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The challenge with any technique of labour analgesia is to provide adequate pain control while minimizing the maternal and fetal adverse effects. Although epidural analgesia is chosen by parturients when available, it may be contraindicated for some and refused by others during labour. In many developing countries, systemic opioids are still offered as the analgesia of choice during labour as hospitals lack epidural facilities and the manpower to provide a 24 hour epidural service.

Pethidine is associated with a high incidence of side effects, such as nausea and sedation, as well as many adverse fetal and neonatal effects. So it is timely that Dr Nizar AJ, et al in their prospective trial, evaluated the analgesic efficacy of pethidine for labour pain relief. This well conducted randomised trial involving a large sample population demonstrated clearly that intramuscular pethidine, a commonly used analgesic in delivery, does not provide satisfactory pain relief throughout labour, pain scores were persistently high after initiating the analgesia and 63% of the patients still required supplementary analgesia.

In centres where there are sufficient resources to provide alternative forms of pain relief, the popularity of pethidine still remains high. The epidural analgesia is now widely accepted as the gold standard in the management of labour pain; as such, its availability is getting more widespread. However, persistent misconceptions and myths about its side effects could have prevented labour epidural pain relief from being more widely used by patients and obstetricians. Several randomised controlled trials and meta-analyses have shown that there is no causal relationship between epidural for relief and increased risk of caesarean section. There is also insufficient evidence to conclude that epidural is associated with a lower rate of spontaneous vaginal delivery. With obstetricians being more aware of the risks of instrumental delivery and modifying their obstetric management plan for patients on epidural for labour, this association is certainly weakening.

Labour pain is unique as it is intermittent in nature, increasing in frequency and intensity as labour progresses, before a significant reduction of pain immediately upon delivery. To match this pattern of pain, the introduction of a short acting opioid with a rapid onset such as remifentanil delivered via patient controlled intravenous analgesia (PCA) could be very desirable indeed. The use of remifentanil to provide pain relief in labour was first described in 1999. When compared with PCA pethidine, PCA remifentanil demonstrated significantly lower pain scores and improved neonate Apgar scores and Neurologic and Adaptive Capacity Scores. Certainly a large scale trial evaluating its feasibility as the mode of pain relief for patients with contraindications or refuse labour epidural is due.

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Challenges And Trend In Labor Analgesia

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Original Article
INTRAMUSCULAR PETHIDINE DURING LABOUR: DO WE PROVIDE ADEQUATE PAIN RELIEF?

ABSTRACT

Intramuscular pethidine for labour pain relief still remains as the most common option among parturient but its effectiveness in controlling labour pain and its effect on newborn has been poorly defined and seldom emphasized. This study aims to evaluate the analgesic effect of the standard dose of intramuscular (IM) pethidine comparing to standard epidural analgesia of ropivacaine with fentanyl for spontaneous labour pain. One hundred and ninety two uncomplicated full term multigravida women with tested pelvis in spontaneous labour were randomized to receive either epidural ropivacaine 0.2% with fentanyl 2 µg/ml or standard IM pethidine analgesia. Both techniques of labour analgesia were commenced during active phase of labour at cervical dilatation of 3-5cm. Epidural significantly provides better analgesia after 15 minutes and at full dilatation compared to IM pethidine groups (p=0.001) with 86% of them experiencing no motor block. Patient satisfaction was significantly higher in the epidural group (p= 0.001) with 84% of them opting for epidural analgesia for next delivery.

Keywords: Labour pain, Pethidine, Epidural ropivacaine with fentanyl, Pain score

INTRODUCTION

Epidural for labour is the most effective and safe labour analgesia and yet the utilization of this novel analgesic technique is still much lower compared with parenteral opioid. Parenteral opioids for labour pain relief still remain a common option for women world wide and have been subject of research for many years. A recent survey of obstetric anaesthetic practice in United State showed that the use of parenteral opioids for labour analgesia was 39% to 56% per 1500 number of births per year and a similar pattern is seen in United Kingdome. Intramuscular (IM) pethidine is the most common parenteral opioid that is advocated for labour pain despite numerous studies which have consistently cast doubt on its effectiveness for maternal pain relief and its effect on newborn. Of the many reasons being is that pethidine has the virtue of familiarity and low cost.

This practice is also partly attributed to the ongoing conflicting opinions about epidural labour among obstetricians. Despite the many advantages of labour epidural, some studies demonstrated prolonged
labour, increased risk of instrumental delivery and emergency cesarean section\textsuperscript{12,13}. As a result, some obstetricians prefer to advocate conventional IM pethidine as the analgesic of choice during labour. In some centres, the epidural service is unable to cope with the growing number of delivery and its demand for labour epidurals. In Hospital Universiti Sains Malaysia (HUSM), about 80\% of delivering mother will receive IM pethidine, 20\% will receive epidural and the remaining 10\% will choose other mode of analgesia.

Even though majority of parturient receives IM pethidine for their labour analgesia, its effectiveness in controlling labour pain and the effect on the newborn has been poorly defined\textsuperscript{6,7}. Previous study reported that IM pethidine provided poor pain relief during labour with maternal dissatisfaction as high as 71\% when compared to placebo (83\%)\textsuperscript{17}. Meanwhile IM pethidine was found to provide reasonable high pain score in term of Visual Analogue Score (VAS) compared to IM tramadol and IM nalbupine in several studies\textsuperscript{18,20,37}. In addition, most of these studies consistently revealed poor maternal satisfaction in term labour pain relief at 1 to 2 hour after administration of IM opioids.

The world wide practice has advocated that maternal request is sufficient indicator for labour pain relief\textsuperscript{9}. Since the practice of IM pethidine for labour pain is rampant and the need to alleviate labour pain is important, it is timely for us to re evaluate the effectiveness of IM pethidine in labour analgesia. This study is to determine the analgesic efficacy of standard IM pethidine when compared with epidural ropivacaine with fentanyl 2 mcg/ml in spontaneous labour pain among full term parturient.

**METHODODOLOGY**

This prospective, randomized controlled trial was conducted in HUSM from the year 2004 until 2005 after approval from Ethical Committee Board of University Sains Malaysia Health Campus, Kubang Kerian, Kelantan. 192 patients were randomized to receive either epidural ropivacaine or intramuscular pethidine for labour analgesia. A trained staff nurse would choose an envelope to allocate the patient randomly (close-envelope technique) to receive either epidural or IM pethidine as their mode of labour analgesia. Even though this study was meant to compare the effectiveness of two different methods of labour analgesia, single blind technique was achieved as the patients were unaware of the current practice for most effective labour analgesia (epidural).

Those women allocated for epidural analgesia received an IV fluids bolus of at least 500ml of Ringers’s Lactate solution. Lumbar epidural analgesia was achieved using an indwelling catheter inserted via 18 gauge Tuohy needle at L2L3 or L3L4 interspaces. A 3ml test dose of 0.2\% ropivacaine was given followed by bolus dose making the total dose of 12ml. This was followed by continuous epidural infusion of 0.2\% ropivacaine with 2mcg/ml fentanyl at 6-10ml/hr. After 15 minutes, effectiveness of analgesia was assessed by loss of sensation to pin prick up to T8 dermatome, whereas motor block was assessed by standard Bromage Scale as following.

<table>
<thead>
<tr>
<th>Bromage Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No motor block</td>
</tr>
<tr>
<td>1</td>
<td>Unable to raise extended leg, able to move knee and foot</td>
</tr>
<tr>
<td>2</td>
<td>Unable to raise extended leg or knee, able to move foot</td>
</tr>
<tr>
<td>3</td>
<td>Complete motor block</td>
</tr>
</tbody>
</table>

Women allocated to intramuscular pethidine group were given 75-100mg pethidine with 25mg of promethazaine hydrochloride at the first request for pain relief. Additional 75mg of pethidine were given upon further request up to a maximum of 300mg in 4 hours. The patients were instructed to self administer entonox gas by inhaling through a face mask for rescue medication when they still had pain despite maximum dose of IM pethidine or epidural ropivacaine.

The parturient were put on left lateral position after the procedures and with continuous external electronic fetal heart monitoring on board. Maternal blood pressures (BP) were recorded every 3 minutes for 15 minutes then every 30 minutes until delivery. Intravenous fluid (normal saline) and Ephedrine 3mg IV were given to treat hypotension (Systolic BP< 90mmHg).
For the objective tool of the pain measurement, a linear 100mm visual analogue pain scale was used in all women after 15 minutes of analgesic techniques and during delivery (second stage). Satisfaction with labour pain relief was determined within 24 hours after delivery using a four-point scale of excellent, good, satisfactory or poor which has been given score of 4, 3, 2 and 1 respectively.

A total parturient of 192 were needed for the study, based on Pocok’s formula which will provide more than 80% power with 95% level of confidence after taking 48% of women are dissatisfied with opioid for labour analgesia. All data were analyzed using SPSS program version 11.0. Non categorical and categorical data were analyzed using independent t-test and chi-square test respectively with P value < 0.05 considered to be significant.

Inclusion criteria were laboring women, ASA I-II, gravida 2-5 with tested pelvis, spontaneous onset of labour, age between 18-40 years old, singleton fetus with cephalic presentation, presenting with cervical dilatation of 3-5 cm, height > 150cm, weight < 100kg, and finally good working epidural (VAS of 30mm and below after 15 minutes administration of ropivacaine epidurally). Exclusion criteria were bad obstetric history, post date, history of allergy to local anaesthetic, patient refusal, failed epidural and those who had contraindications for epidural analgesia.

RESULTS

There were no significant differences in demographic data (Table I) between the two groups. Comparing between these two methods of analgesia, epidural ropivacaine significantly provided better analgesia after 15 minutes (mean VAS at 15 min. was 11.3 mm vs. 68.6 mm, p=0.001) and at full dilatation (25.1 mm vs. 94.4 mm, p= 0.001) (Table 2). Besides, patient satisfaction mean score in epidural group was much higher and statistically significant (3.17 vs 1.53, p = 0.001) whereby 84% of patient from epidural group opted for epidural analgesia for next delivery. Calculated mean dose of IM pethidine in this study was 103.0 ± 5.6 mg, however 63% of them utilized entonox gas for their rescue medication. None of the patients from epidural group received entonox gas for rescue medication. In epidural group, we also noted that 85% of patients experienced completely no motor block (Bromage score of 0) and 13% of them had Bromage Score 1. No difference in neonatal outcomes as shown by Apgar score at 1 and 5 minutes (p= 0.001). This study also showed that there was significant increase in instrumentation delivery in Epidural group (p = 0.008) but there was no significant increase in cesarean section delivery between the two groups (p = 0.187) (Figure 1).

DISCUSSION

In the year of 2000 American College Of Obstetrics and Gynecology (ACOG) and American Society Of Anesthesiology (ASA) have jointly endorsed and reiterated their belief that maternal request is a sufficient medical indication for pain relief during labour8. To date, epidural analgesia for labour is recognized as the most effective labour analgesia9.

Table 1: Demographic Characteristics Of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Epidural (n=94)</th>
<th>Pethidine (n=98)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>86 (91.5%)</td>
<td>96 ((98.0%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Non Malay</td>
<td>8 (8.5%)</td>
<td>2 (2.0%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Age</td>
<td>28.7 ± 5.6</td>
<td>29.5 ± 5.1</td>
<td>0.309</td>
</tr>
<tr>
<td>Height</td>
<td>155.9 ± 5.5</td>
<td>157.3 ± 6.1</td>
<td>0.104</td>
</tr>
<tr>
<td>Weight</td>
<td>64.5 ± 10.6</td>
<td>62.6 ± 7.0</td>
<td>0.139</td>
</tr>
<tr>
<td>Cervical dilatation</td>
<td>3.7 ± 0.71</td>
<td>3.85 ± 0.78</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation
and yet the practice of epidural analgesia for labour has not exceeded the practice of parenteral opioids as the main labour analgesia in our centre. With regards to parenteral opioid, one systemic review reported by Harmer M and Rosen M (1996) emphasized that maternal satisfaction and quality of pain relief were inconsistent in women given parenteral opioid for labour analgesia.\(^1\)

Even though the quality of labour pain relief is believed to be poor, parenteral opioids particularly IM pethidine is still the favorite option among obstetrician as it is associated with shorter duration of labour, less oxytocin augmentation, fewer fetal head malposition and instrumentation vaginal delivery\(^54,56\). In addition, epidural labour is associated with prolongation of duration of labour and increase in instrumentation and operative delivery were cited ranging from 2.2 to 25% based on various meta analysis reports\(^3,16,19\).

Only 192 parturient whom met the strict 10 inclusion criteria were enrolled into this prospective study. This figure meets the requirement to achieve 80% power with 95% level of confidence by assuming 48% of women are dissatisfied with opioid for labour analgesia\(^1\). Comparing between the two methods of analgesia, epidural ropivacaine with fentanyl significantly provided better analgesia after 15 minutes (mean VAS at 15 min. was 11.3 mm vs. 68.6 mm, \(p=0.001\)) and at full dilatation (25.1 mm vs. 94.4 mm, \(p=0.001\)) (figure 2). IM pethidine provided insufficient analgesia with high mean VAS for both phases during VAS measurement undertaken. These findings were compounded by significantly low maternal satisfaction among IM pethidine group compared with epidural group with mean satisfaction score at 1.53 vs 3.17 respectively. Satisfaction score among parturient in epidural group is significantly higher with 84% of them opted for epidural labour for next delivery \(p=0.001\). This finding is somewhat predictable as the results are keeping with current evidences of epidural as the most effective labour analgesia\(^8\).

High mean VAS in IM pethidine group during two phases of measurement (68.6mm and 94.4mm) suggested intractable pain that has to be addressed seriously during process of labour. Allowing patient to be in persistent pain after maternal request for pain relief is incompatible with ACOG recommendation. Unfortunately the practice of IM pethidine for labour

### Table 2: Progress of labour in term of Pain score, Satisfaction Score and Apgar Score and Modes of delivery between Epidural and Pethidine group.

<table>
<thead>
<tr>
<th>Progress of Labour</th>
<th>Epidural n = 94</th>
<th>Pethidine n = 98</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain Score (VAS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS at 15 minutes</td>
<td>11.3 ± 3.7</td>
<td>68.6 ±14.2</td>
<td>0.001</td>
</tr>
<tr>
<td>VAS at full dilatation</td>
<td>25.1 ± 15.3</td>
<td>94.4 ±13.5</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Satisfaction Score</strong></td>
<td>3.17 ± 0.77</td>
<td>1.53 ±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Apgar Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 at 1 minutes</td>
<td>1 (1.1%)</td>
<td>1 (1.0%)</td>
<td>0.976</td>
</tr>
<tr>
<td>7 at 5 minutes</td>
<td>1 (1.1%)</td>
<td>0 (0.0%)</td>
<td>0.306</td>
</tr>
<tr>
<td><strong>Vagina delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>72 (76.6%)</td>
<td>89 (90.8%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Instrumentation</td>
<td>11 (11.7%)</td>
<td>2 (2.1%)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>LSCS</strong></td>
<td>11 (11.7%)</td>
<td>7 (7.1%)</td>
<td>0.187</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± standard deviation.

\(^*\) Intramuscular Pethidine During Labour: Do We Provide Adequate Pain Relief?
pain is currently still predominant in many hospitals worldwide. Ideally the individual efficacy of IM pethidine has to be compared with placebo in order to evaluate its effectiveness in controlling labour pain. Previously only one placebo-controlled trial was suitable and reviewed. As expected, significantly more women were dissatisfied in placebo group. Even though IM pethidine provided some ‘pain relief’, maternal dissatisfaction in IM pethidine group compared to placebo group was comparably high and statistically not significant (71% vs 83%)\(^\text{17}\). Nevertheless, our study was meant to compare objectively the quality of analgesia (VAS) along with maternal satisfaction between IM pethidine with epidural analgesia which is recognized as the best method for labour analgesia.

The selection of analgesic dose for IM pethidine is matter of concern in order to deliver effective labour analgesia. Previous studies revealed that higher IM pethidine dose conferred greater benefit for labour analgesia. In this study, the mean dose of IM pethidine was 103.0 ±5.6 mg at injection dose ranging from 75-175 mg in total. This was considered an adequate dose, comparable with previous studies citing pain relief at dose up to 80-100mg of IM pethidine\(^\text{33,38}\). Reportedly, even though pain score and the need for further analgesia were noticeably less in higher IM pethidine dose group, the maternal dissatisfaction remained high up to 65% of the patients. However, some of these studies were under powered as the sampling size were considerably small (\(n = 20-57\))\(^\text{33,38}\). In our study, 192 patients were enrolled which met 80% power of study at 95% confident interval. Therefore the fact that IM pethidine provides inadequate labour analgesia and greater maternal dissatisfaction should be emphasized.

Intravenous pethidine is another possible option. Reportedly, there was a small unblinded trial comparing intravenous with IM pethidine cited in 2005. It showed that there was significantly lower overall pain score during labour in the intravenous group and significantly more IM pethidine group used Entonox (5% vs 40%, \(p = 0.04\)) for supplementary analgesia\(^\text{39}\).

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**Fig.1:** Modes Of Delivery In Relation To Type Of Labour Analgesia

![Modes Of Delivery In Relation To Type Of Labour Analgesia](image)

**Intramuscular Pethidine During Labour: Do We Provide Adequate Pain Relief?**
Neonatal outcome is often a matter of concern when advocating parenteral opioid for labour analgesia. Previous studies emphasized that parenteral opioid is likely to cross placenta leading to neonatal respiratory depression. Previous studies comparing two different methods of administering pethidine analgesia showed no different in neonatal Apgar Score at 5 minutes

39, whereas another trial comparing two different doses of IM pethidine revealed no significant difference in Apgar Score and incidence of neonatal resuscitation

38. These findings support our finding that there is no difference neonatal outcome between epidural group and pethidine group.

Our study also reveal that epidural ropivacaine with fentanyl is likely to increase instrumental delivery rate by 9.6 % (vacuum or forcep). These findings are in keeping with some of previous randomized trial which demonstrated that the risk of instrumental delivery will be increased by up to two fold in epidural group

3,11. Attention has to be paid to the significant increase in instrumentation delivery in epidural group, as it may result in an increase in maternal trauma (vaginal laceration) which may lead to rectovaginal fistula and increase neonatal risk

12.

Though the incidence for cesarean delivery is relatively higher in the epidural group (11.7% vs 7.1%) but statistically was not significant (p=0.187). On the other hand, the rate of cesarean section was found not to be increased in epidural labour group despite noticeable prolongation of duration of labour and increase in instrumentation delivery. The similar findings have been cited and published from previous large prospective randomized trials comparing nulliparous women who received either epidural bupivacaine or IM pethidine for labour analgesia

9,14,15.

CONCLUSIONS

IM pethidine at dose of 75-175mg provides inadequate labour analgesia with high maternal dissatisfaction compared with standard epidural ropivacaine of 0.2% with fentanyl 2 mcg/ml.

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REFERENCES


INTRODUCTION

Uterine contraction causing “Labor Pain” is a dynamic process that requires variable amount of analgesia through different stages. Epidural analgesia is considered the most effective technique for labor pain relief in modern anesthesia practice. Generally it provides complete relief of pain in 75-85% of parturient and incomplete but sufficient relief in another 10-15%. Thus a total of 90-95% of parturient are satisfied with this procedure.

The reported failure rate even with experienced anesthesiologist may be as high as 8%. This may
be attributed to poor technique or due to abnormal placement of epidural catheter despite a successfully placed epidural needle. Epidural catheter related problem includes blocked, kinked, or bend catheters and migration through an intervertebral foramen or into an epidural vein, subdural & the subarachnoid space. Inadequate pain relief has been reported due to catheter related problems in 1.5–23% of laboring women. Position of women during epidural catheter placement has also been identified as an important factor. In a previous study of a large obstetric population, the distance from skin to the epidural space was found greater when blocks were performed in the lateral position compared with in the sitting position, the reasons for this is unclear. Among the many reasons of failed epidural (inadequate pain relief), catheter related problems are considered the most important.

In current practice there is a great controversy as to the length of epidural catheter that should be left in epidural space to avoid catheter related complications and to provide effective labor pain relief. Inserting epidural catheters 3-4 cm may result in an increase incidence of migration of the catheter out of the epidural space while a greater catheter length increases the likelihood of unilateral blockade or intravenous cannulation. In a few clinical trials, 2-5 cm epidural catheter in space was found to adequately provide satisfactory labor analgesia. However, in other studies, inserting lumbar epidural catheter more than 3 cm increases the risk of transforaminal escape. In spite of the increasing use of epidural block, the optimal length of catheter in epidural space has not been evaluated. This study is designed to compare the quality of pain relief with different lengths of epidural catheter in epidural space for laboring women.

METHODS

The study was conducted after approval from our institutional ethical review committee. A total of 90 primigravida women aged between 20-40 yrs, with cervical dilatation of 2.5-3 cm and having contractions of at least once every 5 minutes were included in our study. Consent refusal, multigravida women, obese women with weight more than 85 kg, women with any co-morbid, with any contraindication of regional anesthesia and with history or allergy to local anesthetic were excluded from the study.

This was a prospective double blinded randomized controlled study. Block randomization technique was used I.e.10 blocks of 9 patients. In group A: 3cm, group B: 5cm and group C: 7 cm of catheter was threaded into the epidural space. The patient and an independent trained observer or nurse who recorded the pain score were blinded to the patient’s group assignment.

After written consent, women in active labor and fulfilling the inclusion criteria were enrolled and randomly allocated in the study groups. All patients were preloaded with crystalloid solution. Baseline heart rate and blood pressure (B.P) were recorded. The epidural was performed with the patient in sitting position at (L3-L4 / L4-L5) with a 16/18-gauge tuohy needle, using the loss of resistance to air technique. A multi-orifice epidural catheter was threaded through the cephalad directed epidural needle to a length base on their group assignment. Women in Group A had the epidural catheter threaded 3 cm, Group B 5 cm and Group C 7 cm, into the epidural space. The catheter was then secured with transparent dressing and the patient placed in the supine position with left lateral uterine displacement. An independent trained observer or labor room nurse was then called for data collection.

For the study we defined intravenous catheter, as catheter from which blood could be aspirated or that was associated with neurological symptoms after the administration of test dose of local anesthetic. Intrathecal catheter was defined, as catheter from which CSF could be aspirated or that was associated with motor block after administration of test dose. Unilateral sensory analgesia was defined as any epidural catheter associated with more than 2 dermatome sensory disparities and associated with patient’s discomfort. Epidural catheter dislodgement was defined as any catheter that functioned well and subsequently ceased to function in spite of additional epidural boluses. Failed epidural in our study was defined as an epidural which never gave pain relief after the first dose of epidural.

After catheter insertion and negative aspiration for blood or cerebrospinal fluid, the catheter was tested with a 2 ml of 2% plain lidocaine for intrathecal test dose (clinical signs of motor blockade) followed by 5 ml of 2% plain lidocaïne for intravenous test dose. The presence of clinical signs of an intravascular
Effects of length of epidural catheter in epidural space on labor pain relief

Injection were sought by asking the patient whether she felt dizzy, had tinnitus, or had a metallic taste in her mouth. This was followed by establishment of T10 block with first bolus of 10-12 ml of 0.25% bupivacaine and 50μg fentanyl. One hour after the establishment of block at T10, 12-15 ml/hr infusion of bupivacaine 0.0625% + 2 μg/ml fentanyl was initiated for the course of labor. During the establishment of epidural block if systolic blood pressure fell more than 25% from the baseline or less than 90mm Hg, ephedrine 5-10 mg IV boluses were given. Maternal heart rate that was less than 50 beats/min and compromising the blood pressure was also treated with atropine 0.5-1mg IV bolus. Patients with unilateral motor block were managed as per departmental protocol for pain management (withdrawing or resiting the catheter), failed epidural was excluded from the study. During the course of labor, analgesia was assessed by asking the patient whether she felt any pain during contractions. She was told to indicate only if she had pain but not pressure feeling. Simple verbal numerical rating scale (0-10, 0: no pain and 10: severe pain) was used for pain score.

Sensory level assessment was done with ice and motor block assessment with 0-3 point scale. [0(none): full flexion of knees and feet, 1(partial): just able to move knees and feet, 2(almost complete): able to move feet only, 3(complete): unable to move feet or knees] The presence of unilateral sensory analgesia was confirmed by using an ice cube to look for difference in cold perception. Confirmed unsatisfactory sensory blockade (epidural catheter dislodgement) was also being assessed as defined earlier.

Pain score, sensory and motor block were monitored at base line (T1), then after test dose (T2) at first epidural bolus (T3), 5 min after that (T4) then 10 mins after (T5) and then subsequently ½ hourly until the baby deliver. On each ½ hourly visit, if the independent observer found 2 segments regression from T10 level or pain score of >2 or if patient herself complained of pain then additional bolus of 5ml of 0.25% Bupivacaine was given and recorded. The patient was monitored until the baby delivers vaginally or the decision of the cesarean section was made.

All the complications mentioned earlier like intravascular or intrathecal catheter placements, unilateral block and failed epidural were also recorded. After the delivery, all patients were interviewed by one of the investigators regarding overall pain management and their satisfaction score graded as excellent/good/satisfactory/unsatisfactory.

Data was double entered in epidata software by two different data operators. Data entry was verified by re-looking at 5% of the questionnaire manually. For analysis purpose data was converted into SPSS version 13.0. Cross tabulation using chi-square for categorical variables like number of episodes of hypotension, bradycardia, unilateral cannulation and patient’s satisfaction used. Analysis of variance was used to see the association of continuous variable like age, weight, mean pain score mean duration of labor by groups. Kaplan Meir test was also used for pain recurrence and sensory level recurrence time.

**RESULTS**

Total of 90 patients were entered in the trial with 30 patients in each group. One patient from Group A was excluded from the study due to failed epidural. All 3 groups were matched for demographic characteristics and duration of labor (Table 1).

Mean pain scores were comparable. In Group A, 63% of all mean pain scores reading fell in a category of mild pain (<2 on pain score), compare to 81% in Group B and 78% in Group C, the difference was statistically insignificant. The difference was also not statistically significant among pain score reading for moderate (Pain score 3-6) and severe (Pain score of >6) pain categories. (Graph 1)

For sensory level regression a statistically significant difference was found with an earlier regression in Group A and a longer sensory block regression time in Group B (log rank x²=30.426; d =2 p-value < 0.001) (Table II). Motor block assessment on 0-3 scale found no differences among all three groups (P value> 0.05).

The highest number of additional local anaesthetic boluses was found in group A and lowest in group B, the difference was statistically significant (Table III). Hypotension was observed in four patients in Group A and one in Group C while bradycardia was reported in only one patient in Group A. These findings are statistically insignificant. In group C,
7 out of 30 patients had resulted in unilateral blockade causing inadequate pain relief (statistically significant p<0.001). These cases were managed as per protocol mentioned earlier (ethical reason) in order to improve pain relieve (Graph II).

No intravenous, or intrathecal catheter placement or epidural catheter dislodgement was observed. No statistically significant difference was found for patient’s satisfaction among the three groups (P value 0.394).

**DISCUSSION**

The epidural analgesia for labor in current clinical practice is achieved by correct placement of the epidural catheter in epidural space. However a suboptimal positioning of the epidural catheter is not a common occurrence in clinical practice and if occurs, results in inadequate pain relief during labor12.

Previous radiographic studies regarding placement of catheter in the epidural space showed that blind
epidural technique using loss of resistance with air or saline did not ensure the correct positioning of the epidural catheter. Sachez et al using radiographic studies also demonstrated that 53% of all epidural catheters did not follow the course in which they were directed. They recommended that if the patient had incomplete epidural analgesia, radiography should be used to determine the location of the catheter\textsuperscript{13}. This is not feasible and difficult to carry out for women in labour. On the other hand, it is practical to measure length of catheter left into the epidural space for making epidural successful.

In our study we evaluated the effects of placing three different lengths of epidural catheter in the epidural space. We found overall mean pain score trends were similar in all 3 groups. In group A additional number of boluses of local anesthetic were required to maintain pain relief. This increased bolus requirement could be due to suboptimal position in the epidural space. Regression of 2 dermatomal sensory block was also reported much earlier in this group than group B and group C. This also showed that small length of epidural catheter is not suitable for local anesthetic solution distribution for labor pain relief requiring extended block (T10-S4). It is

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensory level regression time (in minutes)</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>91.910</td>
</tr>
<tr>
<td>B</td>
<td>315.091</td>
</tr>
<tr>
<td>C</td>
<td>257.253</td>
</tr>
<tr>
<td>Overall</td>
<td>227.370</td>
</tr>
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</table>

**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>30.426</td>
<td>2</td>
</tr>
</tbody>
</table>

*Test of equality of survival distributions for the different levels of Group. df= degree of freedom*

<table>
<thead>
<tr>
<th>Treatment Groups.</th>
<th>Mean no. of Boluses</th>
<th>95% confidence interval for Mean</th>
<th>P-value.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound.</td>
<td>Upper bound.</td>
</tr>
<tr>
<td>A</td>
<td>2.59</td>
<td>1.92</td>
<td>3.25</td>
</tr>
<tr>
<td>B</td>
<td>1.03</td>
<td>0.63</td>
<td>1.43</td>
</tr>
<tr>
<td>C</td>
<td>1.65</td>
<td>1.13</td>
<td>2.04</td>
</tr>
</tbody>
</table>

*Group A = 3cm
Group B = 5cm
Group C = 7cm*
also possible that the multi-orifice catheters, sited at 3cm in our study, might have been dislodged enough (i.e. 1-1.5cm) that the proximal hole was no longer in the epidural space. This finding is consistent with the result of the study by Bhiston et al. who found that catheter has a tendency to both migrate further into and out of the epidural space after they had been secured. They found that 22% of the catheters migrated more than 1cm out of the epidural space and recommended that catheters must be inserted more than 3cm into the epidural space14.

In our study the incidence of hypotension is highest in Group A which is probably due to increased number of local anesthetic boluses. This also showed that length of catheter is important determinant for symmetrical distribution of local anesthetic drugs for desired dermatome in labor through continuous epidural infusion.

Current literature supports that threading too much catheter into the epidural space can direct catheter right or left rather in the middle of the space. In addition there may also be increase chances of intravenous cannulation10. In our study no intravenous cannulation was observed in either group, however the incidence of unilateral cannulation was 23% in group C. For ethical reasons we did intervention (withdrew or resited catheter) when they complained of severe unilateral pain in the first stage of labor, and as a result, the mean pain score reading analysis were comparable.

In our study, patients in group B received less number of boluses and took more time for regression of sensory level resulting in delayed pain recurrence time. This group required no intervention in comparison with group A (additional boluses given) and group C (2 cm length of the catheter withdrawn). This group showed consistent pain relief during labor as evident from highest number of pain score reading in the mild pain category and lowest in the severe pain category.

Previous studies have shown different incidence of epidural catheter migration with different lengths of catheter. Phillips and Macdonald’s studied 100 patients and found that 46 of the epidural catheters migrated by 1cm or more. Out of them 31 catheters migrated by more than 0.5cm inwards and 15 catheters migrated by more than 0.5cm outwards whatever lengths of epidural catheter sited in epidural space15. Considering this unavoidable migration of 0.5cm- 1cm in both inward and outward direction, 5cm catheter length seems appropriate as compared to 3 or 7cm.

**Graph II:** Distribution of Unilateral Cannulation among Patients by Treatment Groups

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Group A = 3cm</th>
<th>Group B = 5cm</th>
<th>Group C = 7cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral Cannulation (%)</td>
<td>100</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>

\( \star = P\text{-value} <0.001 \)
Relationships between migration of epidural catheter and BMI, migration of epidural catheter and body weight and migration of epidural catheter and depth to the epidural space had also been examined in the literature. It is possible that a large amount of subcutaneous fat may affect the accuracy of readings of depth of catheter by allowing more indentation or tenting of the skin along the catheter exit site, or it may allow greater relative movement between the skin exit site and the point of entry into the supraspinous ligament. This would allow greater migration into or out of the epidural space or allow more catheter to coil up in the subcutaneous tissue. Narang and Linter found that unilateral blockade was more likely if there was a deep epidural space because of the greater chance of positioning the epidural catheter laterally within the space\(^\text{12,16}\). In our study we did not measure the epidural space depth. However, in all three groups height and weight were similar but unilateral block happened in-group C (7cm) so we could not establish the relationship of bodyweight and migration. They also suggested that insertion of more than 3cm of catheter in epidural space would reduce the number of failure of analgesia and our study findings also support this\(^\text{12,16}\).

D’Angelo et al had done study similar to our study but using the single orifice catheter while we used multi orifice catheter\(^\text{10}\). Our study results are not consistent with their study where 2cm length has the highest frequency of successful block than 8cm. Obviously, threading the multi-orifice catheter used in our study 2cm into the epidural space, as recommended cannot be expected to produce a satisfactory block. Considering the overall findings of our study and supporting literature available, an epidural catheter length of 5cm in epidural space is a more appropriate choice than 3cm and 7cm.

ACKNOWLEDGEMENT

We would like to extend our thanks to Dr. Khalid Siddiqui, Mr. Iqbal Azam, Mr. Hamza Akram and Mrs. Zohra I Khan for their great support for the completion of our work.

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Original Article

COMPARISON BETWEEN STANDARD AND SEQUENTIAL COMBINED SPINAL EPIDURAL ANAESTHESIA FOR LOWER LIMB SURGERY

C.Y. Teoh*, F. S. K. Lim**, M. Maaya***.

ABSTRACT

Sequential combined spinal-epidural (CSE) block was compared with Standard CSE block for lower limb surgery in term of quality of surgical anaesthesia and haemodynamic stability. Sixty patients with ASA classification I or II, aged between 20 and 65 years were randomised into a sequential CSE (n = 30) and a standard CSE (n = 30) group. In the sequential CSE group, 1.5 ml of 0.5% hyperbaric bupivacaine was injected into the subarachnoid space via the long 27G Pencan spinal needle. In the standard CSE group, 3.0 ml of 0.5% hyperbaric bupivacaine was injected in the same way. The reduction in mean arterial blood pressure (MAP) was significant in both groups compared to their respective baseline values (p<0.05). The difference in blood pressure reduction between the two groups were shown to be significant (p<0.05). 10% of patients in sequential group as compared to 40% of patients in standard group needed treatment for hypotension (p<0.05). Mean Visual Analogue Scale (VAS) score was significantly higher for sequential group as compared to standard group but analysis using clinical indicator (VAS < 2 versus VAS ≥ 2) for determining quality of analgesia found no difference between the two groups. Number of patients needing rescue measure for poor quality analgesia was four in the sequential group and one in the standard group which was statistically insignificant. Our data suggested that sequential CSE technique provided better haemodynamic stability while providing adequate and supplemental intraoperative analgesia for patients undergoing lower limb surgery.

Keywords: Spinal; Epidural; Combined spinal epidural; sequential technique.

INTRODUCTION

Combined spinal epidural (CSE) anaesthesia offers the advantages of a spinal block (excellent operating condition with dense sensory and motor blockade, rapid onset, lower drug dose) with the additional advantage of an indwelling epidural catheter (possibility of supplementary doses to prolong analgesia and postoperative analgesia) while minimizing their respective disadvantages. In particular, for spinal anaesthesia the ultimate level of central neural blockade is much more difficult to control and predict, and thus the risk of high sympathetic blockade and associated haemodynamic changes is much higher compared to epidural anaesthesia.

Recently there has been a trend especially in obstetric anaesthesia to use sequential CSE with a low initial spinal dose of bupivacaine, and subsequent administration of fractionated doses of 0.5% plain

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bupivacaine through the epidural catheter until the desired level of blockade is achieved. But to date there are not many studies which evaluate sequential CSE technique in lower limb surgery.

This study was designed to investigate the haemodynamic stability and the quality of anaesthesia rendered by sequential CSE technique using a low initial intrathecal dose of 0.5% heavy bupivacaine as compared to the standard CSE technique where full dose of intrathecal bupivacaine was given at the onset.

MATERIALS AND METHODS

Sixty patients, aged between 20 to 65 years, ASA I or II, scheduled for orthopaedic lower limb surgery under CSE were selected and randomly allocated into two groups. Approval from institutional ethics committee and informed consent from patient were obtained. Randomization was achieved using sealed envelopes numbered 1 to 60, each envelope containing one of two codes: “standard” or “sequential”. Patients who had contraindications for or who refused regional anaesthesia, with concomitant injury (e.g. head or abdominal injury), and who had suffered significant blood loss were excluded from the study. No premedication was given preoperatively and no sedation was given for the first hour after administration of CSE.

Prior to performing the procedure, patient’s baseline blood pressure (BP) and heart rate were recorded. An 18G intravenous cannula was inserted and 500 ml of Hartmann solution infused over 10 minutes to preload the patient. Heart rate, ECG and peripheral oxygen saturation were monitored continuously and non-invasive blood pressure (NIBP) was measured at 1-minute intervals for the first 10 minutes after spinal injection was given and at 5-minute intervals subsequently throughout the surgery.

The CSE block was performed by a single operator, using standardised CSE set (BD Durasafe plus™). With the patient in the sitting position, an 18G Tuohy needle was introduced into the epidural space at L2-L3 or L3-L4 lumbar interspace under aseptic technique, using the loss of resistance to saline method and a midline approach. Through the epidural needle, a long 27G Whitacre spinal needle was introduced into the subarachnoid space. After obtaining a free flow of cerebrospinal fluid (CSF), 3.0 ml of 0.5% heavy bupivacaine was administered into the subarachnoid space for the standard group, and 1.5 ml of 0.5% heavy bupivacaine was used for the sequential group. The spinal needle was subsequently withdrawn and a 20G multi-orifice epidural catheter was inserted through the Tuohy needle 5 cm into the epidural space for both groups. The patient was then returned to supine horizontal position after the Tuohy needle had been removed and the catheter secured in place.

After subarachnoid injection, the level of sensory blockade was assessed at 5-minute intervals by determining loss of sensation to pin prick using a 25G hypodermic needle, with the aim of achieving at least a level of T10 blockade after 10 minutes. In the event where the block did not reach T10 level in 10 minutes, it was extended by fractionated doses of 0.5% plain bupivacaine given via the epidural catheter. One ml of 0.5% plain bupivacaine was used to aim for extension of one segment of dermatome, with maximum of 3 ml given every 5 minutes until T10 blockade was achieved.

After the procedure was performed patient was given 5L/min oxygen via facemask. Hypotension (defined as decrease in systolic BP of > 20% and / or systolic BP < 100 mmHg) when occurred was treated with fluid infusion and boluses of ephedrine (6 mg each dose).

Patient’s haemodynamic changes were monitored and recorded every minute for the first 10 minutes and every 5 minutes thereafter. Final level of sensory blockade was determined prior to commencement of the surgery, and the time taken from the injection of spinal bupivacaine to the time when a blockade of T10 level was achieved was recorded. The quality of analgesia was assessed by showing the patient a Visual Analogue Scale (VAS) with the range of 0 to 10 (0 = no pain; 10 = worst possible pain), and asking the patient to quantify the severity of pain experienced by giving a number within the range shown. The VAS score was recorded before the CSE block and at 15-minute intervals from the time of skin incision for 60 minutes. In the event where quality of analgesia was unsatisfactory during surgery, appropriate rescue measures in the form of epidural fentanyl, intravenous fentanyl or epidural 0.5% plain bupivacaine were instituted, failing which general anaesthesia was administered.
Sample size was calculated based on type one error of 0.05 and power of 0.8. Patients’ age, weight and height were analysed using Student t-test. Gender and race were analyzed using Chi-square test. Patients’ haemodynamic changes were analysed using ANOVA, and patients’ VAS score was analysed using Mann-Whitney U and Chi-square test. A p < 0.05 was considered statistically significant.

RESULTS

Demographic data are shown in Table I. There were no significant differences between the two groups with regards to age, height, weight, race, gender and ASA classification.

Haemodynamic changes within the first 30 minutes were compared within and between groups. Baseline systolic (SBP), diastolic (DBP) and mean arterial blood pressure (MAP) did not differ between the two groups (Table I). There were significant reductions in systolic, diastolic and mean arterial blood pressure in both groups after institution of CSE block (Figure 1). The greatest reduction in blood pressure were observed in the first 8 minutes during which 3 patients in the sequential CSE group as compared to 12 patients in the standard CSE group needed ephedrine boluses and fluid resuscitation. This difference was statistically significant (p < 0.05). Thereafter SBP, DBP and MAP stabilized to a level which was significantly lower than the baseline values. The standard CSE group experienced a much steeper reduction in SBP, DBP and MAP, and had stabilised blood pressures which were significantly lower as compared to the sequential group.

Within group comparison of baseline MAP versus lowest MAP showed that there was significant reduction in the MAP for both standard and sequential group after institution of CSE (p < 0.05). Comparison between the 2 groups showed that the actual drop in the MAP was significantly greater in the standard CSE group compared to sequential CSE group (p < 0.05).

Mean cephalad spread of sensory block at 10 minute was T12 (range T11 to L1) for sequential group and T7 (range T6 to T8) for standard group (p < 0.05). At 10 minute after the block was performed, 27 patients in the sequential group, as compared to 3 patients in the standard group, did not attained T10 level and needed fractionated doses of epidural bupivacaine. At 30 minutes after the block, the mean cephalad spread of the sensory block was T8 (range T6 to T10) in the sequential CSE group and T5 (range T4 to T6) in the standard CSE group (p < 0.05).

**TABLE I:** Demographic data and baseline blood pressure.

<table>
<thead>
<tr>
<th></th>
<th>Sequential CSE group (n = 30)</th>
<th>Standard CSE group (n = 30)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>38.7 ± 16.0</td>
<td>41.7 ± 15.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.4 ± 7.6</td>
<td>166.5 ± 6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.6 ± 10.9</td>
<td>67.1 ± 15.5</td>
</tr>
<tr>
<td>Race (Malay:Chinese:Indian)</td>
<td>21:8:1</td>
<td>18:12:0</td>
</tr>
<tr>
<td>ASA (I:II)</td>
<td>19:11</td>
<td>20:10</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>18:12</td>
<td>22:8</td>
</tr>
<tr>
<td>Baseline Systolic BP (mmHg)</td>
<td>135.1 ± 16.0</td>
<td>139.8 ± 11.8</td>
</tr>
<tr>
<td>Baseline Diastolic BP (mmHg)</td>
<td>82.0 ± 9.2</td>
<td>80.9 ± 9.7</td>
</tr>
<tr>
<td>Baseline Mean BP (mmHg)</td>
<td>99.7 ± 10.2</td>
<td>100.4 ± 9.2</td>
</tr>
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</table>

Data are presented as Mean ± SD
The quality of analgesia was compared between groups using the VAS score. No significant differences were shown in the baseline VAS score for both groups, but the VAS scores were significantly higher in the Sequential group at 15, 30, 45 and 60 minutes (p < 0.05, Figure 2).

However, during the study we noticed that patients who reported a VAS score of less than 2 usually experienced mild degree of pain, discomfort or pressure sensation which did not require any rescue measure other than reassurance. Hence if a VAS score of less than 2 could be considered as good quality analgesia for surgery, the difference in the number of patients with good analgesia (i.e. VAS < 2) between the 2 groups was statistically insignificant at 15-minute, 30-minute, 45-minute and 60-minute, as illustrated in Table II.

Four patients in the sequential group and one patient in the standard group needed rescue treatment for inadequate analgesia. This was shown to be not significant statistically. All 5 patients were given rescue treatment during the first 15 minutes. One was given IV fentanyl, and four were given epidural fentanyl.

**DISCUSSION**

Ever since its introduction by Soresi in 1937 and subsequently modified by Curelaru, Brownridge, Coates and Mumtaz et al, the CSE anaesthesia technique has gained much popularity over the years. It has been successfully used for many kinds of surgery, especially for obstetric and orthopaedic procedures.

The CSE block results in profound and uniformly distributed analgesia with good muscle relaxation as well as the possibility of peri- and postoperative supplements. An insufficient block during surgery may be extended via the epidural top ups to a satisfactory level and maintained throughout surgery. Various mechanisms have been proposed to explain the rapid extension of spinal block when it was extended by epidural top-ups. Rawal et al, Leach et
al8, Bernards et al9 and Hodgkinson10 postulated that transfer of local anaesthetic through the dura hole made by the spinal needle assist in the extension of the spinal block. However Blumgart et al 11 and Takiguchi et al12 showed that the extension of spinal blockade occurred primarily by a cephalad shift of the intrathecal local anaesthetic caused by compression of the dural sac by the epidurally injected solution. This volume effect notion is supported by the observation that in pregnant or obese patients, the dose requirement for spinal block is reduced due to compression of the dural sac by the engorged venous plexus secondary to increased intraabdominal pressure.

In this study, we compared haemodynamic changes and quality of analgesia between two different ways of administering a CSE block. It was shown that even though both groups had a significant reduction in BP as compared to their respective baseline values, the standard group showed a more significant reduction in systolic, diastolic and mean BP as compared to the sequential group. This could be explained by the fact that the standard group had a significantly higher

<table>
<thead>
<tr>
<th>Table II: Analysis of VAS scores between 2 groups at 15, 30, 45 and 60 min.</th>
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<tbody>
<tr>
<td>N=30</td>
</tr>
<tr>
<td>VAS &lt;2</td>
</tr>
<tr>
<td>15 minutes</td>
</tr>
<tr>
<td>30 minutes</td>
</tr>
<tr>
<td>45 minutes</td>
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<tr>
<td>60 minutes</td>
</tr>
</tbody>
</table>

Data are presented as number of patients.
level of sensory and possibly sympathetic blockade as compared to the sequential group. The result is consistent with data from a previous study carried out in obstetric patients\(^1\). Our study also showed that 10% of patients in the sequential group as compared to 40% in the standard group needed treatment for significant hypotension, the difference was shown to be clinically and statistically significant. The CSE technique makes it possible to combine the advantages of both spinal and epidural anaesthesia, while minimizing the disadvantages of both. By using a small initial subarachnoid dose of local anaesthetic and followed by controlled epidural extension of the block to the desired level of anaesthesia, excessive sympathetic blockade (with its undesirable haemodynamic effects) and intercostal paralysis can be avoided\(^1\). This effect can be achieved by using a considerably smaller amount of local anaesthetic as compared to an epidural block, which in turn reduces the risk of systemic toxicity of the local anaesthetic\(^7\), \(^13\), \(^14\). These advantages make CSE especially useful for caesarean section\(^7\), \(^13\), \(^14\), \(^15\), \(^16\) and high risk patients.

Some authors suggested that initial spinal dose should be reduced in CSE technique as it has been shown that CSE often produces a more extensive block than expected for a stipulated spinal dose of local anaesthetic\(^7\), \(^13\). Kumar\(^16\) postulated that the subatmospheric pressure in the epidural space is alleviated by the insertion of the Tuohy needle, which in turn reduces the volume of the dural sac. Subsequent injection of same volume of local anaesthetic intrathecally would thereby spread further rostrally and extend the level of blockade. The result suggests that the initial dose of spinal heavy bupivacaine (15 mg) could be reduced in the standard group, as suggested in the study by Schneider et al\(^17\) where they found that using a first dose of 7.5mg bupivacaine 0.5% via continuous spinal catheter produced adequate anaesthetic level in patients undergoing lower limb surgery.

The use of VAS scoring system to assess intraoperative pain relief has been criticised for being too subjective and unreliable. Nonetheless it has been used widely for that purpose and some had used it successfully to assess intraoperative analgesia\(^18\), \(^19\). We used VAS score to assess intraoperative analgesia and found that in terms of absolute score, the sequential group had significantly higher mean value as compared to the standard group for the whole hour of study period after institution of CSE block. But looking at the number of patients requiring rescue measure for poor quality analgesia intraoperatively, we found that 4 patients in the sequential group (one with VAS 2, one VAS 3, two VAS 5) required rescue fentanyl whereas only 1 patient in the standard group (VAS 5) needed rescue measure in the first 15 minute, and the difference was shown to be statistically insignificant.

We also noticed that for all patients who reported VAS score of less than 2, the pain sensation were considered mild and tolerable and patients were quite happy for the surgery to be carried on without any supplementation. A VAS score of 2 was a grey area where one patient requested supplementation while others were quite happy with it. VAS score of above 2 consistently required supplementation.

We also noticed that subsequent to the rescue measure instituted at 15 minute, there were no significant differences in the VAS scores at 30 minute, 45 minute and 60 minute between the two groups. One reason that might explain the similarity of the quality of analgesia at a later stage is that the epidural bupivacaine boluses given to extend the spinal block at the onset would have started to work after 30 minutes, which would complement the existing spinal block.

At one glance our study did suggest that while sequential CSE technique improved haemodynamic stability in patients, it did it at the expense of providing good quality analgesia intraoperatively (or at least until rescue measure was instituted). This is contrary to the study done by Thoren et al\(^1\) on caesarean section patients. Whereas there is no doubt that our study showed a much improved haemodynamic profile in the sequential group, there is some uncertainty in the way which we should interpret our VAS result. Analysing it numerically yielded a statistical significant result whereas interpreting it using clinical parameters yielded insignificant conclusion. Perhaps a larger sample size may yield a more conclusive result.

One explanation for the observation noted in our study is that the much less spinal dose of heavy bupivacaine used might have resulted in a block that was less dense. But in the event when the quality of analgesia was deemed poor and inadequate, rescue
measures, in particular epidural fentanyl, could be used successfully to overcome the apparent downside of the sequential technique. Perhaps another way of improving the quality of the block would be to add opioids such as fentanyl or sufentanil into the initial spinal bupivacaine18.

CONCLUSIONS

Both standard and sequential CSE technique provided adequate intraoperative anaesthesia after appropriate supplementation when needed. However, patients under the sequential CSE group demonstrated significantly better haemodynamic stability.

REFERENCES

INTRODUCTION

Benzodiazepines (BZDs) have a prominent role in anesthesia for their anxiolytic and amnesic effects. Increasing doses of BZDs increase receptor occupancy and produce a progressive spectrum of effects from anxiolysis and anticonvulsant effects to amnesia, sedation and eventually hypnosis & anesthesia. Induction with midazolam occurs less rapidly than other intravenous (IV) induction agents but amnesia is more reliable.

BZDs have a specific pharmacological antagonist; flumazenil (FML). It is a competitive antagonist which is known to rapidly and reliably reverse sedation, respiratory depression and amnesia caused by BZD. The possible indications of FML include the diagnostic and therapeutic reversal of BZD agonists. The clearance of FML being high, it has relatively short elimination half life. Thus a high proportion of receptors may again get occupied by agonists, increasing the potential for re-sedation. In some reports, a very high dose of FML (1mg/kg) was

ABSTRACT

We aimed at evaluating the effect of low dose flumazenil in therapeutic reversal of residual effects of midazolam including amnesia, incidence of re-sedation and other side effects.

After institutional ethics committee approval and informed consent, 120 adult female patients posted for minor gynaecological procedures were randomly included in the study. All received fentanyl 2µg/kg intravenous (IV) 3 min before induction of anesthesia with increments of IV midazolam until loss of eyelash reflex. Anaesthesia was maintained with nitrous oxide in oxygen by face mask or laryngeal mask airway and supplemented with midazolam when required. Reversal with flumazenil (FML) was started on shifting patients to recovery room. After an initial bolus of 0.2mg FML, increments of 0.05mg were repeated every 2 minutes until patients began supporting their airway without an oropharyngeal airway.

Flumazenil caused dependable reversal of residual effects of midazolam but with significant sparing of anterograde amnesia (> 50% of patients). Re-sedation was not seen in any patient. Other side effects were minimal. Average FML dose required was 0.35 mg (Approx. 0.007 mg/kg).

When administered in a titrated fashion, flumazenil caused a dependable reversal of residual effects of midazolam, even in low doses. The amnesia (mainly anterograde) was not reversed in > 50% patients.

Implication: Dependable reversal of effects of midazolam by a relatively low dose of flumazenil was studied. We observed that anterograde amnesia was not reversed in many patients, which can be exploited to the benefit of patients in terms of side effects and treatment cost.

Keywords: Midazolam, flumazenil, amnesia: anterograde.
used to reverse the respiratory depression caused by agonist\(^1\).

However, there are now evidences of differential reversal effects on different agonistic actions\(^2\). In presence of high doses of agonists; FML in low doses is expected to attenuate the deep CNS depression i.e. loss of consciousness and respiratory depression but may not abolish the agonist effects that occur at low fractional receptor occupancy, such as, drowsiness and amnesia. Although reversal of respiratory depression and deep sedation in the post-operative period is desirable, reversal of amnesia induced by BZD may not be so. Thus, we hypothesized that the FML in a low dose may spare the amnesia caused by midazolam while reliably reversing other effects of midazolam.

Our study aimed at finding out the efficacy of low dose FML in reversing the residual effects of midazolam (used for induction of anaesthesia) including amnesia and the incidence of re-sedation and other side effects.

**MATERIAL AND METHODS**

We conducted a prospective, randomized, double blind, placebo-controlled study at S. S. University Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi after obtaining approval from institutional ethics committee and informed consent of all participating patients.

120 adult female patients of ASA grade I and II undergoing minor gynaecological procedures such as examination under anaesthesia, dilatation and curettage, and diagnostic laparoscopy were recruited for the study. Patients with history of drug abuse, allergy to opioids or benzodiazepines, seizure disorder, chronic liver disease or any underlying neuropsychiatric disorder were excluded from study. The patients were randomly allocated into two groups - A & B of 60 each, with an aid of an independent observer (the OT attendant in front of the pre-operative area nurse) drawing lots, thus blinding the anesthesiologists, gynecologists as well as the patients. The attendants were blinded as they would simply take out one envelope out of a box filled with both A & B envelopes. The patients in group A received flumazenil and those in group B received placebo (saline) for the reversal of residual effects of midazolam.

None of the patients received any benzodiazepine or narcotic the day before the procedure. All were given IV fentanyl 2µg/Kg, 3 min before induction of general anesthesia (GA). Patients were induced with incremental doses of midazolam until the loss of eyelash reflexes. Anesthesia was maintained with nitrous oxide in oxygen (2:1) by face mask or laryngeal mask airway (LMA) and supplemented with additional doses of midazolam when patient movements were observed. After the completion of the procedure, the patients were shifted to the recovery room (RR) with supplemental oxygen by face mask. The oropharyngeal airway was left in place if patients tolerated it. Patients requiring additional drugs or endotracheal intubation were excluded from the study.

The reversal of the residual effects of midazolam was started immediately after shifting patients to the RR with either flumazenil or placebo as per the group of the patient. The group A patients was given 0.2mg IV FML as the initial dose. If needed, 0.05mg of FML was repeated every 2 min until patients began supporting their airway without an oropharyngeal airway and maintained this thereafter for 3 min. This was then taken as the end point of FML treatment. The maximum dose of FML was limited to a total of 0.50mg.

Patients were assessed for sedation, amnesia, ventilatory adequacy, and side effects, if any, just before and at 5 min, 30 min, 60 min, and 120 min intervals after giving FML or placebo. These observation times were chosen for ease of observation and calculation. Moreover, 120 minutes was chosen as last observation on the basis of approximate 2 hour duration of effect of an I.V. bolus of midazolam, i.e., to exclude the possibility of any re-sedation after flumazenil which has a relatively shorter duration of effect.

The sedation was assessed using the Observers Assessment of Alertness/Sedation Score (OAA/S) (Table 1). Amnesia for both anterograde and retrograde memory was tested at all time intervals. The anterograde amnesia was tested by assessing the memory of the place and surrounding and to the events occurring in the operating (OR) and the recovery rooms (RR). Patients were asked to recall
their spouse and/or parents’ names, dates and toy animals (shown to them just before starting induction with midazolam) to test the retrograde amnesia. The patients’ ventilatory status was assessed by checking whether the patients could maintain their airway or not, could produce effective cough, and by measuring oxygen saturation (SaO₂).

RESULTS

Two patients in group A and 1 patient in group B needed endotracheal intubation due to inability to maintain a patent airway after induction of anaesthesia. Accordingly, these were excluded from the study. There was no difference among the groups in age, weight, duration of anesthesia and dose of midazolam used (Table 2) (P>0.05). Although the percentage of sedated patients (OAA/S score≥3) were comparable before administering FML/saline in both the groups, significantly less patients remained sedated (OAA/S score≥3) at all observation times, except at 60 min in group A compared to group B patients (Table 3). Similarly the incidences of retrograde and anterograde amnesia before administering FML/saline were comparable between the two groups. While the percentage of patients with retrograde amnesia were significantly lower in group A at 5 & 30 min after FML administration compared

Table 1: Observer’s assessment of alertness/sedation score

<table>
<thead>
<tr>
<th>Patient’s Condition</th>
<th>Sedation Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully awake, oriented and anxious</td>
<td>1</td>
</tr>
<tr>
<td>Drowsy, eyes open but not anxious</td>
<td>2</td>
</tr>
<tr>
<td>Drowsy, eyes closed but arousable to command</td>
<td>3</td>
</tr>
<tr>
<td>Drowsy, eyes closed arousable to mild physical stimulus</td>
<td>4</td>
</tr>
<tr>
<td>Asleep, unrousable to mild physical stimulation</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2: Patient characteristics. Values are means (SD).

<table>
<thead>
<tr>
<th>Study Group (A) N=58</th>
<th>Control Group (B) N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>29 (11.5)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>46.5 (9.5)</td>
</tr>
<tr>
<td><strong>Duration of Anaesthesia</strong> (min)</td>
<td>21.8 (2.2)</td>
</tr>
<tr>
<td><strong>Dose of midazolam</strong></td>
<td>5.4 (1.07)</td>
</tr>
<tr>
<td><strong>Dose of midazolam (mg/kg)</strong></td>
<td>0.094 (0.03)</td>
</tr>
<tr>
<td><strong>Dose of flumazenil (mg/patient)</strong></td>
<td>0.35 (0.11)</td>
</tr>
<tr>
<td><strong>Dose of flumazenil (mg/kg)</strong></td>
<td>0.007 (0.003)</td>
</tr>
</tbody>
</table>

*Duration of anaesthesia = from the beginning of induction of anaesthesia to the administration of the drug (flumazenil / placebo).

Data presented as Mean (SD)
to group B, percentage of patients with anterograde amnesia were comparable between groups A & B at all observation time points (Table 4). The incidence of retrograde or anterograde amnesia in group A was comparable before administering FML, but the incidence of retrograde amnesia remained significantly higher than anterograde amnesia at all points of time after FML administration (Table 5A). The incidence of retrograde amnesia at different points of time showed a significant decrease (Table 5B) after FML as compared to that before the administration of FML. In contrast, there was no significant difference in the incidence of anterograde amnesia at any time points after the administration of FML compared to that of before FML administration (Table 5B).

Table 3: Level of sedation at different time intervals

<table>
<thead>
<tr>
<th>Sedation (Score ≥ 3)</th>
<th>Group A (n=58)</th>
<th>Group B (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Before</td>
<td>53</td>
<td>91.37</td>
</tr>
<tr>
<td>5 min</td>
<td>12</td>
<td>20.68</td>
</tr>
<tr>
<td>30 min</td>
<td>7</td>
<td>12.06</td>
</tr>
<tr>
<td>60 min</td>
<td>4</td>
<td>6.89</td>
</tr>
<tr>
<td>120 min</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* p value<0.05

Table 4: Amnesia Assessment

<table>
<thead>
<tr>
<th>Parameters assessed</th>
<th>Group A Patient percentage at different intervals (n=58)</th>
<th>Group B Patient percentage at different intervals (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Just before</td>
<td>At 5 min</td>
</tr>
<tr>
<td>Re-calling Names and dates*</td>
<td>65.50</td>
<td>13.79</td>
</tr>
<tr>
<td>Re-calling Toy animals*</td>
<td>75.86</td>
<td>25.86</td>
</tr>
<tr>
<td>Orientation to place#</td>
<td>84.48</td>
<td>75.86</td>
</tr>
<tr>
<td>OR stay and RR events#</td>
<td>82.75</td>
<td>67.24</td>
</tr>
</tbody>
</table>

Data presented as percentage of patients

* Jointly test retrograde amnesia; # Jointly test anterograde amnesia.

OR = Operating Room; RR = Recovery Room
There was significant improvement in the ventilatory status at 5 min after administering FML whereas this improvement was minimal in the control (B) group (Table 6). After 30 min of administration of the drug, there was no statistically significant difference in the ventilatory status of both groups (Table 6). We observed a significant increase in the SaO2 in group A compared to group B patients after 5 min of administration of the drug/placebo, but not thereafter. The SaO2 level reached to pre-operative value in 100% of patients after 60 minutes in both the groups (Table 7).

Among side effects observed in the post operative period, the postoperative nausea and vomiting (PONV) increased significantly in group A patients 5 min after administering FML. In group B, incidence of PONV decreased gradually with time. There was slight increase in the incidence of uneasiness after giving FML but this was not consistent. Incidence of irritability was also higher in group A compared to group B patients (Table 8).

**DISCUSSION**

The results of the study suggested that IV flumazenil in low doses (0.007±0.003mg/kg) can effectively antagonize the sedation, respiratory depression and retrograde amnesia caused by IV midazolam but may leave the anterograde amnesia caused by the latter intact. As FML remains a fairly expensive drug, this low dose of FML provided a cost effective therapy for the potentially harmful complications of midazolam.

Our study demonstrated that a low dose FML can effectively reverse the sedation caused by midazolam within 5 min of administration. This concurred with Rodriguez et al3, who showed that FML was able to reverse immediately the effects of midazolam with

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**Table 5-A:** Showing Z-test of proportionality between retrograde and anterograde amnesia at different observation times in the study group.

<table>
<thead>
<tr>
<th>Type of amnesia</th>
<th>Just before</th>
<th>5 min</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde amnesia*</td>
<td>70.68</td>
<td>18.96</td>
<td>13.79</td>
<td>3.44</td>
<td>3.44</td>
</tr>
<tr>
<td>Anterograde amnesia#</td>
<td>82.75</td>
<td>70.69</td>
<td>68.96</td>
<td>67.24</td>
<td>55.17</td>
</tr>
<tr>
<td>Z - test</td>
<td>1.643</td>
<td>5.689</td>
<td>6.129</td>
<td>7.348</td>
<td>6.225</td>
</tr>
<tr>
<td>NS</td>
<td>≤ 0.001</td>
<td>≤ 0.001</td>
<td>≤ 0.001</td>
<td>≤ 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as percentage of patients

* Includes the testing of recalling names and dates and of toy animals.
# Includes the testing of orientation to place, OR stay and RR events.

**Table 5-B:** Comparison of retrograde with anterograde amnesia in the study group at different time intervals

<table>
<thead>
<tr>
<th>Just before Vs 5 min</th>
<th>Just before Vs 30 min</th>
<th>Just before Vs 60 min</th>
<th>Just before Vs 120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrograde amnesia</td>
<td>5.689</td>
<td>6.379</td>
<td>7.654</td>
</tr>
<tr>
<td>Anterograde amnesia</td>
<td>1.643</td>
<td>1.934</td>
<td>2.029</td>
</tr>
</tbody>
</table>

p= < 0.001

Data presented as percentage of patients
average reversal time of 1.22+ 0.42 minutes, and also of EL-Attar et al⁴, who reported a rise in the central nervous system function scores to almost the baseline awake values soon after administering FMZ. In addition, we observed that relatively lower dose of FML used by us was not associated with any incidence of re-sedation for upto 2 hours after giving FML. This finding has been supported by previous studies including that of Kankaria et al⁵, who reported full psychomotor function restoration within 30 min in 79% of the patients with no re-sedation upto 3 hours.

Results of our study showed that the amnesia for short term memory and anterograde events was spared by low dose FML; while retrograde amnesia was largely abolished at 60 min. The anterograde amnesia persisted in larger number of patients (31.67 to 58.33%) even after 120 min of giving FML, but the incidence of retrograde amnesia was largely

---

**Table 6: Patients’ ventilatory status at different time intervals**

<table>
<thead>
<tr>
<th>Observations</th>
<th>Group A Patient percentage at different intervals (n=58)</th>
<th>Group B Patient percentage at different intervals (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Just before</td>
<td>At 5 min</td>
</tr>
<tr>
<td>Can cough and cry</td>
<td>43.10</td>
<td>86.20*</td>
</tr>
<tr>
<td>Maintain airway</td>
<td>62.06</td>
<td>100.0*</td>
</tr>
<tr>
<td>Airway needed attention**</td>
<td>37.93</td>
<td>00.05*</td>
</tr>
</tbody>
</table>

* p value<0.05 ** Requiring either manual airway support or an oropharyngeal airway.
Data presented as percentage of patients

**Table 7: SaO2 Levels: Patient percentage**

<table>
<thead>
<tr>
<th>Observations</th>
<th>Group A Patient percentage at different intervals (n=58)</th>
<th>Group B Patient percentage at different intervals (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Just before</td>
<td>At 5 min</td>
</tr>
<tr>
<td>SaO2 in pre-operative range (100-97%)</td>
<td>63.79</td>
<td>87.93*</td>
</tr>
<tr>
<td>&lt; 5% fall in SaO2</td>
<td>22.41</td>
<td>12.06*</td>
</tr>
<tr>
<td>&gt; 5% fall in SaO2</td>
<td>15.51</td>
<td>00.00</td>
</tr>
</tbody>
</table>

Data presented as percentage of patients
* p value<0.05
reduced to a range of 6-7%. However, our study with a higher incidence of residual amnesia after reversal with FML was in contrast to most other studies on FML, including that of Kankaria et al, who found no significant anterograde amnesia in 78% of the patients receiving FML after midazolam. Likewise Tsang et al, also reported that the FML effectively reversed anterograde amnesic effects of BZDs following trans-esophageal echocardiography. On the contrary, the retrograde amnesia was not reversed by FML. Takano et al, noticed only retrograde amnesia after midazolam with nitrous oxide inhalation, which was not reversed with FML.

However, it is often desirable that anterograde amnesia persists in patients undergoing various procedures under sedation as many intra-operative events, conversations or feelings may not be very pleasant for the patient to remember. Sparing of anterograde amnesia caused by midazolam may save patients from unpleasant recall of experiences in the OR and RR etc.

There was a noticeable improvement in the ventilation of our patients within 5 min of giving FML. This finding concurred with the finding of a previous canine model study which concluded that FML administration was effective in reversing the midazolam induced respiratory depression by multiple routes, intravenous being the fastest. Our study was also supported by Oshima et al, who measured nasal resistance to breathing and found that FML abolished the increase in nasal resistance caused by midazolam. Pepperman, studied reversal of midazolam induced sedation and the effect on weaning from ventilation in the intensive care unit with FML. The study concluded that the patients receiving FML were weaned from ventilator and extubated significantly earlier than those receiving placebo. These studies were in accordance with our finding of reversal of sedation and respiratory depression after FML, but our study differed from the others, in that our finding of the show the effectiveness of even a relatively low dose of FML.

Upon IV administration, FML is eliminated almost entirely by hepatic metabolism to inactive products with a half life of about 1 hour. The duration of clinical effects is thus brief, usually persisting for only 30-60 min. Hence, we observed our patients for 120 minutes to look for re-sedation.

The most common side effect seen in our patients was PONV. Other side effects observed were restlessness and irritability but with lower incidence than PONV. The side effects seen in our study were far lesser than those reported in studies using higher doses of FML. Thus, FML in low dose was devoid of troublesome side effects reported with higher doses.

### Table 8: Recovery Room Events

<table>
<thead>
<tr>
<th>Observations</th>
<th>Group A Patient percentage at different intervals (n=58)</th>
<th>Group B Patient percentage at different intervals (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Just before</td>
<td>At 5 min</td>
</tr>
<tr>
<td>PONV</td>
<td>20.68</td>
<td>37.93*</td>
</tr>
<tr>
<td>Restlessness</td>
<td>00.0</td>
<td>8.62*</td>
</tr>
<tr>
<td>Irritability</td>
<td>1.72</td>
<td>5.17</td>
</tr>
<tr>
<td>Violent behavior</td>
<td>00.0</td>
<td>00.0</td>
</tr>
</tbody>
</table>

Data presented as percentage of patients

PONV = Postoperative nausea and vomiting, * p value<0.05
We concluded that even in low doses the flumazenil caused a dependable reversal of residual effects of midazolam, such as undue sedation, respiratory depression and retrograde amnesia. Although the anterograde amnesia was spared in such doses as used by us, re-sedation and other agonistic effects were not seen. Thus we can infer that when needed, flumazenil is useful in reversing the most harmful effects of midazolam even in a relatively smaller dose. Moreover, the remaining anterograde amnesia was not only harmless, it may save the patients from unpleasant memories of their stay in the operating and recovery rooms, reduce the treatment cost, and avoid the troublesome side effects of a full dose.

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**Original Article**

THE EFFECTS OF ONDANSETRON PRETREATMENT ON PAIN DURING INJECTION OF MEDIUM - AND LONG - CHAIN TRIGLYCERIDE PROPOFOL EMULSIONS


**ABSTRACT**

Propofol formulated with medium- and long-chain triglycerides (MCT/LCT) causes less pain on injection than standard propofol, but the incidence of pain persists between 28 and 67 percent. Such a broad range begs the question so we wanted to clarify whether the ondansetron pretreatment results in any clinically significant decrease of pain on injection of propofol-MCT/LCT. We conducted a randomized, prospective, double-blinded study to compare the effectiveness of ondansetron to placebo on pain caused by propofol-MCT/LCT at the injection site. This study included 192 non-premedicated ASA I-II adult patients scheduled for elective surgery under general anaesthesia. Patients were allocated randomly into two groups to receive either normal saline or ondansetron 4 mg intravenously with a 1-min venous occlusion, followed by propofol-MCT/LCT. The patients were observed and graded for any associated pain using a four-point scale. The overall incidence of pain on injection was 24/96 (25%) in the ondansetron group vs. 37/96 (38%) in the control group. The difference in the incidence of pain on injection between groups failed to achieve statistical significance (p = 0.12) and no significant difference in intensity of pain between the two study groups occurred. We conclude that the ondansetron pretreatment does not significantly reduce the incidence or severity of the pain on injection of propofol-MCT/LCT.

**Keywords:** anesthesia, pain on injection, propofol

**INTRODUCTION**

Injection pain, a well-known adverse effect of propofol, is reported to occur in 28%-90% of the patients.1-3 A number of techniques has been used to minimize propofol-induced pain with variable results.3 Lidocaine pretreatment is the most popular method for reducing this pain, but pain on injection of propofol is not completely eliminated and continues to be a problem.3

Propofol formulated in medium- and long-chain triglyceride (MCT/LCT) with similar pharmacokinetics and efficacy as standard propofol,4 is thought to cause less pain on injection, but the incidence of pain still ranges from 28% to 67%.5-7

Ondansetron, a specific 5-HT antagonist, is a commonly used antiemetic drug which has demonstrated some local anaesthetic property, but few studies have evaluated the utility of ondansetron for reducing propofol-induced pain on injection of conventional propofol-LCT.8-9 There is no published study to date in the literature that uses ondansetron to reduce the incidence and severity of pain associated with propofol – MCT/LCT injection. Therefore, the authors conducted a randomized, double-blinded controlled study to determine whether the ondansetron pretreatment further decreases the pain of propofol – MCT/LCT injection.

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METHODS

After obtaining ethical committee approval, 192 patients were included in this study, each aged 18–60 yr, ASA physical status I or II, and undergoing an elective surgical procedure under general anaesthesia. Written informed consent was obtained from all patients. Patients with a neurologic or cardiovascular disorder, history of drug abuse, or egg lecithin or soybean oil allergies, as well as patients breast feeding at the time of surgery, taking sedatives or analgesics within 24 hr preceding surgery or requesting anxiolysis, were excluded from participating in this study. No premedication was given.

Using a computer–generated table of random numbers, patients were allocated randomly by sealed envelope into two groups to receive either 2 ml normal saline or ondansetron (4 mg) IV pretreatment, followed by anaesthetic induction with Propofol – MCT / LCT (Propofol-Lipuro® ; B Braun, Melsungen, Germany). The solutions were prepared by a nurse anaesthetist in unlabelled syringes according to group allocation. As the physical appearances of the two study drugs are identical, the anaesthesia providers and an investigator recording was unaware of the propofol formulation. In this study, we used one investigator for avoidance inter-observer variation and bias.

On arrival in the operating room, routine monitors were applied to patients, for recording heart rate, mean arterial blood pressure, ECG and oxygen saturation values. All patients were cannulated with a 20-gauge venous cannula at the dorsum of the hand, and flushed with 10 ml of normal saline over 5s to ensure pain–free injection. The patients were also prepared for the study and asked to indicate the pain experienced during injection of anaesthetics, classifying its intensity as “none, mild, moderate and severe”.

Each patient was preoxygenated via a facemask with a fresh gas flow of 6 L/min oxygen for 3 min. The study drug was injected over 5s while venous occlusion was applied to the midarm using a rubber tourniquet for 1 min. The occlusion was then released and the patients received one quarter of the total calculated dose of propofol over 5s. During the propofol injection, patients were continuously observed for vocal response, facial grimacing, arm withdrawal, or tearing, suggesting severe pain. Pain was graded using a four-point scale : 0 = no pain, 1 = mild pain (pain reported only in response to questioning without any behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning), and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tearing).10-11 After assessment of pain, induction of anaesthesia was continued as per routine practice. Fentanyl was administered only after induction of anaesthesia. Within 24 h after operation, the injection site was checked for pain, edema, wheal, and flare response by a nurse anaesthetist who was unaware of which drug had been administered.

In a previous study5, the incidence of injection pain following the administration of propofol – MCT / LCT was 38% . A sample size calculation indicated that 96 patients per study group would be needed to detect a statistically significant difference between our two study groups with 80% power, assuming an incidence of pain on injection of 20% in the Propofol - MCT / LCT pretreatment with ondansetron group. Student’s unpaired t-tests were used in comparisons between the groups along all continuous variables. The difference in the incidence of pain on injection of propofol between the groups was evaluated using the chi-square test, or Fisher’s exact test where appropriate. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

No significant difference was found in demographic data (Table 1). The overall incidence and severity of pain during injection of propofol-MCT-LCT in the two groups is shown in (Table 2). No pain was reported by 59 of the patients (62%) in the control group and by 72 of the patients (75%) in the ondansetron group. Although patients who received ondansetron pretreatment had less pain during propofol – MCT/ LCT injection than patients in the control group, but the difference was not statistically significant (p=0.12). No patients in the both groups experienced severe pain. The number of patients who experienced mild to moderate pain was 37 and 24 in the control and ondansetron group, respectively. Statistically, there was no difference between the two groups. No complications, such as pain, edema, wheal or flare...
response were observed at any injection site within
the first 24 h of surgery.

DISCUSSION

Pain during injection of propofol is common problem,
which is sometimes very distressing to patients. The
incidence of propofol injection pain has been
reported to range between 28% and 90% in adults.1-3
Although the etiology of this pain remains obscure,
numerous methods have been used to reduce its
incidence and intensity. Lidocaine is commonly used
to decrease injection-related pain, but its failure rate
is between 32% and 48%.12-13 Propofol formulated in medium- and long-chain
triglycerides (MCT/LCT) is thought to cause less pain
on injection. Kam et al.4 reported that 38% of patients
experiencing pain or discomfort following propofol-
MCT/LCT, while other researchers have reported
the incidence of pain on injection after propofol-
MCT/LCT was between 28 and 67 percent.5-7,14-15 The implication is that propofol-
MCT/LCT alone could not reduce pain on injection perfectly because
of the continued occurrence of free propofol in the
aqueous phase of the emulsion. The present study
is the first double-blinded, randomized, prospective,
placebo-controlled trial in which ondansetron is used
as a local anesthetic to prevent propofol-MCT/LCT
injection pain.

Ondansetron has a well-known prophylactic
antiemetic effect on cancer chemotherapy protocols,
which frequently cause nausea and vomiting16, and its

<table>
<thead>
<tr>
<th>Table 1. Patient demographic data</th>
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<tr>
<td>Control Group (n=96)</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>ASA I</td>
</tr>
<tr>
<td>ASA II</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or number (%)

<table>
<thead>
<tr>
<th>Table 2. Assessment of pain during IV injection of propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group (n=96)</td>
</tr>
<tr>
<td>Pain on injection</td>
</tr>
<tr>
<td>No pain</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Severity of pain on injection</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
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Values are expressed as number (%)
effectiveness in postoperative nausea and vomiting has been demonstrated in various studies. In animal experiments, ondansetron administered intrathecally reduces the nociceptive responses of dorsal horn neurons. Ye and colleagues demonstrated that ondansetron, a specific 5-HT3 antagonist, blocks sodium channels in rat brain neurons. They also found that ondansetron is 15 times more potent than lidocaine in causing numbness when injected under the skin. Although it has been shown that ondansetron attaches to opioid mu receptors with agonist activity but some investigators have shown that ondansetron acts indirectly as an opioid receptor antagonist.

In previous studies it was shown that ondansetron 4 mg is effective in alleviating, but not totally eliminating, the pain of injection caused by standard propofol. The results of this study have demonstrated that the ondansetron pretreatment could not effectively relieve pain on injection of propofol-MCT/LCT although there was a tendency for the injection-pain to be less in patients who received ondansetron pretreatment. It is difficult to explain why ondansetron does not reduce propofol-MCT/LCT injection pain, as the proposed 15 times more potent local anesthetic effect of ondansetron compare with lidocaine.

In conclusion, ondansetron pretreatment did not significantly reduce either the incidence or severity of the pain on injection of propofol-MCT/LCT.

REFERENCES

**Review Article**

**GENERAL VERSUS SPINAL ANESTHESIA FOR TOTAL KNEE REPLACEMENT: LESS HYPOTENSION WITH SPINAL ANESTHESIA: A RETROSPECTIVE REVIEW**

Malinee Wongswadiwat MD*, Brendan T Finucane, MB FRCA FRCPC

**ABSTRACT**

The purpose of this study was to review the intraoperative anesthetic management of patients undergoing total knee replacement and to report the findings to the Quality Review Committee. The anesthetic files of all patients undergoing total knee replacement at the University of Alberta were reviewed during the calendar year 2004. We were particularly interested in the quality of record keeping, cardiovascular events, fluid management and urine output. In patients who had spinal anesthesia we also were interested in the incidence of failure. A total of 211 patients had total knee replacement surgery during calendar year 2004. General anesthesia was administered in 80 cases and spinal in the remaining 131 cases. Failure of spinal anesthesia occurred in 12.7%. Hypotension was observed in 46.2% of patients in the general and 22% of those in the spinal anesthesia group. This difference was significant (P=0.0004) with a relative risk of 2.0. Pre-existing hypertension was a predictor of hypotension in the spinal group (P=0.0008, RR4.9) but not in the general anesthesia group. Poor record keeping was noted in both groups. There was no difference in the amount of fluid administered intraoperatively or in the amount of urine output produced. The overall risk of hypotension was significantly greater in patients undergoing general compared to those undergoing spinal anesthesia for total knee replacement. Preexisting hypertension was a risk factor for intraoperative hypotension in patients undergoing spinal anesthesia. The quality of record keeping needs to be improved.

**Keywords:** Spinal anesthesia, General anesthesia, Total Knee Replacement, Hypotension

**INTRODUCTION**

There are four major choices of anesthesia for total knee replacement (TKR) and these are general anesthesia, spinal anesthesia, peripheral nerve block or a combined regional/general technique. Spinal anesthesia is frequently used for TKR surgery. The purpose of this study was to retrospectively review the quality of care provided intraoperatively in patients undergoing TKR and to compare spinal and general anesthesia.

**METHODS**

The study protocol was approved by the Research Ethics Review Board. The anesthetic files of all patients undergoing TKR surgery at the University of Alberta were reviewed during calendar year 2004. We were particularly interested in the quality of record keeping, preoperative assessment, cardiovascular events, fluid management and urine output intraoperatively. In patients who had spinal anesthesia we were also interested in the type and dose of local anesthetic used, the baricity of the solution, additives used and the incidence of failure. In patients who had general anesthesia, we were also interested in the incidence of airway problems. We
did not record the quality of pain management or length of stay and we confined our observations to the intraoperative period. We defined hypotension as a systolic blood pressure (SBP) < 90 mmHg or a 30% decline in baseline SBP. We defined bradycardia as a heart rate <50 beats per minute (bpm).

Descriptive statistics were used for patient data expressed as mean ± SD, percentage, median or range and numerical data. Relative risk (RR) values were calculated, compared and reported as were confidence intervals (95% CI) and a P value < 0.05 was considered significant.

RESULTS

A total of 211 patients had TKR surgery during calendar year 2004. General anesthesia was administered in 80 cases and spinal in the remaining 131 cases. Femoral nerve block, 3:1 and combined femoral and sciatic block was used in combination with general anesthesia in 9 patients. The demographics in both groups were comparable statistically (Table 1). Preexisting hypertension occurred in 64% of the spinal anesthetic group and 56.3% of the general anesthetic group.

FAILURE OF SPINAL ANESTHESIA

Failure of spinal anesthesia occurred in 12.67% of cases and 6% of these failures were due to the inability to obtain CSF. In the remaining 6.67% of cases CSF was obtained but anesthesia was deemed to be inadequate. The mean age of these patients was 72 years and the mean BMI was 32. These patients subsequently received general anesthesia.

HYPOTENSION

Hypotension was observed in patients who had general anesthesia more frequently than those who had spinal anesthesia and this was highly significant (P=0.0004). Relative risk was 2.0 (95% CI: 1.392 to 3.088). Bradycardia occurred more frequently in patients who had general anesthesia however this difference was not statistically significant. (Table 2) Pre-existing hypertension was a predictor of hypotension in the spinal anesthesia group but not in the general anesthesia group. Relative risk was 4.9 (95% CI: 1.569-15.34). (Table 3)

Table 1: DEMOGRAPHICS

<table>
<thead>
<tr>
<th></th>
<th>General anesthesia</th>
<th>Spinal anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>80</td>
<td>131</td>
</tr>
<tr>
<td>Age (Yr)</td>
<td>67.56 ± 10.19</td>
<td>70.88 ± 8.75</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>83.99 ± 20.32</td>
<td>87.85 ± 19.12</td>
</tr>
<tr>
<td>Height (Cm)</td>
<td>164.40 ± 9.78</td>
<td>164.02 ± 9.82</td>
</tr>
<tr>
<td>BMI</td>
<td>30.89 ± 6.06</td>
<td>32.67 ± 6.70</td>
</tr>
<tr>
<td>Gender (f/m)</td>
<td>F:M 53:27</td>
<td>F:M 89:42</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.77 ± 15.98</td>
<td>141.18 ± 17.37</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76.44 ± 10.17</td>
<td>78.35 ± 10.14</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>72.45 ± 12.79</td>
<td>73.96 ± 11.89</td>
</tr>
<tr>
<td>ASA I</td>
<td>5 (6.3%)</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>ASA II</td>
<td>50 (62.5%)</td>
<td>89 (67.9%)</td>
</tr>
<tr>
<td>ASA III</td>
<td>24 (30%)</td>
<td>37 (28.2%)</td>
</tr>
<tr>
<td>ASA IV</td>
<td>1 (1.3%)</td>
<td>2 (1.5%)</td>
</tr>
</tbody>
</table>

Data presented in mean ± SD, number of patients (%)
SPINAL ANESTHETIC SOLUTION-BARICITY AND DOSAGE

The spinal anesthetic solution was not documented in five anesthetic records. Isobaric bupivacaine was used in 70% of cases and hyperbaric was used in the remaining cases. Isobaric and hyperbaric bupivacaine were used in doses ranging from 10-20 mg and 10-15 mg respectively. The median dose was 15 mg in both types of solution. Adjuvant drugs were added to the spinal anesthetic solution in 80% of cases. Preservative free morphine was added to the local anesthetic in the majority of cases, in doses ranging from 0.1-0.5 mg and 0.2 mg was most frequently used. Fentanyl, in doses ranging from 15 to 25 micrograms was used alone or added to morphine in 22% of cases and epinephrine was added to the local anesthetic in one case. Hypotension occurred most frequently, 30 minutes after the performance of either spinal or general anesthesia. Propofol was the primary induction agent used and fentanyl was the major opioid used and the average maintenance dose of fentanyl used intraoperatively was 250 micrograms (75-1,150 micrograms). Morphine was the opioid of choice for postoperative pain control except in patients who were sensitive or allergic to morphine and this was given in doses ranging from 0-30 mgs intraoperatively and the average dose was 12 mg. The average dosage of vasopressor required to treat hypotension was similar in both groups. (Table 4) There was no difference in the amount of intravenous fluid administered or the amount of urine output produced among the two groups. (Table 5)

RECORD KEEPING AND HAND WRITING

The legibility, accuracy and completeness of records were a problem in the majority of cases.

DISCUSSION

Failure of spinal anesthesia occurred in close to 13% of cases in this study. Six percent of the failures occurred because of the inability to obtain CSF. Failure rates reported in the literature vary between 3.1% and 17% in three studies1-3 and the highest failure rate occurred in a university hospital. Most of the failures reported in the literature were due to lack of free flowing cerebrospinal fluid during the procedure, inadequate dosage and inappropriately anticipated duration of surgery. According to the literature, factors which influence successful location of the subarachnoid space include: the ability to palpate or visualize anatomic landmarks, the adequacy

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**Table 2: Incidence of hypotension and bradycardia in general and spinal anesthesia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General anesthesia (80)</th>
<th>Spinal anesthesia (131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>37 (46%)*</td>
<td>29 (22%)*</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>7 (8.8%)</td>
<td>4 (3.1%)</td>
</tr>
</tbody>
</table>

*P = 0.0004  
Data presented as number of patients (%)

**Table 3: Pre-existing hypertension and Spinal Anesthesia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypotension</th>
<th>No hypotension</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing hypertension</td>
<td>26**</td>
<td>57</td>
<td>83</td>
</tr>
<tr>
<td>No pre-existing hypertension</td>
<td>3</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>102</td>
<td>131</td>
</tr>
</tbody>
</table>

**P = 0.0008 Relative Risk = 4.9 (95% CI: 1.569-15.34)  
Data presented as number of patients.
of patient positioning and the provider’s level of experience. Delayed progression of spinal anesthesia within 20 minutes and inadequate surgical anesthesia were the reasons to subsequently provide general anesthesia in this study. Absence of free flow of CSF was not reported in the record in this study. One might expect a higher failure rate of spinal anesthesia in this population which is elderly, arthritic and obese. One of the perceived disadvantages of spinal anesthesia in this group of patients is the risk of hypotension. The degree of hypotension depends on the extent of sympathetic block. The incidence of hypotension in spinal anesthesia in non-obstetric patients varies between 5.3-55% depending on the definition and varying methods of measurement. Bijker JB et al. conducted a systematic review to summarize the definitions of intraoperative hypotension in the anesthesia literature and noted a wide variation in the definition. Those definitions were based on either systolic or mean arterial pressure or a combination of absolute or relative threshold, episode duration and measurement methods (noninvasive, invasive). The incidence of hypotension appears to be higher with advancing age (40 yrs or greater, Odds ratio 2.5). Other factors that influence the incidence of hypotension include: decreased volume of CSF (elderly), peak block height greater than or equal to T6 (OR 2.4), a baseline systolic blood pressure less than 120 mmHg, (OR 2.4), spinal puncture above L3-4 (OR 1.8) and a combination of spinal and general anesthesia. Hypertensive patients (pre-existing) are particularly vulnerable to hypotension during spinal anesthesia (OR 1.7). This study demonstrated that the relative risk of developing hypotension was 4.9 in hypertensive patients undergoing spinal anesthesia. Many case reports suggest that there is high risk of severe hypotension associated with ace inhibitor treatment for hypertension. The reasons for this are best explained by medial hyperplasia and hypertrophy of the arteries and arterioles increasing vasodilatory capacity leading to a loss of central redistribution of the blood volume during spinal anesthesia. The high incidence of hypotension in the general anesthesia group was somewhat unexpected. The reason for the higher incidence of hypotension in the general anesthesia group was

<table>
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<th>Table 4: COMPARISON OF VASOPRESSOR USE</th>
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<tbody>
<tr>
<td><strong>Spinal anesthesia</strong></td>
</tr>
<tr>
<td>Ephedrine (mg)</td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Used</td>
</tr>
<tr>
<td>Phenylephrine (µg)</td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>Used</td>
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<th>Table 5: COMPARISON OF FLUID MANAGEMENT</th>
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<tr>
<td><strong>Solution</strong></td>
</tr>
<tr>
<td>Crystalloid (ml)</td>
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<tr>
<td>Colloid (ml)</td>
</tr>
<tr>
<td>Urine output (ml)</td>
</tr>
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</table>
not clear but was most likely due to the depressant effects of propofol and inhalation anesthetics on the cardiovascular system. The age-related increase in the incidence of hypotension related to inhalation anesthesia can be explained by the progressive deterioration of the autonomic reflex responses maintaining cardiovascular homeostasis, marked cardiovascular depression and increased peripheral blood flow in the elderly patient compared to that in young adults.\textsuperscript{14} It was interesting to note that the timing of the maximum incidence of hypotension in both groups occurred at 30 minutes. Hypotension was most likely caused by cardiovascular depression from propofol after induction in the early stages of the anesthetic (first 15 minutes) and the inhalation agent at later stages. There were no major airway problems reported in the general anesthesia group.

Accurate record keeping and legibility continues to be a problem that needs to be addressed. Electronic record keeping would solve some of this problems.\textsuperscript{15} One may criticize this study on the basis that it is retrospective and therefore subject to the criticisms of all retrospective studies (lack of randomization and controls). The record keeping was incomplete and absent is some cases. Despite these flaws the information contained in this study challenges those providing care for these patients to improve the quality of care provided. This study also confirms the previous observation that pre-existing hypertension is a risk factor for intraoperative hypotension in patients undergoing spinal anesthesia. It may also come as a surprise to some that the incidence of intraoperative hypotension is increased in patients undergoing general anesthesia for TKR compared to those undergoing spinal anesthesia and this should challenge them to be more judicious in the doses of propofol and inhalation agents used in this population. These observations were reported to the Quality Review Committee in our institution and presented to anesthesia providers and a follow-up survey will be conducted in the future.

In conclusion, hypotension occurred more frequently in patients undergoing general compared to those undergoing spinal anesthesia for total knee replacement. Pre-existing hypertension was a risk factor for hypotension in patients undergoing spinal anesthesia. The quality of record keeping continues to be a problem that needs to be addressed.

REFERENCES

INTRODUCTION

Regional anesthesia and postoperative pain management with local anesthetics have been shown to provide good postoperative analgesia upon mobilization, which reduces the need for opioid analgesics and also reduces postoperative morbidity. Caudal, epidural analgesia and peripheral nerve blocks are, therefore, commonly used in pediatric anesthesia, and epidural analgesia is now an accepted technique for both intraoperative and postoperative pain management in infants and neonates.

Basically, local anesthetics used for providing regional anesthesia take effect by reversibly blocking nerve conduction, resulting in sympathetic, sensory and motor blocks. Their safe use is guided by the adequate dose and concentration for each block, which are based on age and body-scale: weight (Kg) of the patients. Besides their desired effects, local anesthetics may also produce toxic systemic side effects, mainly on the central nervous system (CNS) and cardiovascular system (CVS). These side effects usually occur following an inadvertent intravascular injection at the time of performing the block or by overdosing. The most severe toxic side effects may entail malignant ventricular arrhythmia and cardiac arrest. Following such unanticipated side effects, resuscitation is often difficult or impossible. An additional problem is that in children, regional anesthesia is normally performed with the patients...
already anesthetized and the detection of early symptoms of systemic toxicity due to intravascular injection is extremely difficult\(^7\). In anesthetic practice, besides the use of a test dose, a limited maximum dosing and a slow incremental dosing, the use of agents with less potential toxicity may be safer\(^8,9\).

Bupivacaine, N-butyl-pipecoloxylidide, is the most frequently used local anesthetic for regional anesthesia in adults and children. It possesses a single asymmetric carbon atom and exists as a 50:50 mixture of two isomers, termed S (-) and R (+) isomers. Several experiments have shown the S (-) isomer to be less toxic than the R (+) isomer in rabbits and sheep\(^10,11\). These studies have led to the development of the pure S (-) isomer as a potentially safer alternative to racemic bupivacaine.

Ropivacaine, S (-)-N-propyl-pipecoloxylidide, is a relatively new local anesthetic which was first tested and used in animals in 1988\(^15\) and was registered for clinical use in humans in 1996\(^16\). The reason for introducing ropivacaine was the need for a long-acting local anesthetic that was less cardiotoxic than bupivacaine\(^5,17,18\).

Although the two compounds, ropivacaine and bupivacaine, are very similar in chemical structure (the four-carbon side-chain-butyl group of bupivacaine is replaced with a three-carbon side-chain-propyl group in ropivacaine), bupivacaine is prepared as a racemic mixture while ropivacaine is prepared as the almost pure S (-) isomer associated with a lower lipid solubility. The R (+) isomer of racemic bupivacaine binds to cardiac sodium channels more intensely than do the S (-) isomers of ropivacaine. As a result, ropivacaine is less cardiotoxic than bupivacaine\(^19,20\).

2.1 Metabolism
Ropivacaine is primarily eliminated by extensive metabolism in the liver, with the major metabolite route being aromatic hydroxylation, with only 1% of the dose being excreted unchanged in the urine of humans\(^11,22\). Because ropivacaine has an intermediate to low hepatic extraction ratio of 0.23 - 0.66 (average 0.4), its total clearance is not susceptible to changes in hepatic blood flow and therefore depends mostly on hepatic enzyme activity and plasma protein binding. Four of the metabolites formed in human liver microsomes have been identified as 3-OH-ropivacaine, 4-OH-ropivacaine, 2-OH-methyl-ropivacaine, and 2\(^,\)6\(^-\) pipercoloxylidide (PPX). The Cytochromes P450 (CYP) are involved in its metabolism, CYP1A catalyzes the formation of 3-OH-ropivacaine, the main metabolite formed (38% of the dose), whereas the formation of 4-OH-ropivacaine, 2-OH-methyl-ropivacaine, and PPX is catalyzed by CYP3A\(^21,23\). These enzymes are situated predominately in the centrilobular area of the hepatic lobule, and are prone to hypoxia and seem to be more affected in liver disease than enzymes in the perportal area. In addition, chronic liver disease decreases ropivacaine clearance, on average, by 60%\(^24\).

2.2 Differential blockade
Local anesthetics block the transmission of the action potential along the nerve axon by a blockade of the sodium channel, preventing depolarization of the nerve. A general rule is that larger-diameter fibers require a higher concentration of local anesthetic for block than do smaller-diameter fibers, so the smallest, nonmyelinated, C fibers are most easily blocked, whereas the thicker, myelinated nerves are more difficult to block. The sensitivity of different nerve fibers to blockade by locally acting anesthetics may depend on a number of factors related to the fibers themselves, the drugs or the surrounding tissue. Rosenberg et al. compared the differential sensitivity of A and C fibers of rats at body temperature (35-37 °C) to amide local anesthetics. They found that ropivacaine is a more effective blocker of pain fibers than bupivacaine\(^25\). It also demonstrates a greater degree of block in nerve fibers of pain transmission than of motor function\(^26\).
2.3 Potency
Reports document a variety of local anesthetics administered at different volumes and concentrations with variable effect. The mean of potency is to determine the minimal local anesthetic concentration (MLAC), e.g. MLAC of bupivacaine for spinal anesthesia, defined as the median effective concentration at which a spinal anesthetic produces surgically equivalent anesthesia within 20 min of administration in 50% of human subjects. The concentrations of ropivacaine used in clinical practice range from 0.1% to 0.5%. Deng et al.27 studied 26 children aged 1 to 5 years who were scheduled for hypospadias repair under general anesthesia with 0.5 MAC of enflurane with 1 mL/Kg of caudal ropivacaine. The concentrations of ropivacaine were determined by the analgesic response of the previous patient to the initial skin incision by use of Dixon’s up-and-down sequential allocation. The MLAC of ropivacaine for caudal analgesia under general anesthesia with 0.5 MAC enflurane was 0.11% (95% confidence interval [CI], 0.09%–0.12%), and the 95% effective concentration was 0.13% (95% CI, 0.12%–0.21%). This would indicate that the ropivacaine concentration should be at least 0.13% to provide adequate block.

2.4 Systemic absorption
The systemic absorption rate at different sites of injection are known to be directly related to local blood flow and inversely related to local tissue binding. The intrinsic vasodilatation effect of bupivacaine may accelerate its absorption from the injection site while, in contrast, the vasoconstrictive effect of ropivacaine slows down its absorption28. This is one of the mechanisms responsible for the decreased systemic toxicity of ropivacaine.

Karmakar et al.29 compared the systemic absorption of 2 mg/Kg of 0.2% ropivacaine and 0.2% bupivacaine after caudal administration in children aged 1–7 years undergoing elective hypospadias repair. They found comparable peak plasma concentrations (mean±SD) of ropivacaine (670 ± 160 mcg/L) and bupivacaine (730 ± 230 mcg/L). The median (range) time to peak plasma concentration was significantly longer in children who received ropivacaine (65 (10–120) min) than bupivacaine (20 (15–50) min). They concluded that ropivacaine undergoes slower systemic absorption from the caudal epidural space in children than does bupivacaine, confirming the results of a previous report by Ala-Kokko et al.30

SAFETY OF ROPIVACAINE

3.1 Animal studies
There are several animal studies comparing the systemic toxicity among amide local anesthetics. With regard to the comparative CNS toxicity of these drugs, the convulsive doses were found to be larger for ropivacaine and levobupivacaine than for bupivacaine in awake sheep31-33. Another study found the cumulative dose of ropivacaine required to produce seizure was larger than that of bupivacaine in anesthetized rats34.

Recently, Ohmura et al.13 compared the systemic toxicity of bupivacaine, levobupivacaine and ropivacaine in anesthetized rats. They reported that the cumulative doses of ropivacaine and levobupivacaine that produced seizures were similar and were larger than those of bupivacaine with the ratio of 1.4: 1.4: 1, respectively. With regards to the comparative cardiotoxicity, the cumulative doses of ropivacaine, levobupivacaine and bupivacaine that produced arrhythmia and asystole were in the respective ratio of 6.9: 3.3: 1. Although the number of successful resuscitations did not differ among groups, ropivacaine-induced cardiac arrest appears to be more receptive to treatment than arrest induced by bupivacaine or levobupivacaine.

Cardiotoxicity is not a single condition, but can be expressed in terms of reduced contractility, impaired diastolic function, vasodilatation or vasoconstriction, or effects on conduction and arrhythmogenicity. The mechanism of local anesthetic-induced cardiotoxicity is the blocking of the cardiac Na channels and voltage-gated K channels in both cardiomyocytes and vascular smooth muscles35,36. Royse et al.37 compared the pressure-volume loops among bupivacaine, levobupivacaine and ropivacaine in rabbits. They found that levobupivacaine and bupivacaine significantly impaired contractility at doses exceeding 1.32 mg/Kg, whereas ropivacaine was not different from control at 4.25 mg/Kg. Bupivacaine reduced ejection fraction (EF) and cardiac index, and increased vascular resistance. Levobupivacaine reduced EF and cardiac index and demonstrated a biphasic vascular response, increasing vascular resistance at larger dosages. Ropivacaine increased vascular resistance and reduced EF without
affecting contractility. A significant decline in contractility from control occurred with bupivacaine and levobupivacaine, but not with ropivacaine, at doses achievable in routine clinical practice.

Sztark et al.\textsuperscript{38} compared the bioenergetic effects of bupivacaine and ropivacaine on mitochondrial energy metabolism in rat heart isolated mitochondria and left ventricle fibers. They found that bupivacaine and ropivacaine acted, in isolated mitochondria, as uncouplers between oxygen consumption and phosphorylation of adenosine diphosphate. Further, an inhibitory effect of mitochondrial respiration was evidenced with both anesthetics during maximal respiration and was assigned to a direct inhibition of complex I of the respiratory chain. Mitochondrial adenosine triphosphate synthesis was decreased by both mechanisms. However, both in isolated mitochondria and in permeabilized heart fibers, ropivacaine was less potent than bupivacaine. Adenosine triphosphate synthesis was completely suppressed at 3 mM (approximately 0.1\% bupivacaine, whereas 3 mM ropivacaine induced only about a 40\% inhibition. Ropivacaine, therefore, disturbs mitochondrial energy metabolism less than bupivacaine does. The lower lipid solubility of ropivacaine may be responsible for the lesser dose-dependent effects of this drug on mitochondrial bioenergetics.

However, Chang et al.\textsuperscript{39} found all 3 drugs were equivalent in fatal cardiac toxicity with direct intra-coronary injection.

In summary, the evidence from animal studies demonstrates that ropivacaine is consistently less toxic systemically than bupivacaine.

3.2 Studies in volunteers
The acute tolerance of ropivacaine has been studied in healthy adult subjects, with a finding that the threshold for CNS toxicity was apparent at mean (min - max) unbound plasma concentrations of the order of 560 (340-850) mcg/L ropivacaine and 300 (111-510) mcg/L bupivacaine\textsuperscript{14}. It has also shown a higher threshold for CNS toxicity of the unbound plasma concentration in healthy volunteers compared with bupivacaine\textsuperscript{14}. At doses producing CNS symptoms, cardiovascular changes, depression of conduction and diastolic function were less severe with ropivacaine compared with bupivacaine. The unbound plasma concentration of ropivacaine is approximately 6\% of total plasma concentration\textsuperscript{40}.

CLINICAL STUDIES OF ROPIVACAINE IN CHILDREN
The clinical efficacies in terms of analgesia and motor blockade and safety profile have been extensively evaluated in children. A large number of open and randomized controlled studies have been performed on neonates to older children with ropivacaine compared with bupivacaine in a wide variety of regional blocks.

4.1 Caudal block
Caudal block is the most commonly used regional block in pediatric anesthesia practice. Besides its analgesic effects, it increases FRC, improves ventilation homogeneity, and is beneficial to gas exchange, especially, in anesthetized, spontaneously breathing children\textsuperscript{41}.

Ropivacaine has been compared with bupivacaine in clinical trials in children\textsuperscript{42-47}. Comparing the same concentrations and volumes of drugs for a caudal block, ropivacaine provided comparable analgesic efficacy to bupivacaine, with less residual motor blockade in the postoperative period.

The most important factors determining the efficacy of caudal block for a specific local anesthetic are the volume and concentration used. Many doses and concentrations of ropivacaine have been studied in order to find the most suitable and appropriate doses for different types of operation. Bosenberg et al.\textsuperscript{48} studied 110 children aged 4-12 years, undergoing elective inguinal surgery, comparing 0.1\%, 0.2\% and 0.3\% ropivacaine in a volume of 1 mL/Kg for a caudal block. They found that 0.1\% ropivacaine showed less analgesic efficacy while 0.3\% ropivacaine was associated with higher incidence of motor block without improvement of analgesia, compared with 0.2\% ropivacaine.

Khalil et al.\textsuperscript{49} studied 77 infants aged 1-12 months, undergoing lower abdominal or urologic surgery, comparing 0.1\%, 0.15\%, 0.175\% and 0.2\% ropivacaine in a volume of 1 mL/Kg for a caudal block. They found that in infants, there was no difference between 0.175\% ropivacaine and 0.2\% ropivacaine in providing postoperative analgesia and
duration of analgesia, however 0.175% ropivacaine was associated with fewer motor blocks. Both 0.1% and 0.15% ropivacaine did not provide adequate postoperative analgesia and had a shorter duration.

Pharmacokinetic studies of ropivacaine in children have also been performed to address its safety profile. Habre et al.\(^5\) reported the pharmacokinetics profiles following caudal administration of 1 mL/Kg of 0.25% ropivacaine in 9 healthy children aged 1-6 years. They found the peak plasma concentrations of ropivacaine occurred between 0.33-2.05 hr and ranged from 623-1220 mcg/L, which were lower than the average concentration that produced CNS toxicity in adults (2200 mcg/L). The plasma concentrations of ropivacaine in this study were higher than the range of 340-1020 mcg/L, in the study of Lonnqvist et al.\(^5\) which used 1 mL/Kg of 0.2% ropivacaine, while the analgesic efficacy was comparable.

Because of the diminished clearance of all pipecoloxyldides in neonates and infants, it is important to understand the pharmacokinetics in this specific age group. Rapp et al.\(^3\) evaluated pharmacokinetics, efficacy and safety of ropivacaine in 37 infants aged 0–12 months following a single caudal administration of 1 mL/Kg of 0.2% ropivacaine (2 mg/Kg). The peak plasma concentrations of total ropivacaine ranged from 50–1570 mcg/L at 0.5–5.7 hr and the plasma concentrations of unbound ropivacaine ranged from 12–81 mcg/L within 0.5–1 hr. The observed unbound form in plasma was an average of 6% (1%–14%). The plasma concentrations of ropivacaine were well below threshold levels for toxicity in adults. This is in agreement with the results of other studies\(^5\)\(^2\)-\(^5\).

In summary, for caudal block, available studies indicate that 1 mL/Kg of 0.2% ropivacaine (2 mg/Kg) provides adequate, reliable analgesia for inguinal or lower abdominal surgery with an acceptable incidence and duration of motor block. Duration of analgesia can be prolonged by the use of a larger volume of diluted concentration of 0.175% up to a maximum dose of 3 mg/Kg.

### 4.2 Epidural block

Ivani et al.\(^5\) studied 28 infants aged 1-12 months undergoing urological or colonic procedures comparing the use of 0.7 mL/Kg of 0.25% bupivacaine (2 mg/Kg) with 0.2% ropivacaine (1.4 mg/Kg) for a single lumbar epidural block. They found similar onset, duration of analgesia, and time to first analgesic dose but noted that the lower dose of ropivacaine required provided an increased safety margin.

McCann et al.\(^5\) evaluated the pharmacokinetics of ropivacaine in 7 infants, aged 3–11 months, and 11 young children, aged 12–48 months, undergoing lower abdominal or lower extremities procedures who received 0.85 mL/Kg of 0.2% ropivacaine (1.7 mg/Kg) for a single lumbar epidural block. The median peak plasma concentrations in infants and young children were 610 mcg/L (interquartile range [IQR], 550–725 mcg/L) and 640 mcg/L (IQR, 540–750 mcg/L), respectively. The highest peak plasma concentrations of ropivacaine were 1055 and 1015 mcg/L in the infants and young children, respectively, below the reported maximum tolerated plasma concentration in adults\(^5\)\(^9\). The median times to maximum plasma ropivacaine concentration were 60 min (IQR, 60–120 min) in infants and 60 min (IQR, 30–90 min) in young children.

A continuous infusion is commonly used for providing stable analgesia instead of a single injection, thus it is important to understand the pharmacokinetics of this technique.

Hansen et al.\(^5\) studied a continuous epidural ropivacaine infusion in children 3 months to 8 years old with 0.2% ropivacaine loaded at 1 mg/Kg followed by a constant rate infusion of 0.4 mg/Kg/hr for 36-96 hr. They found total and free plasma ropivacaine levels of 1000-3189 mcg/L and 10-56 mcg/L, respectively, which were within the range of safety in previous studies in adults (1000-3000 mcg/L and 10-150 mcg/L). The highest total plasma concentration of 3189 mcg/L was measured at 48 hrs in the youngest subject, a 3.5-month-old baby. The highest free plasma concentration of 56 mcg/L was found at 1 hr following initial bolus dose in a 6-month-old baby. They suggested that this infusion rate should not be used for more than 36-48 hr.

A recent study of Bosenberg et al.\(^5\) evaluated the pharmacokinetics of ropivacaine during a 48–72 hr continuous epidural infusion of ropivacaine in 55 children aged under 1 year, scheduled for major abdominal or thoracic surgery and separated into age groups: 0–30 (neonate), 31–90, 91–180, and...
181–365 days. An initial bolus dose (0.9–2.0 mg/Kg) of ropivacaine 0.2% was followed by an epidural infusion (0.2 mg/Kg/hr) for infants < 180 days or 0.4 mg/Kg/hr for infants > 180 days). Plasma concentrations of unbound ropivacaine leveled at 24 h, without any further increase at 48 and 72 hr. The maximum free ropivacaine concentration of 220 mcg/L in neonates was higher than that of 130 mcg/L in infants, however both were below the toxic levels in adults. They concluded that epidural infusions 0.2–0.4 mg/Kg/hr of ropivacaine provided satisfactory pain relief in neonates and infants less than 1 year. As plasma concentrations of unbound ropivacaine were not influenced by the duration of the infusion, ropivacaine could be safely used for postoperative epidural infusion for 48–72 hr. However, because of the higher variability of plasma concentrations of ropivacaine in all neonates who underwent surgery during the first week of life, this group should be treated with caution.

In summary, the available studies indicate that a continuous epidural infusion of 0.2% ropivacaine in children at a rate of 0.2 mg/Kg/hr up to 0.4 mg/Kg/hr provides good analgesia with few side effects. However, in neonates and infants aged less than 6 months, this continuous rate should be reduced after 48 hr to avoid toxicity.

4.3 Spinal block
Malinovsky et al.\textsuperscript{61} reported ropivacaine induced dose-dependent spinal anesthesia did not induce any neurotoxicologic lesions in rabbits. Several studies have demonstrated the efficacy and safety of spinal ropivacaine\textsuperscript{62}, but the potency is less than bupivacaine\textsuperscript{63,64}.

Ropivacaine was licensed for intrathecal use in the European Union in 2004\textsuperscript{65}. Since then, there have been 2 reports of spinal ropivacaine use in children. Kokki et al.\textsuperscript{66} evaluated the clinical effects of ropivacaine for spinal anesthesia in 93 children, aged 1–17 yr, undergoing elective lower abdominal or lower limb surgery by using a plain solution of 0.5% ropivacaine at a dose of 0.5 mg/kg body weight (up to 20 mg). The mean highest level of sensory block was T6 (range, T2 to T12), and the mean time to the regression of sensory block to T10 was 96 min (range, 34 –210 min). One child developed transient bradycardia and one hypotension. After discharge four children developed mild transient radiating neurological symptoms and one epidural blood patch was performed for persistent position-dependent headache. The authors found that the block performance of spinal isobaric ropivacaine in children (> 1 yr) was similar to that obtained in adults. This study indicated the effectiveness of ropivacaine for spinal applications, as the success rate of the block, 92%, was the same as has been reported with racemic bupivacaine.

Recently, Frawley et al.\textsuperscript{67} studied 50 neonates less than 55 weeks postconceptual age undergoing inguinal hernia repair to find the optimum dose of spinal ropivacaine. They reported that the motor blocking of median local anesthetic dose (MMLAD) in 50% (ED50) of neonates determined by the Dixon–Massey method was 0.51 (95% CI = 0.38–0.64) mg/Kg, with an estimated ED95 of 1.08 (0.70–1.67) mg/Kg. Overall the mean duration of lower limb motor blockade was 60.0 min (95% CI=51.5–68.5 min). They concluded that ropivacaine is an effective agent for spinal anesthesia in neonates for procedures less than our hour in duration, at a recommended dose of 1.08 mg/Kg.

In summary, isobaric ropivacaine seems to provide effective spinal anesthesia for children undergoing surgery in the lower part of the body. However, it is unclear whether ropivacaine has any advantages over bupivacaine in spinal anesthesia in children.

4.4 Ilioinguinal-iliohypogastric block
An early study by Dalens et al.\textsuperscript{68} found that the use of 3 mg/Kg of 0.5% ropivacaine for ilioinguinal-iliohypogastric block (IINB) can reach a plasma concentration of ropivacaine up to 4770 mcg/L in some patients which is greater than the toxic level; however administration techniques have been refined and it is now safe with the use of lower doses with comparable analgesia. Ala-Kokko et al.\textsuperscript{70} used 2 mg/Kg of 0.75% ropivacaine for IINB with the plasma concentration never above the toxic level in any patient. A recent study of Tsuchiya et al.\textsuperscript{69} found that the use of 0.5 mL/Kg of 0.2% ropivacaine provides sufficient analgesia for inguinal hernia repair in 90% of children with a mean duration of analgesia of 62.80 min. The use of 0.5 mL/Kg of 0.2% ropivacaine was as effective as 0.25% bupivacaine.

Ala-Kokko et al.\textsuperscript{70} showed that the plasma concentrations of ropivacaine and bupivacaine
following IINB were twice and three times higher, respectively, than those following caudal block. This has been explained by the injection into a narrow space which may enhance systemic absorption compared to injection into the caudal space.

In summary, available evidence indicates 0.5 mL/Kg of 0.2% ropivacaine provides effective analgesia for IINB for inguinal hernia repair.

4.5 Brachial plexus block
Because ropivacaine has less CNS toxicity and cardiotoxicity than is related to bupivacaine after intravenous infusion in human volunteers, these may be advantageous for brachial plexus blocks, enabling larger doses to be used. Previous studies in adults found that 0.5% ropivacaine provided effective analgesia and motor blocks71,72 and was as effective as bupivacaine72. Another study found, however, that 0.25% ropivacaine did not provide effective analgesia73. However, Thornton et al74 found that 0.5 mL/Kg of 0.2% ropivacaine used for an axillary brachial plexus block was comparable to 0.25% bupivacaine in children. The analgesic efficacy of lower concentrations of ropivacaine used in children may be explained by its use in combination with general anesthesia.

In summary, available evidence indicates 0.5 mL/Kg of 0.2% ropivacaine provides effective analgesia for axillary brachial plexus block.

4.6 Wound infiltration
There is no study to date which examines the use of ropivacaine in children via wound infiltration or penile block. Ropivacaine has been used successfully for postoperative analgesia by wound infiltration in adults undergoing open cholecystectomy75,76, breast surgery77 and herniorhaphy78,79. One study demonstrated that cutaneous anesthesia produced by ropivacaine is two or three times longer lasting than that produced by bupivacaine, which may be explained by the intrinsic vasoconstrictive properties of ropivacaine80,81.

REPORTS OF SYSTEMIC TOXICITY OF ROPIVACAINE IN CLINICAL USE

Ropivacaine has been used for both central and peripheral blocks and clinical data have shown its safety and efficacy. Although it shows low potential cardiac toxicity, this can still occur. The first report of CNS toxicity was in 199782-91, one year after its first clinical use in humans. The characteristics of ropivacaine-induced seizure are presented in (Table 1).

The first report of cardiotoxicity was in 199983,92,93, with all patients successfully resuscitated92,94-96. Summarized patterns of cardiac arrest compared between bupivacaine and ropivacaine are presented in (Table 2).

The majority of these events occurred after injection of a large volume of ropivacaine for peripheral nerve blocks in elderly patients, from both inadvertent intravenous injection and overdosing.

Ala-Kokko et al97 reported patients who received an overdose of 0.5% ropivacaine 4.5 and 6 mg/Kg for brachial plexus block which led to CNS toxicity. The highest total and free plasma concentrations of ropivacaine were 6000 mcg/L and 660 mcg/L, respectively, but the patients did not have signs of

<table>
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<tr>
<th>Table 1 Characteristics of ropivacaine-induced seizure</th>
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<tr>
<td>- High volume local anesthetic injection: brachial plexus block, sciatic nerve block, epidural block</td>
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<tr>
<td>- All blocks performed with documented negative aspiration of blood</td>
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<td>- All blocks performed without epinephrine test dose</td>
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<td>- Dose ranging from 1.1 mg/Kg (intravenous injection) to 6 mg/Kg (overdosing)</td>
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<td>- Concomitant cardiotoxicity is not severe: hypotension, sinus arrhythmia</td>
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<td>- All patients fully recovered without sequelae</td>
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cardiotoxicity. These cases may demonstrate the high cardiovascular safety level of ropivacaine.

In children, there has been no report to date of systemic toxicity of ropivacaine, although there have been two reports of accidental intravenous injection of ropivacaine in children without any sequelae\(^98,99\).

**CONCLUSIONS**

Local anesthetics are useful and necessary for a wide range of applications in infants and children, with the most frequently used anesthetic being racemic bupivacaine. Concern over reports of serious toxicity and deaths associated with the accidental IV injection of racemic bupivacaine has highlighted the need for a safer local anesthetic. Ropivacaine has an efficacy similar to that of bupivacaine in similar doses, but with both a shorter duration and reduced motor block. Its safety profile is also better than bupivacaine. It is less cardiotoxic and more amenable to resuscitation when unexpected cardiotoxicity does occur. However, the anesthesiologist must maintain a very strict surveillance during the administration of any anesthetic, as even the “safest” local anesthetic can produce toxic side effects.

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**Review Article**

**EARLY VERSUS LATE INITIATION OF EPIDURAL LABOUR ANALGESIA**

Sng BL MMED FANZCA*, Y Lim MMED**

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**INTRODUCTION**

Pain during childbirth is arguably one of the most severe a woman may experience in her lifetime.\(^1,2\) A substantial number of nulliparous women may experience inadequate pain relief during early labour until epidural analgesia is initiated. Epidural labour analgesia has proved to be an effective and safe form of pain relief during labour.\(^2,3\)

There was initial concern of epidural analgesia increasing the rate of caesarean delivery and instrumental delivery\(^4-8\), as epidural could potentially decrease uterine activity, prolong 1st and 2nd stage of labour, relax pelvic musculature and decreased maternal urge or ability to push during 2nd stage. However, recent systematic reviews on the use of epidural in labour have not shown association between epidural with an increase in incidence of caesarean delivery.\(^9-11\) Although, a low dose epidural infusion may be associated with a higher risk of instrumental vaginal delivery\(^12\) and the women receiving epidural analgesia could potentially have a longer second stage of labour, they experienced better pain relief.

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**CONTROVERSY OF EARLY VERSUS LATE INITIATION OF EPIDURAL ANALGESIA**

The current controversy centres on the timing of epidural analgesia in nulliparous women. It has been suggested that early initiation of labour epidural analgesia may be associated with an increased rate of caesarean delivery.\(^4,13,14\) The initial studies were based on retrospective reviews or analyses of secondary outcomes; most did not investigate the timing of the initiation of epidural as the primary outcome. Therefore, in a statement in 2002, the American College of Obstetricians and Gynecologists Task Force on Cesarean Delivery has recommended that when feasible, obstetric practitioners should delay the administration of epidural analgesia in nulliparous women until the cervical dilatation reaches 4 to 5 cm and that other forms of analgesia be used until that time.\(^15\)

Recent randomized controlled trials since 1994 showed no casual relationship between timing of epidural with rate of caesarean delivery.\(^16-21\) Association between early epidural and increased incidence of caesarean delivery may be related to factors other than the epidural per se. Numerous factors including parity, gestational age and fetal weight may affect obstetric outcome. For instance, obstetric labour management plan may influence outcome as rates of obstetric intervention leading to increased instrumental delivery were highest in private patients.\(^22\) Also, early labour presentation at hospital is associated with higher obstetric intervention than advanced labour.\(^23\) Severe pain in the latent phase of labour may be associated with an increased likelihood of dysfunctional labour and the incidence of instrumental delivery.\(^24\) Fetal macrosomia is a known risk factor for caesarean delivery and is associated with greater need for analgesia as depicted by a higher rate of breakthrough pain during epidural analgesia.\(^25\) Epidural local anaesthetic requirements...
during labour were higher among women who eventually underwent caesarean section for dystocia than in women who delivered vaginally.  

**EARLIER RETROSPECTIVE AND COHORT STUDIES**

The recommendations of the American College of Obstetricians and Gynecologists (ACOG) were mainly based on retrospective studies and secondary analysis of prospective studies that did not look specifically at effect of timing of epidural. Retrospective and non-randomised cohort studies may show an association between epidural analgesia and risk of adverse outcomes, but the association does not imply causation. Earlier studies found that regional analgesia may influence uterine activity. Although some studies showed significant decrease in uterine activity, others showed no effect or only transient decrease in uterine activity. Guidozzi et al reported that continuous low dose epidural analgesia resulted in a transient 2.9% reduction in uterine activity if cervical dilatation was between 3 to 4 cm. However, no reduction of uterine activity was noted in the active phase of labour when cervical dilatation was 5 cm or more.

Thorpe et al retrospectively reviewed 500 consecutive nulliparous women who had spontaneous onset of labour at term and delivered in their hospital in 1988. The incidence of caesarean section for dystocia was 15.6% in the epidural group and 2.4% in the non-epidural group. The relative risk of cesarean section was 6, reaching 20.6% if epidural analgesia was initiated at cervical dilatation 3cm or less, compared with 3.4% if placed at 5cm or more. Hence, the recommendation was to delay initiation of epidural analgesia until the cervix was at least 5 cm dilated, since non-randomised early administration was associated with an increased risk of caesarean delivery.

Thorpe et al performed a prospective study in which nulliparous indigent women either received epidural bupivacaine or intravenous pethidine analgesia. Women in the epidural group received an initial bolus of 0.25% bupivacaine followed by maintenance of 0.125% bupivacaine infusion. All the subjects had spontaneous onset of labour, but 9 of 48 women in the epidural group and 3 of 45 women in the pethidine group were receiving intravenous oxytocin at the time of the 1st dose of drug. Twelve (25%) of 48 women in the epidural group, versus 1 (2%) of 45 women in the pethidine group, underwent caesarean section. It was noted that 11 of the 12 caesarean sections in the epidural group were performed in women who received epidural analgesia before 5cm cervical dilatation. However, this study was not powered to analyse the effects of early initiation of labour epidural analgesia, not blinded and the authors assumed responsibility for decisions regarding the method of delivery.

**PROSPECTIVE RANDOMIZED TRIALS**

Retrospective and nonrandomized cohort studies were not adequate study designs to study the effect of timing of labour epidural analgesia, due to selection bias and confounding factors. Several randomized controlled trials to date have addressed several obstetric and fetal outcomes.

Two studies by Chestnut et al studied the effect on progression and outcome of labour in nulliparous women with early versus late epidural placement. One study was performed in 150 nulliparous women receiving intravenous oxytocin while the other study was in 344 nulliparous women in spontaneous labour. In both studies, the late epidural group had intravenous 10mg nalbuphine till cervical dilatation of at least 5cm. Epidural 0.25% bupivacaine was administered to achieve a sensory block to at least T10 on initiation of epidural analgesia, and epidural 0.125% bupivacaine infusion 12ml/H used for maintenance.

In both studies, randomization occurred only after the following conditions were met: (1) the patient request pain relief at that moment (2) a lumbar epidural catheter had been placed (3) the cervix was at least 3 cm but less than 5 cm dilated. Patients in the early group immediately received epidural bupivacaine analgesia. Patients in the late group received intravenous 10mg nalbuphine. Late group patients did not receive epidural analgesia until they achieved a cervical dilatation of at least 5cm or until at least 1 hour had elapsed after a second dose of nalbuphine.

There were no differences in the caesarean section rate in nulliparous women randomly assigned to
early epidural analgesia (cervical dilatation 3 to 5 cm) or late epidural analgesia (cervical dilatation 5 cm or greater after systemic opioid analgesia of intravenous nalbuphine), regardless whether the parturient was receiving intravenous oxytocin or in spontaneous labour. However, one argument is that the median cervical dilatation in the early groups of 4 cm (receiving intravenous oxytocin) and 3.5 cm (in spontaneous labour) however, were not parturients in very early labour.

In the study by Luxman et al,19 60 nulliparous women were recruited in a randomized controlled trial. The subjects were assigned to either early initiation of epidural of cervical dilatation of less than 4 cm or late initiation of epidural. Unlike Chestnut et al studies20,21, there was no systemic opioid used in the late initiation group, eliminating the effects of opioids. There was no significant difference between the 2 groups in rate of cervical dilatation, duration of 2nd stage, instrumental deliveries, caesarean delivery or APGAR scores. However, the sample size was small and maternal satisfaction was not discussed.

EARLY EPIDURAL AND RISK OF CAESAREAN SECTION

Early administration of epidural did not result in an increased incidence of caesarean section in nulliparous women receiving intravenous oxytocin or in spontaneous labour. In patients receiving intravenous oxytocin,21 18% of 74 women in the early group and 19% of 75 women in the late group underwent caesarean section (relative risk for the early group 0.94; 95% confidence interval 0.48-1.84). For patients in spontaneous labour,20 Chestnut showed 10% of 175 women in the early group and 8% of 162 women in the late group underwent caesarean section (relative risk for the early group 1.22, 95% confidence interval 0.62-2.40). Expectedly, patients requiring intravenous oxytocin for induction or augmentation in early labour were at higher risk for caesarean delivery than in spontaneous labour.

Currently, there are many women who request for epidural analgesia in very early labour and there are concerns on its effect on obstetric outcome. In the study by Ohel et al16, 449 term nulliparous women were recruited in a randomised controlled trial, at less than 3 cm of cervical dilatation, in very early labour. The subjects were assigned to either immediate initiation of epidural at 1st request (very early) or delay of epidural until the cervix dilated to at least 4cm (late). In the late group, analgesia was provided by intravenous pethidine and promethazine. Due to the obstetric management of vaginal examination before epidural, the late epidural group had significantly more subjects who did not receive epidural analgesia (did not receive epidural, early 4.5% vs late 13.6%, p=0.008) and systemic analgesia was required more often (p<0.001). Delaying epidural analgesia until greater cervical dilatation therefore resulted in more cases of labour progressing to near completion before epidural can be initiated.

EARLY EPIDURAL AND RISK OF CAESAREAN SECTION

The rate of caesarean section was not significantly different between the groups (13% vs 11%, p=0.77).16 No difference was found in the rate of caesarean section for the indication of failure of progress (7% vs 8%, p=0.86), either in the first or second stages of labour. Very early epidural was conducted at a mean cervical dilatation of 2.4cm, giving further assurance that risk of caesarean section is not increased even in very early stages of labour. The obstetric management, however was left to the responsibility of the obstetric team. The obstetric team made decisions regarding operative deliveries according to maternal or fetal indications. In this study, the only factor that affected the rate of caesarean section was the cervical dilatation at admission (p=0.02).

The effect of combined spinal-epidural analgesia in very early labour was investigated by Wong et al17. Seven hundred and fifty term nulliparous women in spontaneous labour or spontaneous rupture of membranes were recruited in a randomized controlled trial. All subjects had a cervical dilatation of less than 4cm. Women were randomly assigned to receive intrathecal fentanyl (very early) via combined spinal-epidural technique or systemic hydromorphone (late) at 1st request of analgesia. Epidural analgesia was initiated in the intrathecal group at 2nd request for analgesia and in the systemic group at cervical dilatation of 4cm or greater, or at the 3rd request for analgesia.

The rate of caesarean section was not significantly different between the groups (17.8% vs 20.7%, 95% CI –9.0 to 3.0%, p=0.31). The median cervical dilatation in the early group was 2cm, also confirming that the risk of caesarean section was not increased in very early stages of labour. Similarly in Rogers et
al, the rate of caesarean section was not significantly different between early vs late epidural placement (14.5% vs 7.9%, p=0.21). Therefore, there is no evidence to suggest that early epidural placement increases the risk of Caesarean section.

**EARLY EPIDURAL AND RISK OF INSTRUMENTAL DELIVERY**

Epidural infusion using a high concentration of local anaesthetics resulted in motor blockade and may increase the risk of instrumental vaginal delivery. Epidural analgesia with 0.25% bupivacaine infusion resulted in higher instrumental delivery rate than low dose 0.0625% bupivacaine with fentanyl. Other studies have also suggested that epidural administration of dilute local anaesthetics results in fewer cases of malposition than administration of a more concentrated solution. Some studies have suggested that early epidural analgesia results in pelvic floor relaxation interfering with internal rotation of the fetal head during labour. There is initial concern that epidural analgesia decreases maternal expulsive efforts during 2nd stage of labour.

Recent retrospective and prospective studies did not show an increase in instrumental delivery with early epidural placement. Chestnut et al did not find an increase in instrumental delivery in both nulliparous women receiving intravenous oxytocin or in spontaneous labour with early epidural placement. There was no increase in incidence of malposition of vertex at delivery. The rate of instrumental delivery was 43% in early epidural vs 49% in late epidural placement (not significant) in patients receiving intravenous oxytocin. The rate of instrumental delivery was 37% in early epidural vs 43% in late epidural placement (not significant) in patients in spontaneous labour. The results were consistent with earlier studies that showed the lack of effect of epidural analgesia on uterine contractile response due to oxytocin.

Modern epidural is administered using low dose local anaesthetics and adjuvant medications, allowing adequate pain relief without clinically significant motor weakness. Wong et al demonstrated that the risk of instrumental vaginal delivery was not increased with very early initiation of combined spinal-epidural analgesia with intrathecal fentanyl followed by low dose epidural infusion (19.6% very early vs 16% late) (p=0.13). Similarly, Ohel et al showed that the risk of instrumental delivery was not increased with very early initiation of epidural analgesia with 10ml 0.2% ropivacaine and fentanyl 50mcg (17% very early vs 19% late) (p=0.63). Therefore, the recent large randomized controlled trials appear to support that modern low dose local anaesthetic infusion for labour analgesia does not increase risk of instrumental delivery.

**EARLY EPIDURAL AND EFFECT ON PROGRESS OF LABOUR**

As introduced by O’Driscoll et al, active management of labour results in shortened labour in nulliparas, but its effect on rate of caesarean delivery is unclear. Active management of labour reduced duration of labour when compared to control protocol. In early epidural placement, there was a 1.4 hours reduction with active management of labour (10.9 ± 4.7 vs 12.3 ± 4.3, p=0.04). In late epidural placement, there was a 3.6 hours reduction with active management of labour (11.0 ± 3.6 vs 14.6 ± 6.2, p=0.004).

In Rogers et al, early epidural placement had shorter labour than late placement (11.6 ± 4.6 vs 13.2 ± 5.6 hours, p=0.02). The reduction of labour length is true regardless of when the epidural was placed, with no difference in rate of caesarean delivery. Chestnut et al showed that there was no prolonged 1st stage of labour with early epidural placement in both patient receiving intravenous oxytocin or in spontaneous labour.

A meta analysis of randomized trials comparing epidural with opioid analgesia showed that patients receiving epidural analgesia had longer labour. Autonomic imbalance has been proposed as an explanation for the association between epidural analgesia and prolonged labour. However, this has not been shown in recent studies. In fact, 2 studies showed that early epidural significantly shortens duration of first stage of labour. This effect could be potentially more profound with combined spinal-epidural technique. Tocodynamic parasympathetic efferent nerves are blocked by local anaesthetics, but presumably not by neuraxial opioids. This may explain why cervical dilatation is faster in combined spinal-epidural compared to plain epidural analgesia.
Intrathecal fentanyl decreases circulating adrenaline concentration and reduces maternal stress. This may reduce adrenaline-induced tocolysis, resulting in faster labour.

In the study by Ohel et al, at initiation of epidural analgesia, the mean cervical dilatation was 2.4 cm in early epidural and 4.6 cm in late epidural group (p<0.001). The mean duration from randomization to full dilatation was significantly shorter in the early compared to late epidural group (5.9 hours vs 6.6 hours, p=0.04). Similarly in Wong et al, the median time from the initiation of analgesia to complete dilatation was significantly shorter after intrathecal fentanyl via combined spinal-epidural technique than after systemic analgesia with hydromorphone (295 min vs 385 min, p<0.001), as was the time to vaginal delivery (398 min vs 479 min, p<0.001). The duration of 1st stage of labour was approximately 90 minutes shorter after intrathecal opioid administration than after systemic opioid administration. Additionally, some investigators found this could also be associated with combined spinal-epidural technique, as compared with conventional epidural technique.

There was no increase in duration of second stage of labour comparing early with late initiation of epidural analgesia. In patients receiving intravenous oxytocin, there was no significant difference in duration of 2nd stage of labour (91 min vs 77 min). Similarly, there is no significant difference in duration of 2nd stage of labour in patients in spontaneous labour (85 min vs 88 min). Even when epidural analgesia was commenced at very early labour, the 2nd stage of labour was not prolonged.

Different opioids may have different effects on uterine contractile activity in vitro. Fentanyl and meperidine inhibited uterine contractility in a concentration-dependent manner in human uterine muscle, whilst sufentanil and morphine had no significant effects on uterine contractility. However, the study was conducted at supraclinical concentrations. Opioids do not have a significant effect on spontaneous contractions of gravid human uterine muscle at their clinically relevant concentrations.

EARLY EPIDURAL AND ITS EFFECT ON NEONATAL OUTCOMES

In the study by Ohel et al, the mean APGAR scores at 1 and 5 minutes were similar in early vs late epidural placement groups. There were no cases of neonatal fever and sepsis workup done in all instances of maternal intrapartum fever was negative.

In the 2 studies by Chestnut et al using intravenous nalbuphine in the late epidural placement group, infants in the late group had lower umbilical arterial and venous blood pH and higher umbilical venous blood carbon dioxide tension measurements at delivery. It is likely that mild maternal hypercarbia resulted from administration of nalbuphine, followed by administration of epidural analgesia. However, the late group infants did not have an increased risk for hypoxaemia or metabolic acidosis at delivery. There were concerns of intrathecal fentanyl when compared with non-intrathecal techniques for the administration of opioid neuraxial analgesia due to a higher incidence of fetal bradycardia. Prolonged persistent variable and late fetal heart rate decelerations developing within 30 minutes after 1st analgesic intervention is more often in intrathecal than systemic analgesia group. However, the incidence is low and did not result in any adverse neonatal outcomes or emergency caesarean section due to non-reassuring fetal status.

The incidence of 1-minute APGAR scores below 7 was significantly lower after intrathecal fentanyl than systemic analgesia with hydromorphone (16.7% vs 24.0%, p=0.01). This is consistent with a previous study showing lower 1-minute APGAR scores in women assigned to receive systemic opioid analgesia compared to epidural analgesia, even though the opioid was administered early in labour, hours before the delivery. Systemic opioids readily cross the placental barrier and this may be associated with maternal sedation, lower 1-minute APGAR score and increased need for naloxone reversal. However, the 5-min Apgar score did not differ significantly.

EARLY EPIDURAL AND ITS EFFECT ON MATERNAL OUTCOMES

Pain Scores

Patients in the early epidural placement group had lower pain scores between 30 and 150 minutes after randomization compared to late epidural placement group with intravenous nalbuphine. Patients in the early group had analgesia of better quality and
were more satisfied with their analgesia, at 60 and 120 min after randomization. Pain scores after first intervention with intrathecal fentanyl (early) is significantly lower than after systemic analgesia with hydromorphone (late) (2 vs 6 on a 0 to 10 scale, p<0.001).¹⁷

**Maternal satisfaction**
Maternal satisfaction during delivery is an important outcome, as management of childbirth should be patient-centred. The Labour Agency Scale is an instrument measuring expectancies and experiences of personal control during childbirth based on psychometric and field studies.⁵⁷ It is a questionnaire in which higher scores would indicate greater degree of control felt by the mother throughout the process of labour and delivery. In the study by Ohel et al¹⁶, the mean score was 48.5 in early group and 46.7 in late group (p=0.046).

Two additional questions were asked: 1) following your particular experience with the timing of initiation of epidural analgesia, would you prefer, next time, to be allocated to the other study group? 2) were you satisfied with the epidural analgesia? When questioned after delivery regarding their next labour, the women indicated a preference for early epidural. In the late epidural group, 78.0% stated that in their next labour, they would prefer to be in the early group, whilst in the early epidural group, 7.0% prefer to be in the late group (p<0.001). This clearly shows that women prefer to have early epidural if given a choice. Therefore, delaying the epidural may lead to negative perception of labour pain, while earlier epidural may lead to better maternal satisfaction.

**Other maternal outcomes**
Women with epidural analgesia lasting more than 5 hours could have a higher risk of developing fever.⁵⁸,⁵⁹ Although women assigned to early initiation of epidural had long duration of labour, in 2 studies¹⁶,¹⁷, there were no differences in the rates of fever between early and late initiation of epidural analgesia. Two studies¹⁶,¹⁸ did not show difference in meconium staining of amniotic fluid and the need for manual removal of the uterus for retained placenta. There was no difference in estimated blood loss or episiotomy rates between early versus late epidural placement.¹⁸

**CONCLUSIONS**
We have found that the sample size of the many current studies might not detect a small difference in the rate of caesarean delivery. Obstetrical providers with differing management styles as well as hospital protocols, including oxytocin usage, may influence outcome of labour. Subjects with spontaneous or induced labour may have different outcomes based on oxytocin usage. Many of the studies reviewed were not blinded, as it may be difficult to conceal the randomization to epidural catheter insertion logistically. However, it is unlikely that the decision of the type or timing of analgesia would influence the obstetrician’s decision on delivery since epidural analgesia was provided eventually.

It was common belief that labour epidural analgesia should be started only after 4 to 5 cm of cervical dilatation. The parturient would need to endure hours of unnecessary discomfort and severe pain while on less optimal pain relief such as systemic opioids, with possible side effects to themselves and newborn.

In the recent 2006 review, ACOG has acknowledged that the impact of timing could have been overemphasized. The review states “ACOG previously recommended that practitioners delay initiating epidural analgesia in nulliparous women until the cervical dilatation reached 4 to 5cm. However, more recent studies have shown that epidural analgesia does not increase the risks of cesarean delivery”.⁶⁰

Our review has shown that since there were no adverse obstetric outcomes (e.g. increase in rate of caesarean section, instrumental delivery and duration of labour) associated with early initiation of epidural, it may be prudent to accommodate to the patient’s preference for early epidural analgesia. This would lead to better maternal satisfaction and lower pain scores, whilst not affecting obstetric and neonatal outcomes. To quote ACOG recent practice guidelines for obstetric analgesia in 2002 that “there is no other circumstances where it is considered acceptable for a person to experience severe pain amenable to safe intervention, while under a physician’s care and that maternal request is sufficient justification for pain relief during labour.”⁶¹
REFERENCES


The purpose of reliability and validity is to ensure that test that we used is able to capture the information where it suppose to capture. Usually, the tests largely are in the form of questionnaires. Most of the time, we adopt international questionnaires and since we are differed from one and another in terms of socio and cultural aspect, there is a need to validate the questionnaire (in its original form of English as well its translated version) to determine its application in local settings. Similarly, validation is needed if there are constructions or development of new questionnaires involved.

**RELIABILITY**

Reliability refers to consistency or stability of a measure. Reliability is a correlation coefficient (r) and is expressed from -1 to +1.

**TYPES OF RELIABILITY**

There few types of reliability. Among them are a) Test-retest reliability b) Inter-rater reliability c) Internal consistency

a) **Test-retest reliability**

Test-retest reliability is degree to which a measure correlates positively with itself over time (consistency of the measure over time). It measure the same person at two or more points of time. Retest can be done at 7-day, 14-day etc. If the retest is done at a longer period, there is possibility that the subject’s symptoms/response or inventory scores may change

The time 1 (test) is baseline and time 2 (retest) can be at 7-day or 14-day etc.
Table 1.0a: Possible responses at baseline and 7-day

<table>
<thead>
<tr>
<th>Item</th>
<th>Baseline No (0), Yes (1)</th>
<th>7-day No (0), Yes (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you feel anxious today?</td>
<td>?</td>
</tr>
<tr>
<td>2</td>
<td>Do you feel depress today?</td>
<td>?</td>
</tr>
<tr>
<td>3</td>
<td>Do you feel tired today?</td>
<td>?</td>
</tr>
<tr>
<td>4</td>
<td>Do you feel stress today?</td>
<td>?</td>
</tr>
</tbody>
</table>

The subjects are assessed at baseline and 7-day. In the baseline and 7-day, the subjects provide one answer, Yes or No. Table 1.0b showed different responses while Table 1.0c showed similar responses at baseline and 7-day.

Table 1.0b: Different responses at baseline and 7-day

<table>
<thead>
<tr>
<th>Item</th>
<th>Baseline</th>
<th>7-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you feel anxious today?</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Do you feel depress today?</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Do you feel tired today?</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Do you feel stress today?</td>
<td>1</td>
</tr>
</tbody>
</table>

The responses for the 4 items above at 7-day are different to the responses at baseline.

Table 1.0c: Similar responses at baseline and 7-day

<table>
<thead>
<tr>
<th>Item</th>
<th>Baseline</th>
<th>7-day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you feel anxious today?</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Do you feel depress today?</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Do you feel tired today?</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Do you feel stress today?</td>
<td>1</td>
</tr>
</tbody>
</table>

The responses for the 4 items above at 7-day are similar to the responses at baseline.

Table 2.0: Depression scores of subjects at baseline and 7-day

<table>
<thead>
<tr>
<th>Subject</th>
<th>Depression total scores</th>
<th>Mean Difference</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>7 days later</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>12</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>13</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>17</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>13</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>8</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>9</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10.10</td>
<td>10.30</td>
<td>-0.2</td>
<td>0.758</td>
</tr>
<tr>
<td>SD</td>
<td>3.07</td>
<td>3.59</td>
<td>1.99</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.0 showed the depression scores at baseline and 7-day of 10 subjects. If majority of subjects giving the same answer/response at baseline and 7 or 14-day, the reliability (coefficient) value would be high. In this example, the Pearson’s correlation coefficient, $r$ between baseline and 7-day for the 10 subjects is 0.83 ($p=0.01$) and this showed that the reliability is high.

Since the mean difference of the depression scores did not change much from baseline to 7 days, therefore, the $p$ value obtained is not statistically significant. If there are changes in the depression level at baseline or 7-day, then the $p$ value may be statistically significant but not in this case. In the above case, the subjects are in stable condition and usually this group is used as control group.

**b) Inter-rater reliability**
Inter-rater reliability is a degree to which independent raters/observers agree on an observation. It comprises two or more judges/observers to rate the same people. These judges or raters are trained and they are independent.

**Table 3.0: Measures of agreement between the raters**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Rater /Observer 1</th>
<th>Rater /Observer 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia (0=No, 1=Yes)</td>
<td>Schizophrenia (0=No, 1=Yes)</td>
</tr>
<tr>
<td>Patient 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Patient 8</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
The measures of agreement between the two raters are called Kappa statistic and given by the value ranging 0 (poor agreement) - 1.0 (perfect agreement). In the above example, the Kappa value generated is 1.0. Both raters give same ratings/scores for all the patients (Table 3.0).

INTERNAL CONSISTENCY

Internal consistency is a degree to where all specific items of a measure behave the same way (The degree to which scores of each question correlate with the overall test score) (Do the questions agree with each other?) It measures the same person (outcome) with multiple items e.g. different questions/items in a survey. The low internal consistency indicates that there are problems with the items in the test.

There are many ways to assess internal consistency of a measure / instruments / questionnaires. Among them are mean inter-item correlations, split-half reliability, Cronbach’s alpha.

a) Mean inter-item correlations
Mean inter-rater correlations is a correlation between each possible pair of items (Table 4.0) and followed by averaging the correlation values

E.g.  
• Correlation between item 4 and item 5 = 0.85  
• Correlation between item 5 and item 6 = 0.90  
• Correlation between item 4 and item 6 = 0.89  
• Mean inter-item correlation =\( \frac{0.85+0.90+0.89}{3} = 0.88 \)

<table>
<thead>
<tr>
<th></th>
<th>Item 1</th>
<th>Item 2</th>
<th>Item 3</th>
<th>Item 4</th>
<th>Item 5</th>
<th>Item 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Item 1</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Item 2</td>
<td>0.86</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Item 3</td>
<td>0.87</td>
<td>0.89</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Item 4</td>
<td>0.90</td>
<td>0.84</td>
<td>0.95</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Item 5</td>
<td>0.85</td>
<td>0.91</td>
<td>0.88</td>
<td>0.85</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Item 6</td>
<td>0.94</td>
<td>0.86</td>
<td>0.930</td>
<td>0.89</td>
<td>0.90</td>
<td>1.00</td>
</tr>
</tbody>
</table>
b) Split half reliability
Split half reliability is a measure where the test/questionnaire is split into first half and second half. The items are randomly assigned and divided/split into 2 subgroups and the consistency of the total scores is examined across the 2 subgroups. The scores for one half of the test are then correlated with the scores of the other half of the test (Figure 1.0).

![Diagram of test/questionnaire divided into two subgroups]

Figure 1.0: The items in the test/questionnaire is divided into two subgroups

c) Cronbach’s alpha
Cronbach’s alpha is the mean reliability coefficient from all possible split-halves (SH). Usually, a cut-off for internal consistency is 0.70 and Cronbach alpha can be directly generated from statistical software.

![Diagram of reliability coefficients of all possible split-halves]

Figure 2.0: Reliability coefficients of all possible split-halves
**VALIDITY**

Validity refers to the accuracy of a measure. A good measure must not only be reliable but also valid. A valid measure measures what it is intended to measure. Table 5.0 shows type of validity and its examples.

<table>
<thead>
<tr>
<th>Type of Validity</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face validity</td>
<td>Judgments made by the researcher/observer based on surface appearance.</td>
<td>Examine the wording of the items by expert panels/judges.</td>
</tr>
<tr>
<td>Content validity</td>
<td>The extent where a measure represents a balanced and adequate sampling of relevant domains, knowledge &amp; skills.</td>
<td>E.g. QoL questionnaire where questions covers physical/functional, mental health, social status etc.</td>
</tr>
</tbody>
</table>
| Criterion related validity| Criterion is an independent measure/instrument which acts as standard or reference for another measure.  
Is a standard where the measure is being judged or evaluated. | Depression measures / inventories that distinguishes between subjects who are depressed and those who are not.                     |
| -Convergent validity      | Correlate the scores which obtained from your measure with another scores from another measure that claims to measure the same concept or construct. | A new depression scale correlate the scores with the scores of BDI (which is a well established and has good psychometric properties).  
To have a good convergent validity, the two measures need to correlate highly (i.e. >0.80).          |
| -Discriminant validity    | Discriminant validity is the degree to which scores on a measure/test do not correlate with scores from other measures/tests which are not designed to assess the same construct. | Anxiety and Depression Measures                                                                                                                                                                 |
| Construct validity        | The degree / extend to which a measure is measuring a concept or construct which it claims to measure  
Does the measure or instrument actually measure the concept or construct? | Does the new anxiety measure actually measure anxiety?  
Measures that are lacking in construct validity are not good.                                                                                         |
Table 5.0: Type of validity

1) Convergent validity

Table 6.0: Example of convergent validity (criterion related validity)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Depression Inventory (Total scores)</th>
<th>New Depression Inventory (Total scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 6.0 showed an example of convergent validity. Spearman’s correlation coefficient (correlation between the scores of depression inventory and the scores of new depression inventory) is 0.92.

2) Construct validity

Construct validity can be examined by using Exploratory Factor Analysis (EFA) with Principal Component Extraction method (PCA) and Varimax rotation. The function of EFA is to reduce the number of items in the inventory which proven to be problematic or inserted the item back into the inventory after changes or revision on the item is done following EFA. The factor analysis is widely used in development of new questionnaire/inventory and test whether the items are good to be included or otherwise.
The following are the factor matrix derived from the PCA with Varimax rotation analysis

**Table 7.0: Factor matrix from Factor analysis**

<table>
<thead>
<tr>
<th>Items in the inventory</th>
<th>Varimax rotation factor matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Factor 1</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
</tr>
<tr>
<td>Item 1</td>
<td>0.72</td>
</tr>
<tr>
<td>Item 2</td>
<td>0.68</td>
</tr>
<tr>
<td>Item 3</td>
<td>0.65</td>
</tr>
<tr>
<td>Item 4</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
</tr>
<tr>
<td>Item 5</td>
<td>0.13</td>
</tr>
<tr>
<td>Item 6</td>
<td>0.23</td>
</tr>
<tr>
<td>Item 7</td>
<td>0.09</td>
</tr>
<tr>
<td>Item 8</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td></td>
</tr>
<tr>
<td>Item 9</td>
<td>0.31</td>
</tr>
<tr>
<td>Item 10</td>
<td>0.26</td>
</tr>
<tr>
<td>Item 11</td>
<td>0.29</td>
</tr>
<tr>
<td>Item 12</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Table 7.0 showed the distribution of factor loading for the items in the inventory. Factor 1 correspond with Depression with loading from 0.65 to 0.76, Factor 2 correspond with Anxiety with loading from 0.68 – 0.79 and Factor 3 correspond with most items with loading from 0.67 – 0.78 except item 12 which associated with Factor 2. This item 12 either needs be revised to improve the item or removed from the inventory. These three factors are found clearly associated with the construct of depression, anxiety and stress as can be seen as a clear distribution/association with their relevant items except for item 12.

**CONCLUSION**

A measure can be reliable but not valid. To be valid it must be reliable. Both reliability and validity are important for any research study that requires accurate measurement.

**References**

**Case Report**

**ACUTE TRACHEOSTOMY TUBE FRACTURES: POTENTIALLY FATAL COMPLICATIONS**

M. Shahnaz Hasan, M. Anaes; F. Y. Yap, M. Anaes; Y. K. Chan, FFARCS

**ABSTRACT**

Tracheostomy tubes are alternative airways that can be life-saving but may also be life-threatening especially if they unexpectedly fracture. It is important to realize how they should be managed if they fracture in order not to escalate into life-threatening events. The distal fractured portion if not removed properly can be the cause of fatal obstruction.

**Keywords**: acute, fractured tracheostomy tube, fatal

**INTRODUCTION**

Tracheostomy tubes are used as alternative airways either in life saving arrangements or as a means to better control the airway especially in patients who need prolonged ventilatory support or are likely to require prolonged support. Most times they serve very useful functions of allowing patients’ airway to be controlled and allowing care providers to tide over life-threatening situations in patients.

They can however prove to be the source of threat to life and if complications are not responded to appropriately these threats may spell the end of the patients’ life. We report here two cases of newly inserted tracheostomy tubes which sustained fractures causing near fatal consequences.

**CASE REPORT 1**

Mr. A was a 77 year old Chinese man with a perioperative cerebral infarct who needed a tracheostomy to facilitate weaning from the ventilator. An open tracheostomy was performed on the fourth post operative day using a size 7.5 mm poly-vinyl chloride (PVC) tracheostomy tube.

Four hours following the tracheostomy, on returning to the Post Anaesthetic Care Area (PASCA) after a repeat CT scan, the patient was placed back on synchronised intermittent mandatory ventilation. However, on connecting the patient to the ventilator a huge air leak was noted around the tracheostomy site; this was not present previously. On further inspection, the tube was found to have fractured at the neck level and the distal portion had migrated into the trachea with the pilot balloon still attached (Fig. 1).

The initial management was directed at maintaining a patent tracheostomy tract despite a fractured distal portion. However, his vital signs did not remain stable for too long. He desaturated as obstruction developed and a decision was made to deflate the cuff of the tracheostomy tube to enable ventilation through the orotracheal route via a hand held face mask and bag (Fig. 2). This proved to be successful and the surgical team proceeded to explore the tracheostomy wound for removal of the fractured distal portion (Fig. 3). Following retrieval of the distal portion via the...
tracheostomy wound, a new tracheostomy tube was reinserted and ventilation resumed (Fig. 4).

CASE REPORT 2

Mrs. B was a 35 year old Chinese lady who was on long term ventilation in the Intensive Care Unit for complications resulting from Hereditary Hemorrhagic Telangectasia.

An elective open tracheostomy was performed on the third week of ICU admission. The procedure was uneventful, and a PVC tracheostomy tube size 7.5mm was inserted. At the end of the procedure, on transfer of the patient to the transport trolley, a big leak in the breathing system occurred and the tracheostomy tube was noted to have similarly fractured at the neck level, with the distal portion migrating into the trachea. The immediate management by the surgical team was an attempt to extract the distal portion, guided by the pilot balloon. Fortunately, this proved successful and subsequently the patient was intubated orally and ventilation controlled as the surgical team prepared to re-xplore the tracheostomy wound and reinsert a new tracheostomy tube.

DISCUSSION

The two case reports displayed 2 different ways of handling the fractured distal end of the tracheostomy tube. In the first case, the care-providers opted not to pull the distal end out via the pilot balloon. This was because snapping of the tenuous connection of the pilot balloon with the distal end could occur and
may spell total obstruction of the airway under those circumstances. The option was to let the air out of the cuff in the distal part of the tracheostomy tube so as to allow an airway passage to be created at least around the tube for the patient to be ventilated without loss of the airway.

The care providers in the second case opted to pull out the distal portion of the tracheostomy tube via the pilot balloon. They were in the vicinity of an area where exploration could be immediate if the pilot balloon snapped whereas this was not so in the first case.

Fracture of a tracheostomy tube is a rare complication following open tracheostomy. Late breakage and aspiration of part of the fractured tube (broken tube, flange, introducer) has been documented in a few cases in adults and children and they are a major cause of morbidity and mortality.

Most cases of fractured tubes in the literature have been associated with usage for a longer duration than recommended. Fractures could be attributed to chemical stress (alkaline tracheobronchial secretions, corrosive cleaning fluids) or mechanical stress (repeated removal-reinsertion, boiling, cleaning, sterilization). Some had been on irregular follow up and some practised their own method of tracheostomy tube care.

The fractured tubes in the reported cases were successfully removed with either a rigid or flexible bronchoscope as their clinical presentations were more insidious. Bronchoscopy is the commonly used procedure for removal of foreign bodies and rarely was a thoracotomy or bronchotomy required.

In contrast, early breakages are from detachments at the wing-tube junction and are most likely due to manufacturing defects and perhaps a design flaw. (Fig. 5)

Both the patients were fortunate because prompt exploration by the surgical teams allowed retrieval of the fractured tubes. The operating theatre was prepared and aids to intubation and ventilation including flexible fibreoptic and rigid bronchoscope were made available should removal of the tube under direct vision prove unsuccessful.

On examination, both the tracheostomy tubes were noted to be cleanly separated, rather than fractured, from the wing (Fig. 6). The tracheostomy is manufactured in two parts with the body and wing glued together. Surgeons should check for...
manufacturing defects before the first use of tracheostomy tubes. Designing a tracheostomy tube that comes in one piece may reduce the occurrence of this rare but life-threatening complication. The manufacturers have since been alerted together with the batch numbers of the tracheostomies associated with the incidents.

REFERENCES

10. Smith FV October. An unusual complication of tracheostomy. *Anaesthesia October* 1999; 54; 1011-1012.
Case Report

PERSISTENT CEREBROSPINAL FLUID LEAK FOLLOWING COMBINED SPINAL-EPIDURAL ANAESTHESIA

Sumiati M. Daud FFARCSI (Ire), Lee Choon Yee M Med (Anaes) UKM, FANZCA.

ABSTRACT

The combined spinal-epidural (CSE) technique has become increasingly popular in obstetric anaesthesia and analgesia. Persistent cerebrospinal fluid (CSF) leak following the CSE technique is a rare complication. The natural history and pathophysiology of this complication is unknown and the optimal management is still yet undetermined. In our case report, we describe our experience with a parturient who received a CSE block for labour and subsequent caesarean delivery, but developed a persistent fluid leak from the insertion site after epidural catheter removal. We discuss our diagnosis, management options and their possible complications. We opted for conservative management, which proved to be successful and the patient was discharged with no sequelae.

Keywords: Combined spinal-epidural complications; cerebrospinal fluid leak.

INTRODUCTION

Combined spinal-epidural (CSE) technique has become increasingly popular particularly in obstetric patients during labour and caesarean section. Persistent cerebrospinal fluid (CSF) leak following CSE is an apparently rare complication. Many of the cases of persistent CSF leak reported previously have been following surgery where there was a risk of surgical breach of the dura, such as neuro-surgical procedures, spine surgery or thoraco-abdominal aortic aneurysm repair.

In 2004, Chan described three cases of persistent CSF leak following the CSE technique¹, and discussed the uncertainty of diagnosis, management and implications of the persistent CSF leak. This report prompted a few letters to the editor reporting similar cases of fluid leak from an epidural site²³. We describe one parturient who had undergone CSE anaesthesia but developed persistent fluid leak from the insertion site after epidural catheter removal.

CASE REPORT

A 31-yr-old nulliparous woman at 39 weeks gestation was admitted to the delivery suite in our hospital in early labour. She requested for epidural analgesia after 12 hours in labour when cervical os was 6 cm dilated. With the parturient in the sitting position and under aseptic technique, a combined spinal-epidural (CSE) block was performed at the L3-4 interspace. The procedure was uncomplicated and the block was successful after the first attempt. The CSE kit used was one that was routinely available in our unit – BD Durasafe™ Plus, which contains an 18G Weiss epidural needle, a 27G Whitacre spinal needle and a 20G polyamide closed-end multi-orifice epidural catheter. As per protocol in our unit, 0.2% ropivacaine 1.0 ml with fentanyl 25 μg was

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administered intrathecally, followed by an epidural infusion of 0.0625% ropivacaine with fentanyl 2 μg/ml at 12 ml/hr. Effective pain relief was immediately achieved, and sensory level to pinprick was tested to be at the T10 dermatome.

An hour later, the obstetrician decided to proceed with caesarean section due to poor progress of labour. Epidural anaesthesia was established with a total of 5 ml 2% lignocaine, 10 ml 0.75% ropivacaine and 100 μg fentanyl, administered in divided doses. The patient developed lower limb motor blockade and a sensory loss to pinprick up to T3. She was comfortable throughout the caesarean section and did not complain of any symptoms that might suggest a high spinal blockade.

The surgery concluded uneventfully. In the recovery ward, the patient developed post-partum haemorrhage with an estimated blood loss of 1 L. She was transfused two units of packed cells and treated with oxytocics. The problem settled and no surgical intervention was deemed necessary. Her post-transfusion haemoglobin was 9.4 g/dl. Epidural was not utilized for postoperative analgesia because the obstetrician was concerned that the epidural might potentiate hypotension should it occur. The epidural catheter was left in situ and was only removed on the second postoperative day before the patient was discharged from the ward.

The patient returned to the hospital 15 hours after discharge with a complaint of a “wet back” and was readmitted to the post-natal ward. According to the patient, she was aware of the wetness even prior to discharge but regarded it as merely perspiration at the back. After she returned home, her clothes became very wet and she had to use four to five pieces of facial cotton taped together to cover the epidural insertion site. These were changed about five times over the 15 hours, and they were soaking wet when removed. Clear fluid was seen dripping down her back from the epidural insertion site. She had no complaints of headache, dizziness, nausea, vomiting, numbness, weakness or fever.

The patient was well and afebrile. Neurological examination was normal, and examination of all other systems was unremarkable. Inspection of her back revealed a soaked pressure bandage which was applied by the staff in the emergency department. There was no back or sacral oedema. When the bandage was removed, clear fluid was seen dripping from the epidural insertion site. This was exacerbated when digital pressure was applied around the puncture site and when the patient was asked to cough. The fluid tested positive for glucose, measured at 4.7 mmol/l on glucometer (Optium™, Abbott, USA), while plasma glucose from the blood sample taken simultaneously was 5.0 mmol/l.

Management of the patient was along similar lines to the management of post-dural puncture headache (PDPH). She was advised to have complete rest in bed, preferably in the supine position for at least six hours. As it was already evening, she was kept in bed overnight. She was advised to increase oral fluid intake, in addition intravenous fluid was administered to ensure adequate hydration. The epidural insertion site was covered with compression bandage, subcutaneous heparin was prescribed for prophylaxis against deep venous thrombosis and analgesia was prescribed as required. The patient was asked to report any headaches or other neurological symptoms. A total of 1.5 L of crystalloids was infused over 12 hours, she did not require any analgesia and she used a bed-pan to empty her bladder while in bed.

The patient remained asymptomatic when she was reassessed the following morning. Both the bandage and the epidural insertion site were dry and no fluid was observed even on applying pressure around it. Pressure bandage was re-applied and the patient was allowed to ambulate. She was re-examined eight hours later. The bandage and the epidural insertion site remained dry. She was allowed home the following day. She remained well and had no further complaints on follow-up.

**DISCUSSION**

The combined spinal-epidural (CSE) technique has become increasingly popular, particularly in obstetric patients during labour and caesarean section. In labour, the intrathecal component gives an almost instantaneous and excellent pain relief, while the epidural infusion provides continuous analgesia during labour and delivery. For caesarean section, the intrathecal component provides a dense sensory and motor blockade of rapid onset, while the epidural component can be used to supplement an
occasional inadequate anaesthesia and for provision of postoperative analgesia. The popularity of the CSE technique has also extended to anaesthesia for other surgical procedures, in particular gynaecologic, urologic and orthopaedic surgeries.

Persistent cerebrospinal fluid (CSF) leak is a rare complication which has been reported following epidural anaesthesia as well as continuous spinal anaesthesia. Chan described three cases of persistent CSF leak following the CSE technique. In all three cases, the patients were asymptomatic and did not develop any complications of CSF leak such as PDPH, fever, meningism or neurological deficits. They were ultimately treated by insertion of skin sutures to the epidural site to reduce the risk of meningitis, but one patient required further suturing of the fistulous tract due to persistent leak. In two of the cases described, the fluid was tested using β2-transferrin immunofixation assay which confirmed the presence of CSF. This assay almost unequivocally identifies the presence of CSF and can be performed on very small samples of fluid (< 0.1ml). Another diagnostic test which has been described is the nephelometric assay of β-trace protein, which is considered the best method of detecting CSF rhinorrhoea and otorrhoea. McArthur et al evaluated the technique in term parturients and concluded that the nephelometric measurement of β-trace protein might prove a useful diagnostic test for CSF-cutaneous fistulae after CSE in parturients. Unfortunately, these assays are not available in our institution. However, the presence of glucose in the fluid from our patient which corresponded closely with her plasma glucose level convinced us that the leaking fluid was indeed CSF.

In the absence of reliable tests for CSF, the nature of the fluid may be open to question. Ennis reported an asymptomatic patient with persistent cutaneous fluid leak from the puncture site following a CSE technique. The fluid tested positive for glucose at a level similar to the plasma level. However, they concluded that this fluid was actually interstitial oedema fluid when the fluid aspirated 4 cm lateral to the epidural site and 1 cm deep to the skin also tested positive for glucose. In this particular case, the leak only occurred five days after removal of the epidural catheter in contrast to our patient where the leak occurred soon after the epidural catheter was removed. In all similar cases that have been previously reported, the leak occurred within 48 hours of removal of the epidural catheter. Bansal reported similar findings in a patient who had an epidural infusion for postoperative analgesia following laparotomy. The epidural catheter was removed after the second postoperative day, and three hours later clear fluid was seen leaking from the epidural puncture site. On examination, the patient was asymptomatic, and the back revealed dependent oedema along the length of the back and a normal epidural puncture site. The fluid was tested with a reagent strip, which was consistent with the fluid being interstitial fluid and not CSF. The leak subsided spontaneously on the fifth postoperative day without any further active management.

In our institution, approximately 2500 CSE blocks per year have been performed since 1998, for both obstetric as well as surgical indications. This is the first case in which a persistent leak of CSF has been encountered. The persistent CSF leak suggests continuity between the subarachnoid space and the epidural insertion site, created by 1) the spinal needle, 2) the epidural needle, or 3) the epidural catheter.

1) The spinal needle
The puncture in the dura made by the spinal needle may not have been able to close and a fistulous tract may have formed. However, it is surprising that a tiny dural puncture made by a 27G spinal needle could result in such a large volume of CSF leak.

2) The epidural needle
Another possibility is that of an accidental, unrecognized breach of the dura made by the 18G epidural needle. Difficulty in performing the technique requiring multiple attempts is a risk factor for inadvertent dural puncture. However, it is interesting to note that in approximately 30% of parturients with PDPH following epidural, the procedure was documented to be uneventful. In our case report, the absence of difficulty encountered during the procedure, evidence of dural puncture, and clinical features of PDPH make this possibility highly unlikely.

3) The epidural catheter
Intrathecal migration of an epidural catheter is a rare occurrence and is usually facilitated by a
unrecognized partial breach in the dura during the procedure. This may cause a fistulous tract to form, even though inflammatory fibrous reaction around the intrathecal catheter is postulated to result in oedema or fibrin exudates, sealing the dural tear and reducing leakage of CSF after catheter removal\textsuperscript{10,11}. In the presence of an epidural catheter sited intrathecally, administration of large volumes of local anaesthetic meant to achieve epidural anaesthesia would result in a high or total spinal. In our patient, the sensory level and motor blockade were consistent with the volume of local anaesthetic administered through the epidural catheter to provide surgical anaesthesia for caesarean section, and there were no signs or symptoms suggestive of a high or total spinal.

In the absence of reports, it is questionable whether persistent CSF leak after a CSE technique is truly a rare occurrence or that it has been under-diagnosed or under-reported. It is possible that leakage of fluid – be it interstitial fluid or CSF – may be much more common than currently acknowledged in the literature\textsuperscript{12}. We routinely use a transparent, occlusive dressing (Op-Site\textsuperscript{®}, Smith & Nephew, UK) over the epidural insertion site to allow ease of inspection. A small fluid collection within the transparent dressing may be mistaken for tissue oedema or back-tracking of the epidural solution along the catheter onto the skin. If a fistulous tract had formed, there would be overt leakage after removal of the epidural catheter. Following removal of the epidural catheter, we routinely place a small bandage onto the epidural insertion site. A small leak wetting the bandage may be mistaken as perspiration or oedema fluid and hence remain unrecognized and undiagnosed. Only a sufficiently large leak would become problematic enough for the patient to seek medical advice.

The natural history and pathophysiology of this complication is still unknown and the optimal management is still yet to be determined. This is due to its apparent rare occurrence resulting in a lack of experience in the management. If left untreated, the patient may risk developing meningitis or an incapacitating headache. In the report by Chan, all three patients had the epidural insertion site closed with skin sutures; and one patient required further suturing of the fistulous tract due to persistent leakage\textsuperscript{1}.

Katz suggested epidural blood patch as treatment for persistent CSF leak\textsuperscript{13}. He argued that suturing the skin closed would be inadequate if indeed a fistula was present, since the pathology would persist, namely a fistulous communication of the subarachnoid space with more superficial tissues. An epidural blood patch would disrupt the fistula at the most proximal site of the leak, i.e. at the hole in the dura. However, epidural blood patch is not without possible complications. Infection could be blood-borne or could be introduced during the procedure itself. The presence of an open fistula connecting the epidural blood patch with the skin is potentially an easier route of entry for bacteria to cause infection. If the risk of meningitis from a subarachnoid cutaneous fistula is high, the risk of epidural abscess following a blood patch is also likely to be high\textsuperscript{14}.

Since our patient was completely asymptomatic other than the CSF leak, we felt that it was appropriate to adopt an initial conservative approach of complete bed rest with measures to prevent PDPH and deep vein thrombosis. This proved to be successful for our patient. We postulate that with bed rest, there was reduced leakage through the breach in the dura and allowed spontaneous closure of the dural puncture. Had the patient continued to leak from the epidural site the next day, further measures might have to be taken, which may include an epidural blood patch with or without suturing of the skin at the epidural insertion site.

REFERENCES

Guide to Contributors.

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Three copies of each manuscript should be submitted. It should be typewritten double-spaced on one side of A4 sized paper with 3 cm margins all around and organized as follows, with each section on a separate page.

Title page:
The title page should indicate
- Title of the article
- Name, highest qualifications and full address of each of the authors
- Department / Institution (s) where the work was done
- Telephone, fax number and e-mail address of the author responsible for correspondence

Abstract
The abstract and should concisely describe the main purpose of the study, salient findings and conclusions. Statements such as “the findings will be discussed” should be avoided.

Text
The text should include the following sections with sub headings where relevant to the paper:
- Introduction
- Materials and Methods / Methods including statistical analysis
- Results
- Discussion
- Articles involving research conducted in human subjects must include a statement that Institutional Ethics Committee approval and patient consent has been obtained
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Illustrations
Line drawings, charts or graphs should be computer generated, black on white on high quality paper. Black and white photographs should be supplied as glossy prints - not mounted. They should be protected adequately for mailing and the surface should not be marred by clips or staples. All figures must be cited in the text, numbered in order of appearance and should indicate the orientation. Brief legends should accompany all figures and must be typed double-spaced on a separate sheet of paper.

The three copies of the manuscript should be accompanied by three sets of illustrations / figures.

All photographs should be clearly numbered at the back with a soft pencil, with reference to the text. An arrow should indicate the top of the illustration, where appropriate.

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Tables should be typewritten double spaced on a separate page and numbered in order of appearance in the text using Arabic numerals and accompanied by a brief descriptive title. Abbreviations used in the table should be explained in the legend to the table. Each table should consist of two or more columns. Tables with one column will be treated as lists.
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Acknowledgements
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References should be restricted to those that have a direct bearing on the work described. Except for review articles, long lists of references are usually inappropriate. All references should be numbered consecutively in the order in which they are first mentioned in the text. References in the text, tables and legends should be identified by Arabic numbers appearing as superscript. When a reference is cited at the end of a sentence, the number should appear after the full-stop (period). Unpublished data and personal communications should be indicated as such in the text in brackets and not listed in the references.

A maximum of 30 references is acceptable for an original article and 10 for short communications such as case reports.

The list of references should be typed in the Vancouver style and the abbreviations of journal titles should follow that of Index Medicus. The first four authors followed by the abbreviation et al should cite references with more than four names. The following examples should serve as a guide. It is extremely important that all references quoted are accurate.

Journals

Monographs

Following acceptance of the article the following should be submitted:
1. The revised manuscript both as a hard copy (2 copies) and on a 3.5” HD disk PC (IBM) saved as a Microsoft Word file (Version 6) - (Windows 2000 operating system should not be used). The disk should be clearly labeled and only the final version of the article should be found on the disk.
2. The software used to generate charts, diagrams, graphs should be indicated.
3. A letter signed by all authors agreeing to transfer the copyright of the article to the publisher with a statement that all authors have read and agreed with the contents of the manuscript.

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