percentage points; P=0.31) It was also found that median time from the beginning of analgesia to complete dilatation was significantly shorter after intrathecal analgesia than after systemic analgesia (295 minutes vs. 385 minutes, P<0.001), as was the time to vaginal delivery (398 minutes vs 479 minutes, P<0.001).

Pain scores after the first intervention were significantly lower after intrathecal analgesia than after systemic analgesia (2 vs. 6 on a 0-to-10 scale, P<0.001). The incidence of one-minute Apgar scores below 7 was significantly higher after systemic analgesia (24% vs 16.7%, P=0.01).Conclusion: Neuraxial analgesia in early labour did not increase the rate of caesarean delivery, and it provided better analgesia and resulted in shorter duration of labour than systemic analgesia.[40-45]

Effects on the rate of Instrumental Deliveries

There are many factors that affect the rate of instrumental vaginal delivery. These include maternal pain and the urge to bear down, neuraxial analgesia-induced motor blockade, and position of the foetal vertex and station. Due to these many confounding factors it is difficult to interpret data that suggests a link between neuraxial labour analgesia and instrumental vaginal delivery. A study was done at Tripler Army Hospital. It compared the rate of instrumental vaginal delivery in patients receiving epidural analgesia and those who did not.

Results showed that there was no increase in the rate of instrumental delivery in the epidural group vs the non-epidural group (11.1% vs 11.9%)[48-50]. Similarly, a study conducted at National Maternity Hospital in Dublin, showed that the rate of instrumental delivery remained unchanged in spite of there being a greater than five-fold increase in epidural rate[55]. These findings were confirmed in a systematic review of seven impact studies involving more than 28 000 parturients, which showed no difference in instrumental vaginal delivery rates (mean change, 0.76%; 95% CI –1.2 to 2.8).[56]

On the other hand, there are also conflicting results from a meta-analysis conducted by Halpern and Leighton.[60] Although, the rate of Caesarean Section was the primary outcome, this study showed that neuraxial analgesia is associated with an increased risk of instrumental delivery. Also confusing is the effect other factors (e.g. the technique used, the concentration of the local used, the total dose of anaesthetic) have on the degree of analgesia provided by neuraxial techniques. Studies have also investigated the effect of bupivacaine concentration on the rate of instrumental vaginal delivery, with conflicting outcomes.[45.46.47,48]

James and colleagues noted that women randomly assigned to receive epidural bupivacaine 0.1% with fentanyl 2 mg had a lower incidence of instrumental vaginal delivery than women who received epidural bupivacaine 0.25% (6% vs 24%, P¼0.03)[59,60]. Similarly, in a larger study by Olofsson and colleagues, women randomized to 'low-dose' bupivacaine 0.125% with sufentanil had a lower instrumental vaginal delivery rate compared with those who received 'high-dose' bupivacaine 0.25% with adrenaline.[62-64] The choice of how epidural analgesia is maintained is also another factor that affects the density of the block.

Continuous infusion techniques tend to result in higher total doses of bupivacaine (and, thus a greater degree of motor blockade) when compared with intermittent bolus techniques. Smedstad and Morris conducted a trial that compared to determine the rate of instrumental delivery when a continuous infusion was used compared to bolus injections. Results showed a higher rate of instrumental delivery with the infusions.[60] However, two later studies (a 2006 study by Wong and colleagues and the COMET study[60]) showed that there was no difference in the instrumental vaginal delivery rate between groups who received 'low-dose' bupivacaine/ fentanyl by either intermittent bolus or continuous infusions.

Other studies have looked at what the impact of specific neuraxial techniques (i.e. CSE vs epidural) had on instrumental vaginal delivery rates. Collis and colleagues found no difference in the rates between parturients randomized to receive 'low-dose' CSE (intrathecal bupivacaine/fentanyl followed by intermittent boluses of epidural bupivacaine 0.1%/fentanyl 2 mg ml21) vs traditional 'high-dose' epidural (0.25% bupivacaine).[65-69] These findings show that the impact of specific neuraxial techniques on the degree of neuraxial blockade, and therefore the incidence of instrumental vaginal delivery, is still unclear.

Figure 3: Neuraxial vs. systemic opioid analgesia and mode of vaginal delivery

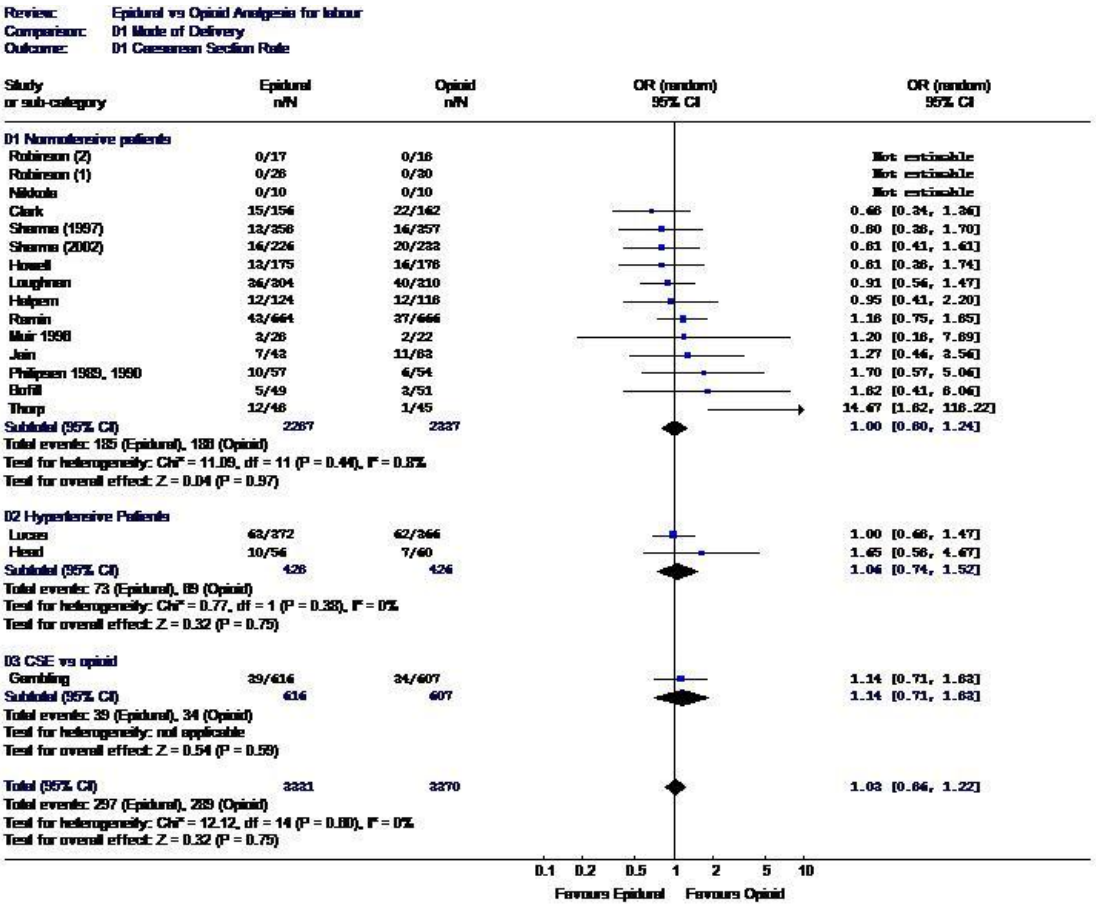


Table 2: Impact of Neuraxial analgesia on labour outcomes: available evidence

Labour outcome	**Evidence**
Incidence of Caesarean delivery	When neuraxial analgesia is started in the latent stage of labour the risk of C/S does not increase
Incidence of instrumental vaginal delivery	Many factors affect the rate of instrumental delivery. No consensus reached
Duration of first stage of labour	There is no increase or difference noted in the first stage of labour
Duration of the second stage of labour	Evidence shows that effective neuraxial analgesia DOES increase the length of second stage

EPIDURAL ANAESTHESIA AND PRE-ECLAMPSIA

Whether epidural analgesia is appropriate for use in severely preeclamptic women has been controversial. Although there is no question that this method of analgesia provides better pain relief than parenteral opioids and pudendal block, some obstetricians have withheld epidural analgesia from their preeclamptic patients because of fear of severe hypotension and foetal distress.[65,66,67] Recently, the safety of epidural analgesia for preeclamptic parturients has been established. In a large retrospective review of parturients with severe preeclampsia, Hogg et al found no difference in the incidence of caesarean section for foetal distress between patients who received epidural analgesia and those who did not.[69, 70]. None of the patients in either group experienced pulmonary oedema or renal failure.

In a randomized controlled trial of 738 patients that compared epidural analgesia to intravenous opioid analgesia, Lucas et al found no difference in the total incidence of caesarean delivery or caesarean delivery for foetal distress between the groups[55, 56, 57]. Neonatal outcome, as measured by need for intensive care, Apgar scores, and umbilical artery pH, was similar. Of note, there was a 20-fold increase in the use of naloxone in neonates in the intravenous opioid group.[58]Analgesia was superior in the epidural group.Current evidence suggests that epidural analgesia is safe and desirable for parturients with preeclampsia provided that there is no contraindication (such as severe coagulopathy) and blood pressure is maintained appropriately. The direct benefits include excellent pain relief for the parturient without concomitant neonatal depression. In some patients, general anaesthesia can be avoided by placing an epidural catheter early in labour.[55-60]

MATERNAL HYPER-PYREXIA

The cause of fever in labouring women receiving neuraxial analgesia is unclear. There are however, many theories. One such theory, is that an increase in maternal temperature is as a result of a non-infectious inflammatory process. Increases in maternal cytokine levels supports this theory. It is postulated that labour analgesia either starts or worsens this increase in maternal temperature.[55] Other studies by Frolich et. al., suggest that non-anaesthetic factors may play a role in increasing maternal temperature. These include Body Mass Index and time from rupture of membranes to delivery. This study did not observe an epidural effect on the change in maternal temperature.[56] There have also been some recent literature that suggest that epidural labour analgesia may be linked to intrauterine inflammation and that this maylead to neonatal neurologic injury.

BREASTFEEDING

There has always been controversy as to whether neuraxial analgesia hampers the initiation of successful breastfeeding. In a study by Beilin et.al. 177 healthy multiparous parturients with uncomplicated pregnancies were divided into three groups during labour and all received epidural analgesia.[21, 55, 68]

(i) Received no fentanyl in their epidural
(ii) Intermediate-dose fentanyl (150ug or less)
(iii) High dose fentanyl (more than 150ug)

Neonatal outcomes and breastfeeding outcomes were looked at by investigators. They found that 24 hours after delivery, the rate of difficulty with breastfeeding was similar between all the groups. At 6 weeks postpartum, a telephonic survey found that the mothers in the high dose group had the most difficulty with breastfeeding. Wilson et.al. published a trial involving 1054 healthy nulliparous pregnant patients who had uncomplicated pregnancies.

These patients were divided randomly into various groups:

(i) Control group – which received high-dose, bupivacaine-only labour epidural
(ii) Low-dose bupivacaine with fentanyl
(iii) Combined spinal-epidural with fentanyl
(iv) No neuraxial analgesia (351 patients)

In the group not receiving neuraxial analgesia, 151 received pethidine and 200 received other forms of analgesia or none at all.The investigators collected data on breastfeeding within 2-48 hours postpartum and 12months postpartum. The results showed that the group receiving pethidine had the most difficulty with breastfeeding. When comparing the epidural groups overall and the patients that had neither a neuraxial technique nor pethidine, there was no difference in the breastfeeding initiation rate. These two trials provide the only evidence that neuraxial labour analgesia does not significantly affect breastfeeding. Therefore, considering the evidence we can conclude that neuraxial labour analgesia using low dose local anaesthesic/low-dose fentanyl regime does not affect breastfeeding and should be offered to mothers wanting to breastfeed their babies.

RISK OF POST TRAUMATC STRESS DISORDER

One often hears the statement ‘‘pain never killed anyone’’ on the labour floor. Severe, prolonged pain may cause serious psychological and potentially physical damage to the parturient, however. In susceptible patients, the birth experience may trigger posttraumatic stress disorder. This disorder, characterized by fear, helplessness, and other psychological disturbances such as flashbacks, avoidance behaviour, and poor sleep, was first described among veterans of the Vietnam War.

Subsequently, it has been recognized in numerous traumatic settings, including childbirth. During the event, the person feels seriously threatened by death or severe injury and is often helpless to prevent it. Women are more susceptible to posttraumatic stress disorder if they suffered previous trauma. Although the exact incidence is unknown, predisposing factors include lack of consent for procedures, lack of a sense of control, and a sense of powerlessness. The incidence also is correlated with the amount of physical pain experienced.

The psychological impact of posttraumatic stress disorder can vary greatly; however, it may manifest in future pregnancies. Women may choose to have an abortion instead of reliving the experience of a vaginal delivery. Some women also request a caesarean delivery without ‘‘medical’’ indication. In one series, 30% of women who requested a caesarean section for personal reasons cited fear of excruciating, unrelieved pain as the reason. These women place themselves at higher risk than necessary because of their past traumatic experience.[55.60.65]

CONCLUSION

The amount of pain experienced by a woman during labour is influenced by many factors. Neuraxial labour analgesia has the potential to affect the course, duration and outcome of labour. Although there are known risks and side effects, there are many benefits and the problems are attributed to the technique without appropriate scientific assessment. Some observations, such as the increased use of forceps and prolonged second stage of labour, are associated with epidural analgesia, but there is not enough evidence to categorically state whether the technique caused the problems. These topics warrant continued investigation.

There is no single, universal way of managing labour pain that will fit all circumstances or fulfil every parturients needs. However, modern epidural techniques & medications have resulted in more consistent, predictable & effective analgesia during labour. There have recent advancements in new delivery systems and new drugs that allow us to provide safe and effective analgesia during labour. The use of low concentrations of local anaesthetics, combined with lipid-soluble opioids does not impede the progress of labour or depress the new-born. The addition of patient-controlled epidural analgesia and innovations using new technologies enhance patient satisfaction. Ultimately, it is each anaesthetist's responsibility to take into consideration all these factors and to provide the parturient safe and effective labour analgesia.

REFERENCES

1. Halpern SH, Leighton BL. Epidural analgesia and the progress of labour. In: Halpern SH, Douglas MJ, eds. Evidence-based Obstetric Anaesthesia Oxford, UK: Blackwell, 2005:10-22
2. Sharma SK, McIntire DD, Wiley J, Leveno KJ. Labour analgesia and caesarean delivery: an individual patient meta-analysis of nulliparous women. Anaesthesiology 2004; 100:142-8
3. Impey L, MacQuillan K, Robson M. Epidural analgesia need not increase operative delivery rates. Am J Obstet Gynecol 2000;182:358-63
4. Yancey MK, Pierce B, Schweitzer D, Daniels D. Observations on labor epidural analgesia and operative delivery rates. Am J Obstet Gynecol 1999;180:353-9
5. Segal S, Su M, Gilbert P. The effect of a rapid change in availability of epidural analgesia on the cesarean delivery rate: a meta-analysis. Am J Obstet Gynecol 2000;183:974-8
6. Johnsrud ML, Dale PO, Lovland B. Benefits of continuous infusion epidural analgesia throughout vaginal delivery. Acta Obstet Gynecol Scand 1988;67:355-8
7. Chestnut DH, Vandewalker GE, Owen CL, Bates JN, Choi WW. The influence of continuous epidural bupivacaine analgesia on the second stage of labor and method of delivery in nulliparous women. Anesthesiology 1987;66:774-80
8. Chestnut DH, Laszewski LJ, Pollack KL, Bates JN, Manago NK, Choi WW. Continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl during the second stage of labor. Anesthesiology 1990;72:613-8
9. Chestnut DH, Bates JN, Choi WW. Continuous infusion epidural analgesia with lidocaine: efficacy and influence during the second stage of labor. Obstet Gynecol 1987;69:323-7
10. Luxman D, Wolman I, Niv D, Cohen JR, Lottan M, Pauzner D, Groutz A, David MP. Effect of second-stage 0.25% epidural bupivacaine on the outcome of labor. Gynecol Obstet Invest 1996;42:167-70
11. Chestnut DH. Epidural anesthesia and instrumental vaginal delivery. Anesthesiology 1991;74:805-8
12. Torvaldsen S, Roberts CL, Bell JC, Raynes-Greenow CH. Discontinuation of epidural analgesia late in labour for reducing the adverse delivery outcomes associated with epidural analgesia. Cochrane Database Syst Rev 2004:CD004457
13. Comparative Obstetric Mobile Epidural Trial Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. Lancet 2001;358:19-23
14. Nageotte MP, Larson D, Rumney PJ, Sidhu M, Hollenbach K. Epidural analgesia compared with combined spinal-epidural analgesia during labor in nulliparous women. N Eng J Med 1997;337:1715-9
15. Bogod DG, Rosen M, Rees GA. Extradural infusion of 0.125% bupivacaine at 10 mL/hr to women during labor. Br J Anaesth 1987;59:325-30
16. Boutros A, Blary S, Bronchard R, Bonnet F. Comparison of intermittent epidural bolus, continuous epidural infusion and patient controlled-epidural analgesia during labor. Int J Obstet Anesth 1999;8:236-41
17. Smedstad KG, Morison DH. A comparative study of continuous and intermittent epidural analgesia for labour and delivery. Can J Anaesth 1988;35:234-41
18. van der Vyver M, Halpern S, Joseph G. Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. Br J Anaesth 2002;89:459-65
19. Zaric D, Nydahl P, Philipson L, Samuelsson L, Heirson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers. Reg Anesth 1996;21:14-25

20. Lacassie HJ, Habib AS, Lacassie HP, Columb MO. Motor blocking minimum local anesthetic concentrations of bupivacaine, levobupivacaine, and ropivacaine in labor. Reg Anesth Pain Med 2007;32:323-9
21. Beilin Y, Guinn NR, Bernstein HH, Zahn J, Hossain S, Bodian CA. Local anesthetics and mode of delivery: bupivacaine versus ropivacaine versus levobupivacaine. Anesth Analg 2007;105:756-63
22. Vallejo MC, Ramesh V, Phelps AL, Sah N. Epidural labor analgesia: continuous infusion versus patient-controlled epidural analgesia with background infusion versus without a background infusion. J Pain 2007;8:970-5
23. Halpern SH, Carvalho B. Patient-controlled epidural analgesia for labor. Anesth Analg 2009;108:921-8
24. Wong CA, Ratliff JT, Sullivan JT, Scavone BM, Toledo P, McCarthy RJ. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. Anesth Analg 2006;102:904-9
25. Lim Y, Sia AT, Ocampo C. Automated regular boluses for epidural analgesia: a comparison with continuous infusion. Int J Obstet Anesth 2005;14:305-9
26. Chua SM, Sia AT. Automated intermittent epidural boluses improve analgesia induced by intrathecal fentanyl during labour. Can J Anaesth 2004;51:581-5
27. Fettes PD, Moore CS, Whiteside JB, McLeod GA, Wildsmith JA. Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. Br J Anaesth 2006;97:359-64
28. Ralston DH, Shnider SM, DeLorimier AA. Effects of equipotent ephedrine, metaraminol, mephentermine, and methoxamine on uterine blood flow in the pregnant ewe. Anesthesiology 1974;40:354-70
29. Hall PA, Bennett A, Wilkes MP, Lewis M.Spinal anaesthesia for caesarean section: comparison of infusions of phenylephrine and ephedrine. Br J Anaesth 1994;73:471-4
30. LaPorta RF, Arthur GR, Datta S. Phenylephrine in treating maternal hypotension due to spinal anesthesia for caesarean delivery: Effects on neonatal catecholamine concentrations, acid base status and Apgar scores. Acta Anaethesiol Scand 1995;39:901-5
31. Moran DH, Perillo M, LaPorta RF, Bader AM, Datta S. Phenylephrine in the prevention of hypotension following spinal anesthesia for cesarean delivery. J Clin Anesth 1991;3:301-5
32. Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. Br J Anaesth 1996;76:61-5
33. Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002;94:920-6
34. Cooper DW, Carpenter M, Mowbray P, Desira WR, Ryall DM, Kokri MS. Fetal and maternal effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2002;97:1582-90
35. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. Br J Anaesth 2004;92:469-74
36. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and foetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology 2009;111:506-12
37. Ngan Kee WD, Khaw KS, Lau TK, Ng FF, Chui K, Ng KL. Randomised double-blinded comparison of phenylephrine vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective Caesarean section. Anaesthesia 2008;63:1319-26

38. Ngan Kee WD, Lee A, Khaw KS, Ng FF, Karmakar MK, Gin T. A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on foetal acid-base status and hemodynamic control. Anesth Analg 2008;107:1295-302
39. Dyer RA, Reed AR, van Dyk D, Arcache MJ, Hodges O, Lombard CJ, Greenwood J, James MF. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009;111:753-65
40. Hanss R, Bein B, Francksen H, Scherkl W, Bauer M, Doerges V, Steinfath M, Scholz J, Tonner PH. Heart rate variability-guided prophylactic treatment of severe hypotension after subarachnoid block for elective cesarean delivery. Anesthesiology 2006;104:635-43
41. Ueyama H, He YL, Tanigami H, Mashimo T, Yoshiya I. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective Cesarean section. Anesthesiology 1999;91:1571-6
42. Dyer RA, Farina Z, Joubert IA, Du Toit P, Meyer M, Torr G, Wells K, James MF. Crystalloid preload versus rapid crystalloid administration after induction of spinal anaesthesia (coload) for elective caesarean section. Anaesth Intensive Care 2004;32:351-7
43. Ko JS, Kim CS, Cho HS, Choi DH. A randomized trial of crystalloid versus colloid solution for prevention of hypotension during spinal or low-dose combined spinal-epidural anesthesia for elective cesarean delivery. Int J Obstet Anesth 2007;16:8-12
44. Dahlgren G, Granath F, Wessel H, Irestedt L. Prediction of hypotension during spinal anesthesia for Cesarean section and its relation to the effect of crystalloid or colloid preload. Int J Obstet Anesth 2007;16:128-34
45. Siddik SM, Aouad MT, Kai GE, Sfeir MM, Baraka AS. Hydroxyethylstarch 10% is superior to Ringer's solution for preloading before spinal anesthesia for Cesarean section. Can J Anaesth 2000;47:616-21
46. Morgan PJ, Halpern SH, Tarshis J. The effects of an increase of central blood volume before spinal anesthesia for cesarean delivery: a qualitative systematic review. Anesth Analg 2001;92:997-1005
47. Teoh WH, Sia AT. Colloid preload versus coload for spinal anesthesia for cesarean delivery: the effects on maternal cardiac output. Anesth Analg 2009;108:1592-8
48. Siddik-Sayyid SM, Nasr VG, Taha SK, Zbeide RA, Shehade JM, Al Alami AA, Mokadem FH, Abdallah FW, Baraka AS, Aouad MT. A randomized trial comparing colloid preload to coload during spinal anesthesia for elective cesarean delivery. Anesth Analg 2009;109:1219-24
49. Ngan Kee WD, Khaw KS, Ng FF. Prevention of hypotension during spinal anesthesia for cesarean delivery: an effective technique using combination phenylephrine infusion and crystalloid cohydration. Anesthesiology 2005;103:744-50
50. Reynolds F. Neurological infections after neuraxial anesthesia. Anesthesiology clinics 2008;26:23-52
51. Schneeberger PM, Janssen M, Voss A. Alpha-hemolytic streptococci: a major pathogen of iatrogenic meningitis following lumbar puncture. Case reports and a review of the literature. Infection 1996;24:29-33
52. Bacterial meningitis after intrapartum spinal anesthesia - New York and Ohio, 2008-2009. MMWR Morb Mortal Wkly Rep;59:65-9
53. Siegel J, Rhinehart E, Jackson M, Chiarello L, Committee' tHICPA. 2007 guidelines for isolation precautions: preventing transmission of infectious agents in healthcare settings. http://wwwcdcgov/ncidod/dhqp/gl_isolationhtml 2007
54. Hebl JR. The importance and implications of aseptic techniques during regional anesthesia. Reg Anesth Pain Med 2006;31:311-23

55. American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Practice Advisory for the Prevention, Diagnosis, and Management of Infectious Complications Associated with Neuraxial Techniques: A Report by the American Society of Anesthesiologists Task Force on Infectious Complications Associated with Neuraxial Techniques. Anesthesiology 2010;112
56. Kinirons B, Mimoz O, Lafendi L, Naas T, Meunier J, Nordmann P. Chlorhexidine versus povidone iodine in preventing colonization of continuous epidural catheters in children: a randomized, controlled trial. Anesthesiology 2001;94:239-44
57. Birnbach DJ, Meadows W, Stein DJ, Murray O, Thys DM, Sordillo EM. Comparison of povidone iodine and DuraPrep, an iodophor-in-isopropyl alcohol solution, for skin disinfection prior to epidural catheter insertion in parturients. Anesthesiology 2003;98:164-9
58. Cascio M, Pygon B, Bernett C, Ramanathan S. Labour analgesia with intrathecal fentanyl decreases maternal stress. Can J Anaesth 1997;44:605-9
59. Clarke VT, Smiley RM, Finster M. Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of foetal bradycardia? Anesthesiology 1994;81:1083
60. Nielsen PE, Erickson JR, Abouleish EI, Perriatt S, Sheppard C. Fetal heart rate changes after intrathecal sufentanil or epidural bupivacaine for labor analgesia: incidence and clinical significance. Anesth Analg 1996;83:742-6
61. Eberle RL, Norris MC, Eberle AM, Naulty JS, Arkoosh VA. The effect of maternal position on foetal heart rate during epidural or intrathecal labor analgesia. Am J Obstet Gynecol 1998;179:150-5
62. Palmer CM, Maciulla JE, Cork RC, Nogami WM, Gossler K, Alves D. The incidence of foetal heart rate changes after intrathecal fentanyl labor analgesia. Anesth Analg 1999;88:577 - 81
63. Abrao KC, Francisco RP, Miyadahira S, Cicarelli DD, Zugaib M. Elevation of uterine basal tone and foetal heart rate abnormalities after labor analgesia: a randomized controlled trial. Obstet Gynecol 2009;113:41-7
64. Landau R, Carvalho B, Wong C, Smiley R, Tsen L, Van de Velde M. Elevation of uterine basal tone and foetal heart rate abnormalities after labor analgesia: a randomized controlled trial. Obstet Gynecol 2009;113:1374
65. Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. Br J Obstet Gynaecol 2002;109:274-81
66. Van de Velde M, Teunkens A, Hanssens M, Vandermeersch E, Verhaeghe J. Intrathecal sufentanil and foetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. Anesth Analg 2004;98:1153-9
67. Wong CA, Scavone BM, Loffredi M, Wang WY, Peaceman AM, Ganchiff JN. The dose-response of intrathecal sufentanil added to bupivacaine for labor analgesia. Anesthesiology 2000;92:1553-8
68. Wong CA, Scavone BM, Slavenas JP, Vidovich MI, Peaceman AM, Ganchiff JN, Strauss-Hoder T, McCarthy RJ. Efficacy and side effect profile of varying doses of intrathecal fentanyl added to bupivacaine for labor analgesia. Int J Obstet Anesth 2004;13:19-24
69. Riley ET, Vogel TM, El-Sayed YY, Meyer PM, Cohen SE. Patient selection bias contributes to an increased incidence of foetal bradycardia after combined spinal-epidural analgesia for labor [abstract]. Anesthesiology 1999;91:S1054

NOTES