PERIODICUM BIOLOGORUM
VOL. 115, No 2, 209–218, 2013

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Original scientific paper

An different approach to CSE-EVE for reducing hypothension during Caesarean section under spinal anaesthesia

LADA KALAGAC FABRIS[1]
DRAGAN BELCI[1]
LIVIJA ŠAKIĆ[1]
ZLATKO HRGOVIĆ[2]

[1]Departement of Anesthesia and ICU
General Hospital Pula, Pula, Croatia

[2]Departement of Anesthesia and ICU,
Clinical Hospital "Sveti Duh" Zagreb
School of Medicine-University Zagreb,
Croatia

Correspondence:
Lada Kalagac Fabris, MD.
Departement of Anaesthesiology
and Intensive Care,
General Hospital Pula,
Pula – 52100, Croatia
E-mail: lada1966@gmail.com

Key words: Combined spinal-epidural anaesthesia, epidural volume expansion, levobupivacaine, hemodynamic, caesarean section

Received May 20, 2013.

Abstract

Background and Objectives: *Spinal anaesthesia is the most preferred anaesthetic technique for elective as well as for unplanned Caesarean section. Spinal-induced hypotension remains the most important side effect with a reported incidence between 20% and 100%. It can cause maternal discomfort (nausea and vomiting) and impaired utero-placental perfusion. The present study was designed to examine the influence of epidural volume effect on the spread and duration of low dose hyperbaric levobupivacaine. The aim of this study was to evaluate the influence of epidural restriction (injection of saline) on the distribution of anaesthesia as well as the incidence of hypotension during the spinal anaesthesia.*

Methods: *After the approval by Ethics Committee, 60 full term parturient women (ASA I or II) with uncomplicated pregnancies were prospectively randomized into two groups: SA group (single shot spinal anaesthesia) included 37 patients and CSE-EVR (combined spinal-epidural anaesthesia) included 39 patients were we induced the restriction of the spinal space by epidural volume compression. The blocks were performed at L2/3 or L3/4 level in sitting position, in CSE-EVR group using the needle through-needle technique. The initial dose for CSE-EVR was exactly half of the SA dose (0,5 mg per 10 cm height of hyperbaric levobupivacaine and 20microg fentanyl). After spinal injection, an epidural catheter was located in the CSE-EVR and injected a volume of 20 ml saline solution. After injection women, were turned supine with a left uterine displacement. Surgery was allowed when a sensory block at or above T8 dermatome was established. We evaluated the height of the block by the pinprick method and the motor block by Bromage scale, 10 minutes after spinal injection, during the operation time and at the end of surgery. Hemodynamic monitoring (NIBP, HR) was assessed every 2 minutes until the childbirth, then every 5 minutes during operative time. Anaesthetic efficacy was evaluated for breakthrough pain by visual analogue pain score (VAPS), Apgar score at birth, umbilical artery-pH, and epinephrine consumption.*

Results: *The level of anaesthesia 10 minutes after the induction was significantly higher in spinal group (SA) than in CSE-EVR T5 (T4-T7) vs.T7(T6-T8).The SA group experienced complete motor block during the time of anaesthesia, while the CSE-EVR group demonstrated significantly faster motor recovery. The incidence of hypotension and ephedrine supplementation was significantly lower in the CSE-EVR group (19 patients vs.35) than in the SA group ($p<0.05$).The neonatal outcome and umbilical*

artery-pH was higher in the CSE-EVR group. Both groups were comparable in demographic data, VAS scores, preloading and infusion volume, atropine or ephedrine use, and adverse effects as nausea or skin pruritus.

Conclusions: *We demonstrated a possible restriction of the spread of spinal anaesthesia by using epidural volume restriction with 20 ml saline as part of a combined spinal epidural technique. The study shows that CSE with EVR with only 50% of the levobupivacaine dose provided adequate anaesthesia for elective caesarean delivery, as well as better maternal hemodynamic stability.*

INTRODUCTION

Regional anaesthesia had become the most preferred technique for elective operative delivery as well as for unplanned Caesarean section since the general anaesthesia is associated with higher maternal morbidity and mortality *(1, 2)*. However, there is a great risk of hypotension after the subarachnoid block for caesarean delivery, with a reported incidence greater than 80% *(3, 4)*. Hypotension can cause maternal discomfort with detrimental effects on uterine blood flow and fetal acidosis. Apgar scores and umbilical artery pH are measures for neonatal outcome. Several strategies have been adopted to prevent and treat hypotension; left uterine displacement, intravenous fluid preload, compression stocking on the legs and prophylactic vasopressors *(5, 6, 7)*. However, no method has proved satisfactory and even some of these strategies resulted in side effects: large volumes of i.v. fluids increase the risk of iatrogenic pulmonary oedema, prophylactic ephedrine has been associated with fetal acidosis or phenylephrine can cause maternal arrhythmias *(8, 9, 10, 11)*.

Some studies have indicated that the main source of this problem is caused by the local anaesthetics, so the aim of the reasonable spinal anaesthesia is to reduce the dose of the drugs *(12)*. For this reason in some obstetric units anaesthesiologists introduced the use of combined spinal-epidural anaesthesia technique (CSE). Spinal block offers a rapid onset, while the presence of an epidural catheter allows flexibility in extending the block and provision of postoperative analgesia *(13)*. Recently, this technique has undergone several modifications designed to increase its safety and efficacy.

All previous studies have administered some local anaesthetics or saline for epidural volume extension-restriction (EVR) through the epidural catheter to induce compression of the subarachnoid space and to promote the spread of the local anaesthetics previously introduced in the subarachnoid space *(14, 15, 16)*. This provides reinforcement of spinal anaesthesia by the epidural volume effect. Takiguchi et al, using myelography, demonstrated that the diameter of the subarachnoid space decreased to less than 25% of its original value after injection of 10 ml of saline, explaining the mechanism of action of the epidural volume effect *(17)*.

In clinical situations it is common the use of hyperbaric anaesthetic solution for keeping the spinal block primly about the lumbar-sacral region of the patients *(18)*.

We hypothesized that with deeper positioning of the epidural catheter and an appropriate volume of saline solution (20 ml) for the epidural volume extension, we can provide a transitory stenosis of the subarachnoid space and delay the cephalic spread of the reduced dose of local anaesthetics we used.

This prospective, randomized study was designed to evaluate the effect of epidural injection of saline on the maximal segmental spread of spinal anaesthesia with low dose hyperbaric levobupivacaine, on the rate of the maternal hypotension and ephedrine use, the quality of anaesthesia and postoperative recovery. Thus, the secondary outcome of this study was set to define if this modification of technique allows us to reduce the total amount of local anaesthetics for spinal anaesthesia for Caesarean delivery.

METHODS

The Ethical Committee of General Hospital Pula (Pula, Croatia) approved the study protocol, and written informed consent was obtained from all patients. We studied 76 parturient women, American Society of Anaesthesiologists (ASA) physical status I or II, with a singleton uncomplicated pregnancy more than 37 weeks gestation who were undergoing elective Caesarean section under regional anaesthesia. All females suffering from pre-eclampsia and hypertension were excluded, as well as patients in active labour or presenting for emergency Caesarean section, multiple pregnancies and body weight exceeding 110 kg. All patients were unaware of group allocation, placed in a moderate 15^0 left lateral tilt position during the surgery.

All patients received 500 ml of Ringer's solution, and were premedicated with metoclopramid 10mg i.v. and ranitidin 75 mg i.v.

Following the application of routine monitoring (EKG, NIBP, SatO2), the patients were put in sitting position to perform regional anaesthesia. After infiltrating the skin with 2% lidocaine, at the L3-4 or L4-5 vertebral level, in 39 women from Group CSE-EVR a Tuohy needle was introduced into the epidural space via a midline approach using the hanging drop technique. Subsequently the 27G spinal Whitacre needle was introduced. Following appearance of CSF, the low dose of 0.5% hyperbaric levobupivacaine (0.025 mg per centimetre high) dissolved in 10% glucose were slowly injected. Then the epidural catheter was introduced and withdrawn leaving 10–12 cm into the epidural space. Immediately through the catheter was injected 18–20 ml of saline solution. After securing the catheter, patients were placed in a lateral tilt supine position.

The classic subarachnoid block was performed in 37 women from Group SA with 25–27G Whitacre spinal

needle in a midline approach. Conventional dose of 0.5% hyperbaric levobupivacaine (0.05 mg per centimetre high) dissolved in 10% glucose was administered into the subarachnoid space after the confirmation of free flow in CSF. The patients were keep sitting for 3 minutes to "anchor-fix" the block and than placed in a lateral tilt supine position.

Spinal anaesthesia was performed by slow, continuous injection without "barbotage".

All parturient women received fentanyl intrathecally (15 μg –in women less than 165 cm high /25 μg-in women up than 175 cm high) as part of the spinal injection.

During the surgery was not allowed to inject any epidural drug to avoid interference with the follow up of the distribution of the spinal block and the haemodynamic changes.

After obtaining the baseline haemodynamic variables, the blood pressure and heart rate were measured every 2 minutes until delivery and then every 5 minutes until the completion of surgery. We defined hypotension as a fall of systolic pressure more than 20% from baseline or <90 mmHg. It was treated it with intravenous ephedrine by incremental boluses. The primary outcome was the haemodynamic changes during intraoperative time.

The secondary outcome was the sensory block height, 10 minutes after spinal injection. It was evaluated by pinprick with the 25-G hypodermic needle, and with the loss of cold sensation to ether bilaterally at the midclavicular line. The lower limb motor block was assessed using a modified Bromage score (0 = able to rise leg above table, 1 = able to flex knees, 2 = able to move feet only, 3 = no movement in legs). Intraoperative pain was assessed using a verbal rating scale from 0 to 10 (0 = no pain at all, 10 = the worst pain). If breakthrough pain or discomfort was detected during surgery intravenous supplementation of 100 mg Thiopenthal was allowed. These categories were defined as failure of block, and signed with other additional data like incidence of hypotension, nausea and vomiting, ephedrine consumption, total administered infusions, neonatal outcome (umbilical-pH, Apgar score). After delivery a paediatrician assessed the condition of the baby at 1 and 10 minutes.

Time needed for motor recovery and return to active mobilisation and the first analgesia request was noted by a blinded anaesthetist in the recovery ward. All data concerning the postoperative complication, including postspinal headache were gathered from documents in the ward. Data are presented as mean +/–SD, number of patients or median (range) where appropriate. Statistical analyses were performed using the SPSS 13.0 for windows (SPSS Inc., Chicago, IL,USA). Comparisons between groups were performed by using one-way analysis of variance (ANOVA) "Wicoxon U-test" analysis, χ^2 test when appropriate, and General Linear Model for repeated measures-Multifactorial model with two factors to detect intergroup difference and intragroup change overtime. Statistical significance was see at $p<0.05$.

RESULTS

There was no difference in patients demographics with respect to age, weight, parity and the duration of the pregnancy (Table 1).

One patient from the CSE-EVE group was not included in the study because of an accidental dural puncture with the epidural catheter, but all the other patients finish the designed study. Uterine exteriorization was performed in all cases.

TABLE 1

Patient characteristics and duration of surgery (median).

	Spinal anesthesia (n = 39)	CSE – EVR (n = 37)
Age (yr)	32 +/–5	30 +/–5
Parity (*I-para*)	16	24
Gestation; week	38.8	39
Height (cm)	165 +/–6	168 +/–8
Weight (kg)	80 +/–10	83 +/–11
Hgb (g/L)	0.34	0.33
Htc (L/L)	116	117
Surgery time. (min)	34 +/–5	37 *+/–4*
Time to childbirth (min)	12.6	12.8
Neonatal weight (gr)	3511	3455
Neonatal hight (cm)	49.9	50.3

All the patients received the same volume of preloading infusion before the anaesthesia, (F test 1.716; $p=0.194<0.05$). Statistically this will have no impact on the interpretation of the intraoperative haemodynamic changes because we noticed volume independency between the groups (Table 2).

The CSE-EVE group (Table 2) received less than 45% of levobupivacain comparing to the spinal group which is statistically significant difference, $p=0.000<0.05$. However the opioids dose was the same in both groups. To explain the haemodynamic change, only effects of the local anaesthetic and of the epidural volume extension have relevant impact, because in all patients we infused the same amount of fluid volume.

The levels of sensory analgesia 10 minutes after spinal anaesthesia (Fig.1.-box plot-blue) were significantly higher in the spinal group (Th5-dermatome) than in the CSE-EVR group, were it reached the Th7-dermatome. The level of achieved thoracic dermatome didn't delay start of the operation by suprapubic incision of the skin (Pfannenstiel). All the surgical operation procedures were regular. Epidural injection of saline resulted in significant decreases in the maximum level of analgesia in the CSE-EVR group ($F=74.304$, $p=0.000<0.05$).

TABLE 2

Characteristics of anaesthesia techniques:

		Group	
		Spinal Anesthesia (mean, min-max)	**CSE-EVR** (mean, min-max)
Volumen of preload (0.9% NaCl ml)		500	500
Spinal dose of drugs	**Levobupivacain 0.5%* (mg)**	9.3 (6–12)	5.3 (4–6)
	Fentanyl ** (mcg)	20.8 (15–25)	19.4 (10–25)
Epidural volume expansion (ml)		Without	19
Total amount of infusion volume* **		1000 (847.3)	1000 (910.4)

* F test 272.718; $p=0.000$
** F test 1.524; $p= 0.221$
*** F test 1.716; $p= 0.194$

TABLE 3

The Motor block profile 10 minute after spinal injection before skin incision, and at the end of the surgery time.

			Group		All
			Spinal	**CSE-EVR**	
Motor block at skin incision	**Bromage 2**	No.patients	0	18	18
		% of Group	0%	46.2%	23.7%
	Bromage 3	No.patients	37	21	58
		% of Group	100%	53.8%	76.3%
Motor block at end surgery	**Bromage 0**	No.patients	0	22	22
		% of Group	0%	56.4%	28.9%
	Bromage 1	No.patients	3	9	12
		% of Group	8.1%	23.1%	15.8%
	Bromage 2	No.patients	14	8	22
		% of Group	37.8%	20.5%	28.9%
	Bromage 3	No.patients	20	0	20
		% of Group	54.1%	0%	26.3%

From the same graph (Fig. 1) it is evident that the regression of the sensory analgesia at the end of the surgery (box plot- green) is faster in the CSE-EVR group (Th11-dermatome) comparing to the spinal group (Th6--dermatome).The dose of levobupivacaine and the epidural injection of saline resulted in significant rapidity of analgesia dissolution ($F=238.778$, $p=0.000<0.05$). On the basis of statistical analysis by Wilks test ($=0.236$, $p=0.000<0.05$) we can conclude that the two analyzed regional blocks behaved differently considering the distribution and regression of analgesia. CSE-EVR group had lower extension and faster recovery of the sensory block.

All the patients in the spinal group (37/37) had a complete motor block at incision time while the majority of patients receiving the CSE-EVR (18/39) were still able to flex ankles at that moment (46.2%, Table 3). Such a different distribution of the motor block is statistically relevant ($\chi^2=22.377, p=0.000<0.05$), and confirms that the two techniques are different indeed. The degree of motor block in the CSE-EVR group didn't influence the operation performance, therefore we can conclude that such a technique is suitable for the Caesarean section since such a operation doesn't need complete paralysis of the legs.

At the end of the surgery, more patients in spinal group (54.1%) had still complete motor block than the CSE-EVR group, were 22 out of 39 patients were able to move over the operating table spontaneously (Table 4). Only one patient in the spinal group had the complete recovery of the motor function, opposed to 22 (56.4%) patients in CSE-EVR group.

Statistical difference in the grade of motor regression between the groups is significant ($\chi^2=46.616, p=0.000<0.05$), therefore we can confirm our hypothesis that with the CSE-EVR we can achieve faster recovery from anaesthesia.

TABLE 4

Comparison of haemodynamic changes and ephedrine use:

Measure	Group	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Systolic pressure	Spinal	115.81	1.71	112.4	119.22
	CSE-EVR	124.83	1.67	121.5	128.16
Diastolic pressure	Spinal	63.36	1.20	60.97	65.75
	CSE-EVR	70.28	1.17	67.95	72.61
Pulse	Spinal	87.56	2.17	83.22	91.89
	CSE-EVR	88.85	2.12	84.63	93.07
Ephedrine (mg)	Spinal	14.14	**Median* 15**	2	25
	CSE-EVR	12.68	**Median* 13**	3	20

In the CSE-EVR the mean time to motor recovery and turn back to walk was 135.51 minutes (minimum 90 minutes /maximum 210 minutes), in comparison to the SA group were the mean time was 209.32 minutes (minimum 140 minutes /maximum 285 minutes).

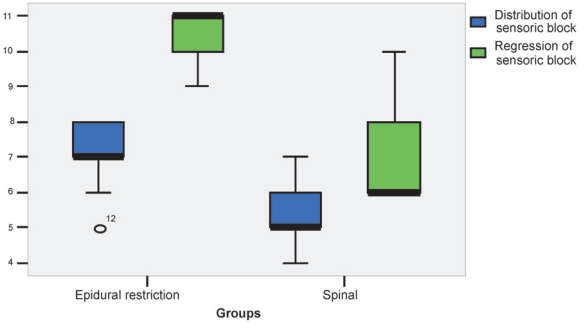

Figure 1. *Extension (blue plot) and regression (green plot) of spinal block at start and at end of surgery time.*

Statistical analysis confirm (*F* test 92.229; $p=0.000<0.05$) that CSE-EVR allows patients faster recovery to the preoperative motor activity.

After intratechal injection of levobupivacaine, changes in systolic and diastolic blood pressure and pulse occurred in both groups, comparing to the baseline values (Table 4).

The multivariate analysis define that there is a statistically significant difference between the CSE-EVR and SA group for all the hemodynamic variables (Wilks $=0.796$, $p=0.001<0.05$). In both groups there was manifestation of some hypotension during the 3rd interval time (4th minute from the beginning of spinal block) and 4th interval time (6th minute from the spinal block). From the 6th interval time (10th minute from the spinal block) and 7th interval time (15th minute from the spinal block) both groups show same haemodynamic stability (Fig. 2).

On the basis of multivariate analysis for repeated measures within the two groups for the linear variable (systolic/diastolic blood pressure, pulse) the results show changes on define time intervals independently of the groups (Wilks $=0.064$, $p=0.000<0.05$). But the dynamics of each group on fixed interval (*EVR-CSE* vs. *SA*) act in different manner (Wilks $=0.335$, $p=0.000<0.05$).

For the detection of the difference in the dynamics of the mean value of variables (systolic, diastolic, pulse) between the group we used the Univariate approach with the Greenhouse-Geisser correction. The CSE-EVR group differ from SA group in all pressure values ($F=14.211$, $p=0.000<0.05$ for systolic and $F=17.095$, $p=0.000<0.05$ for diastolic pressure) but not in the variable of pulse ($F=0.180$, $p=0.672>0.05$) because hypotension was less present in the CSE-EVR group. Statistically, the difference in pressure value between the two techniques was $p<0.05$, but for the dynamics of the pulse value was at $p>0.05<0.10$.

The incidence of ephedrine use was comparable between the two groups. In the CSE-EVR group 19 out of 39 patients (48.7%) had the systolic pressure fall under the 90 mmHg and they needed correction with ephedrine. In the SA group 35 out of 37 patients (94.6%), needed therapeutic support for maintenance of the systolic pres-

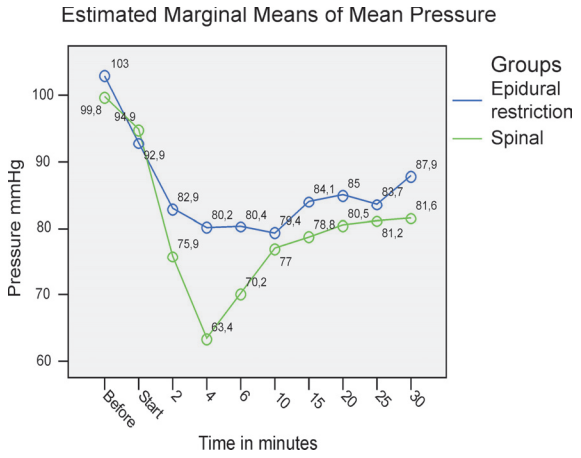

Figure 2. *Changes in haemodynamic levels (mean blood pressure) following spinal anaesthesia in SA and CSE-EVR groups.*

sure above 90 mmHg; $\chi^2=46.616$, $p=0.000<0.05$ confirming that the CSE-EVR group was haemodynamic more stable.

The statistic analysis of ephedrine use detects that there is no difference between groups in the quantity of ephedrine used ($p>0.05$), since the levobupivacaine is the main cause of hypotension, but the different technique approach CSE-EVR may restrict the incidence of this adverse effect.

Intraoperative bradycardia (beats <50/minute) was also registered and we used of 0.7 mg atropine. In each group only 6 patients needed therapeutic support (SA 6/37, CSE-EVR 6/39), and there is no statistical significant difference between the groups ($\chi^2=0.010$ $p=0.921>0.05$). Intraoperative nausea and vomiting was not present in the two groups.

The breakthrough pain and discomfort during surgery time was defined as failure of block and was marked as additional category. In the spinal group (SA) 7 patients (18.9%) complained about pain or discomfort after the childbirth, during uterine exteriorization comparing to 11 patients (28.2%.) from the CSE-EVR group. The discomfort because uterine draw out was treated by analgo--sedation with i.v. Thiopenthal 100 mg.

The analysis of break pain by Wicoxon-U test define ($\chi^2= 0.906$ $p=0.341>0.05$) no significant difference between the groups. This incidence is possible in usual population no matter of the techniques used.

At the end of the surgery 13 patients (33.3%) in the CSE-EVR group and 5 patients (13.5%) of the SA group reported sensations of skin pruritus around the navel. The difference was no statistically significant (Pearson Chi-Square=4.126; Asymp.Sig.=0.059), and in all cases there was no need for therapeutic approach.

The neonatal outcome was similar between the groups because all the Caesarean sections were elective procedures. The mean pH value of the umbilical cord was 7.25 in the SA group while in the CSE-EVR group was 7.33. Clinically, both values are acceptable but statistically (F test 32.709; $p=0.000$ <0.05) we can notice that the EVR-CSE group had better outcome. The mean Apgar score at the 1st minute was 9 in SA group, and 10 in the CSE-EVR group, and in the 10th minute it was the same in the both groups. Statistically there is no difference in Apgar scores of the newborns between the groups (F test 637.50; $p=0.101$ <0.05). The haemodynamic stability of the CSE-EVR group is reflected in the better cord-pH value and Apgar score.

As we well know, the mean pressure and the use of ephedrine have great impact on the estimated cord-pH value, so we used a multivariate model of analysis, including the variable of mean pressure and ephedrine.

From the upper equation we can postulate that ephedrine, as separate variable in the interpretation of the pH trend line, have statistically significant influence on the worth of the cord-pH ($t=-2.687$, $p=0.009<0.05$). Patients who did not receive ephedrine had the mean pH value 7.329. For every mg of ephedrine received there is associated decrease in pH value of 0.003 units. The coefficient of determination ($R^2=0.089$) explain that with ephedrine we can interpret 8.9% of the pH trend line.

When in the regression analysis we incorporate all the other variables like the group belong, ephedrine consumption, and intraoperative mean pressure we achieve the next regression:

From the determination coefficient is discernible that with these three variables we can explain 39.1% of cord--pH variance. On the basis of the upper equation the statistical meaning variables to explain the cord-pH are the mean value of all the mean pressure intervals ($t=3.146$, $p=0.002<0.05$), and the group belonging ($t=-4.727$, $p=0.000<0.05$), until the dose of ephedrine, after all the variables are included, become less important ($t=1.071$, $p=0.288>0.05$). The rising of the mean pressure of 10 mmHg increases the value of cord-pH for 0.003 independently of the dose of ephedrine, or of the group belonging. In our study, spinal anaesthesia SA group express 0.072 unites less value of cord-pH for the same dose of ephedrine and the same mean pressure in comparison to the CSE-EVR group.

The upper diagram (Fig. 3) confirms that the increment of the mean pressure results in the value of the cord-pH, and also that the CSE-EVR group with the same mean pressure have higher value of cord-pH in comparison with the Spinal group ($p=0.004<0.05$). None of the patients developed a postspinal headache and maternal satisfaction was comparable in both groups.

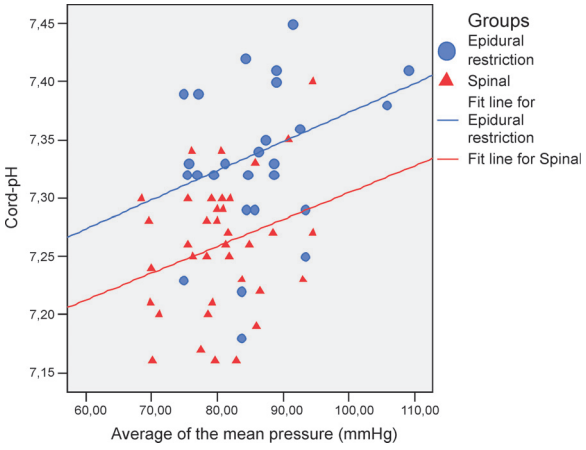

Figure 3. *Linear link between cord-pH and mean of mean blood pressure inside the groups.*

DISCUSSION

In our study, we examined how a low dose combined spinal-epidural anaesthesia can become effective by using epidural volume extension as a force to induce compression-restriction of the subarachnoid space, achieving a transitory hindrance of a rostral spread of the local anaesthetic. Takiguchi et al. using myelography, demon-

strated that the diameter of the subarachnoid space decreased to less than 25% of its original value after injection of 10 ml of saline *(17)*.

The most important result in our study shows that the CSE-EVR group with saline restriction results in no extension of the spinal block with hyperbaric levobupivacaine. We confirmed our primary hypothesis that CSE-EVR technique decreases the sensory and motor block profile, increases the recovery profile and reduces the incidence of maternal hypothension. We also confirmed our secondary hypothesis that it is possible to reduce the total amount of local anaesthetics used for spinal anaesthesia, using only high spinal block to ensure effective anaesthesia for caesarean section with low skin incision approaches.

Gestational exposure to high levels of progesterone and endorphins may alter perineural structures to increase drug permeability through the nerve sheath, or may induce changes in nerve membrane structure that enhance sensitivity to local anaesthetics and intrathecal opioids *(19)*.

The ED_{50} and ED_{95} of intrathecal levobupivacaine do not differ from the ED_{50} (7.5 mg) and ED_{95} (13.0 mg) of intrathecal isobaric bupivacaine combined with fentanyl and morphine previously reported by Carvalho and colleagues, although some previous studies have suggested that levobupivacaine is less potent than bupivacaine for Caesarean section *(20, 21)*. It has been reported by Khaw *et al.* that ED_{50} for levobupivacaine in 8% glucose was 9.3 (CI 95%: 8.3–10.8) mg, but Bouvet *et al.* demostrated that when opioids are added to levobupivacaine the ED_{50} was 6.2 mg (CI 95%: 2.6–7.6) and ED_{95} was 12.9 mg (CI 95%: 11.1–17.9) mg *(22, 23)*. It is general rule to take a height as a significant variable in adjusting the spinal dose of local anesthetic and for predicting the final level of the block. In our study, women received two different doses of spinal levobupivacaine according to their height. In SA group the mean dose was 9.3 mg and in CSE-EVR group it was 5.3 mg of 0.5% levobupivacain. All the dose were supplemented with opioids (Fentanyl 20mcg) and the success rate of intraoperative anesthesia were comparable.

The incidence of the breakthrough pain during the exteriorisation of the uterus (profound surgical stimulus) is usually considered as failure of anaesthesia during the operation. In the study of Ben-David and Choi, using less than ED_{95} of bupivacaine, the incidences of visceral pain and discomfort were respectively of 50% and 35% *(24, 25)*. In the study of Ginosar *et al.*, the ED_{50} for successful was 6.7 mg of bupivacaine, and the ED_{95} for successful operation was 11.2 mg of bupivacaine respectively. They concluded that with the intrathecal dose of 10 mg or greater of bupivacaine, only 7% of patient will report VAP assessment greater than 10mm during the intraoperative time *(26)*. The Bouvet *et al.* study group reported that intrathecal levobupivacaine with opioids for CS had the overall success rate of 47% in the 6mg levobupivacaine group, and 71% with 8 mg, while more than 82% of success rate if the dose was incremented above 10 mg of levobupivacaine *(23)*. Our study showed that 7 patients from spinal group (SA) and 11 patients from CSE-EVR group complained of breakthrough pain VAPS > 40 mm and required rescue analgesia supplementation. The incidence was similar between the groups and was comparable with the previous study results. Our results confirm that the total dose of 0.5% levobupivacaine for CS, no matter of the techniques used, does not need to exceed more than 10 mg, and suggest that CSE-EVR technique gives us the possibility to reduce the spinal dose of local anaesthetics even more, while keeping the anaesthesia effective.

The presence of an epidural catheter might be of use to reinforce the anaesthesia block during usual CSE anaesthesia, especially for breakthrough pain. We did not add any epidural supplement in order to avoid limitations of the validity of our data.

In our study the regional block was performed in sitting-upright position, and the time needed for insertion of the epidural catheter inevitably determinate a little longer sitting position of the patient after the spinal drug injection. Kohler et al. injected 14mg hyperbaric bupivacaine in mothers maintaining the sitting position for either 0 or 3 minutes, thus mimicking a CSE situation. They found that the longer interval was associated with a delay of the first occurrence of hypotension as well as a smaller number of blocks extending to dermatomal levels higher than Th1 *(27)*. Nevertheless, Povey et al. demonstrated that sitting for as long as 25 minutes, in non pregnant patients, did not affect the sensory level as compared with sitting for 2 minutes *(28)*. Coppejans et al evaluated the sitting versus lateral position during initiation of small-dose CSE anaesthesia. They concluded that the sitting position was technically easier and induced less sensory block (dermatome Th6), less severe hypotension, less ephedrine supplementation, and better umbilical artery pH *(29)*. We postulated that in the pregnant patient, the sitting position may mark the gravity and counteract the rostral spread of hyperbaric levobupivacaine as postulated by Coppejans.

Kucukguclu et al. investigated the effect of density on cephalic spread following epidural volume extension in parturient and observed that CSE anaesthesia with plain bupivacaine resulted in a higher sensory block (Th2-Th10, mean Th4) than with hyperbaric bupivacaine, but epidural volume extension did not affect the sensory block height *(30)*.

In our study all the patients had the regional block in sitting upright position with hyperbaric solution and consequently had a sensory block reaching at least Th7, but the maximal spread of the sensory block was more extended with the spinal anaesthesia group (dermatome Th5) without prolonged upright position. The CSE-EVR group had less extending spread of block (Th7 dermatome) since it was empowered by the epidural volume. The regression of the sensoric block was more pronounced in the CSE-EVR group (dermatome Th11 at 45 minutes) and can be comparative to Kucukguclu *et al*. - EVE study

were regression to Th10 was registered after 100 minutes after the block was induced *(30)*.

The spinal group SA also had higher degree of motor block at incision time in comparison to the CSE-EVR group, were only 53.8% of parturient women reach Bromage 3 score ($p<0.05$).The patients in the CSE-EVR group demonstrated significantly faster motor recovery to Bromage 0 (56.4%) at the end of surgery. Our motor recovery profile can be compared to Lew et.al who reported recovery after 73+/–33 minutes with 5mg bupivacaine and 136+/–32 with 9mg bupivacaine for CS procedures *(31)*.

We can presume that the injection of saline in the epidural space may actually have accelerated the spread of a fraction of spinal hyperbaric levobupivacaine towards the sacral segments by means of the volume effect. As the sacral roots do not contribute to motor function of the lower limb, this may explain a lower incidence of Bromage score-3 grade in the CSE-EVR group.

In our institution the average time for surgery is 35–45 minutes. However the mean time for our parturient women to turn back to mobility after single shot spinal anaesthesia was 210 minutes. The CSE-EVR technique produces faster motor block regression time by approximately 135 minutes. This one hour difference may not seem clinically important, but may have impact on reducing or bypassing post-anaesthesia intensive care unit stay.

Several trials have reported an infrequent incidence of hypotension when small doses of bupivacaine were used. Vercauteren *et al.* compared 6.6 mg hyperbaric bupivacaine with sufentanil 3.3 microgram, using CSE techniques, and concluded that occurrence of hypotension was 58% without prophylactic use of ephedrine *(32)*. Van de Velde tested low dose bupivacaine 6.5 mg combined with sufentanyl 2.5 microgram as a part of CSE technique and compared to higher 9.5 mg bupivacaine doses. More patients in the 9.5 mg group experienced hypotension, comparing to the low 6.5 mg bupivacaine group (68% versus 16%; $p<0.05$) *(33)*. Parpiglioni *et al.* showed that with 10.5 mg levobupivacaine the incidence of hypotension was 38.5% in comparison to 60% incidence with 14.22 mg ropivacaine for CS *(34)*. Coppejans and Vercauteren compared three plain local anaesthetics in CSE techniques for CS and showed that only 6% of patients in levobupivacaine group had hypotension experience in comparison to 20% in bupivacaine and ropivacaine groups, while the ephedrine supplementation was identical *(35)*. All of these studies concluded that low dose spinal anaesthesia with bupivacaine or levobupivacaine are better in preserving maternal haemodynamic stability. However, the anaesthesias were equally effective in all studies with limited time duration. Authors suggested that these low doses can be used only if the block can be reinforced with epidural catheter *(33, 34, 35)*.

Our study shows smaller incidence of hypothension in the CSE-EVR group, as a result of the restriction of the sensoric and motoric block. There was a high change in blood pressure (94.4%) within the first 10 minutes with higher doses of intrathecal levobupivacaine in SA group ($p=0.001<0.05$). This may be a result of a higher distribution of the spinal block and large difference in total dose of levobupivacaine between the groups (9.3mg *vs.* 5.3 mg =total dose difference 4mg levobupivacaine). The requirements for ephedrine were less in the CSE-EVR group (19/39) than in the SA group (35/37) ($p<0.05$), but the total amount of the used drug was similar between the groups. We did not report any nausea and vomiting among parturient.

This study demonstrated a relatively frequent incidence of hypotension in both patient groups. This could be a result of inadequate uterine displacement and fluid preloading. We administered only 500 ml of NaCl infusion for preloading, as the literature does not support the routine practice of large volumes of crystalloid solution to prevent hypotension. Even the colloids that are more reliable are associated with increased risks *(36)*. During the anaesthesia time we administered the same amount of infusion to all our patients, to emphasize correctly the affects of CSE-EVR on the haemodynamic stability.

It is difficult to compare the various studies that have evaluated hypotension during caesarean delivery, as different end-points and definition are used. Regardless of the outcome variables used, our results are consistent with those of Coppejans and Vercauteren *(35)*. The slower and more limited cephalic spread of sensory block may explain the reduced incidence of hypotension.

Although the Apgar score was statistically lower in the Spinal group than in the CSE-EVR group, these values were well within the normal range. The large study of NganKee et Lee found that the significant factor predicting cord-pH were: use of ephedrine, uterine incision-to delivery time, maximum decrease in systolic blood pressure and the interaction between ephedrine use and duration of hypotension (adjusted $R2=0.52$, $F15.321=25.0$, $p<0.0001$) *(37)*. Van de Velde *et al.* showed that low cord-pH values (<7.2) were noted in 4% of patients in the Low-6.5 mg group compared with 16% in the High-9.5 mg bupivacaine group *(33)*. Our multivariate analysis of cord-pH confirmed the findings of Ngan Kee and Van der Velde stating that the variation on fetal acid-base status is moderated by the mean arterial pressure, and that the use of ephedrine can proportionally depress cord-pH.

A critical point of view in our study was performance of the CSE technique by using the hanging drop. Actually we wanted to avoid uncontrolled epidural injection of air or saline into the epidural space. Epidural volume restriction was performed to achieve a transitory hindrance on cephalic spread of the local anaesthetic, using 20 ml saline immediately after injection of spinal anaesthesia based on the MR study of Higuchi *et al. (38)*. Their study indicates that CSF volume is the main factor that influences the spread of hyperbaric bupivacaine in spinal anaesthesia, and that the duration of anaesthesia is influenced when the injection is made in a seated position.

The effects or the lack of effects of epidural volume extension on CSF flow dynamics may explain the varia-

tions in sensory block heights and of induced dural compression 30 minutes after the injection.

Until our study, all the authors were concentrated to extend the spinal block making modification of the first Rawal attempt *(14)*. The primary goal of their studies was to reduce the total amount of local anaesthetic used for Caesarean section using the epidural extension to reach large dispersion of the spinal block. Many of them were not completely satisfied with these results *(13, 14, 15, 16)*.

Basically, we denied the need for large spinal block for the caesarean section. Our statement is that if we want to have less hypotension side effects, we have to reduce the dose of anaesthetics and to keep it on the proper lumbar-sacral level. To reach that goal, we need to control the cephalic spread of local anaesthetics, by reconsidering Takiguchi and Higuchi MR-findings *(17, 38)*.

In conclusion, epidural injection of 20ml of saline immediately after low dose spinal anaesthesia in parturient women in sitting position can provide restricted but adequate anaesthesia for elective caesarean section. The study shows that enhancement of the spinal block by CSE-EVR allows us to decrease the dose of local anaesthetic, with the consequent reduction of hypotension, faster sensoric and motoric recovery and better neonatal outcome.

REFERENCES

1. HAWKINS J L, KOONIN L M, PALMER S K, GIBBS C P 1977 Anesthesia-related deaths during obstetric delivery in the United States, 1979–1990. *Anesthesiology 86:* 277–284
2. JENKINS J G, KHAN M M 2003 Anaesthesia fir Caesarean section: a survey in a UK region from 1992 to 2002. *Anesthesia 58:* 1114–1118
3. PINDER A 2006 Complicationof obstetric anaesthesia. *Current Anaesthesia & CriticalCare 17:* 151–162
4. DRESNER M, BRENNAN A, FREEMAN J 2003 Six year audit of high regional blocks in obstetric anaesthesia. *Int J Obs Anesthesia 12:* 202
5. EMMETT R S, CYNA A M, ANDREW M, SIMMONS S W 2001 Techniques for preventing hypothension during spinal anaesthesia for caesarean section.*Cohrane Database Syst Rev 2001(3):* CD002251
6. TERCANLI S, SCHNEIDER M, VISCA E, HOSLI I, TROEGER C, PEUKERT R, HOLZGREVE W 2002 Influenze of volume preloading on uteroplacental and fetal circulation during spinal anaethstesia for caesarean section in uncomplicated singleton pregnancies. *Fetal DiagnTher 17(3):* 142–6
7. ROOFTHOOFT E, VAN DE VELDE M 2008 Low dose spinal anaesthesia for caesarean section to prevent spinal-induced hypothension. *Current Opinion in Anaesthesiology 21:* 259–262
8. LEE A, NGAN KEE W D, GIN T 2004 A dose – rasponse meta-analysis of prophylactic intravenous ephedrine for the prevention of hypothension during spinal anaesthesia for elective cesarean delivery. *Anesth Analg 98:* 483–490
9. WARWICK D, NGAN KEE 2010 Prevention of maternal hypothension after regional anaesthesia for caesarean section. *Current Opinion in Anaesthesiology 23:* 304–309
10. NAHED F, KHED R 2011 Preventive measures to reduce post-spinal anesthesia hypothension for elective cesarean delivery. *Journal of American Sciencie 7(2):* 634–640
11. BURNS S M, COWAN C M, WILKES R G 2001 Prevention an management of hypothension during spinalanaesthesia for elective Cesarean section: a survey of practice. *Anesthesia 56:* 668–674
12. HARTEN J M, BOYNE I, HANNAH P,VAEVERIS D, BROWN A 2005 Effects of a height and weight adjested dose of local anaesthetic for spinal anaesthesia for elective Caesarean section. *Anaesthesia 60:* 348–353
13. BEALE N, EVANS B, PLAAT F, COLUMB M O, LYONS G, STOCKS G M 2005 Effect of epidural volume extension on dose requirement of intrathecal hyperbaric bupivacaine at caesarean section. *Br J Anaesth 95:* 500–503
14. RAWAL N, SCHOLLIN J, WESSTROM G 1988 Epidural vs. combined spinal epidural block for cesarean section. *Acta anaesthesiol Scand 32:* 61–66
15. STIENSTRA R, DAHAN A, ALHADI B Z, VAN KLEEF J W, BURM A G 1996 Mechanism of action of an epidural top-up in combined spinal epidural anaesthesia. *Anesth Analg 83:* 382–386
16. BLUMGART C H, RYALL D, DENNISON B, THOMPSON--HILL LM 1992 Mechanism of extension of spinal anaesthesia by exdradural injection of local anesthetic. *Br J Anaesth 69:* 457–460.
17. TAKIGUCHI T, OKANO T, EGAWA H, OKUBO Y, SAITO K, KITAJIMA T 1997 The effect of epidural saline injection on analgesic level during combined spinal and epidural anaesthesia assessed clinically and myelographically.*Anesth Analg 85:* 1097–2100
18. YAMAZAKI Y, MIMURA M, HAZAMA K, NAMIKI A 2000 Reinforcement of spinal anesthesia by epidural injection of saline: a comparison of hyperbaric and isobaric tetracaine. *J Anesth 14:* 73–76
19. CAMORCIA M, CAPOGNA G, COLUMB M O 2011 Effect of seks and pregnancy on the potency of intrathecal bupivacaine: determination of ED50 for motor block with the up-down sequential allocation method. *European Journal of Anesthesiology 28(4):* 240–244
20. CARVALHO B, DURBIN M, DROVER D R, COHEN S E, RILEY E T 2005 The ED_{50} and ED_{95} of intrathecal isobaric bupivacaine with opioids for cesarean delivery. *Anesthesiology 103:* 606–12
21. BREMERICH D H, FETSCH N, ZWISSLER B C, MEININGER D, GOGARTEN W, BYHAHN C 2007 Comparison of intrathecal bupivacaine and levobupivacaine combined with opioids for Caesarean section. *Curr Med Res Opin 23:* 3047–54
22. KHAW K, NGAN KEE, NG F, LEUNG P 2004 Dose-finding comparison of spinal levobupivacaine for caesarean section. *Int Journ of Obst Anest 13:* S17
23. BOUVET L, DA-COL X, CHASSARD D, DALERY F, RUYNAT L, ALLAOUCHICHE B, DANTONY E, BOSELLI E 2010 E D_{50} and ED_{95} of intrathecal levobupivacaine with opioids for Caesarean delivery. *British Journal of Anaesthesia October 30:* 1–6
24. BEN DAVID B, MILLER G, GAVRIEL R, GUREVITCH A 2000 Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med 25:* 235–9
25. CHOI D H, AHN H J, KIM M H 2000 Bupivacaine-sparing effect of fentanyl in spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med 25:* 240–5
26. GINOSAR Y, DURBIN M, DROVER D R, COHEN S E, GINOSAR Y, RILEY ET 2004 The ED_{50} and ED_{95} of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology 100:* 676–82
27. KOHLER F, SORENSEN J F, HELBO-HANSEN H 2002 Effect of delayed supine positioning after induction of spinal anaesthesia for Caesarean section. *Acta Anaesthesiol Scand 90:* 441–6
28. POVEY H M, OLSEN P A, PIHL H 1987 Spinal anesthesia with hyperbaric 0.5%bupivacaine.Effects ofdifferent patient positions. *Acta Anesthesiol Scand 31:* 616–9
29. COPPEJANS C H, HENDRICKX E, GOOSSENS J, VERCAUTEREN M 2006 The sitting versus right lateral position during combined spinal-epidural anesthesia for cesarean delivery: block characteristics and severity of hypothzension. *Anesth analg 102:* 243–7
30. KUCUKGUCLU S, UNLUGENC H, GUNENC F, KUVAKI B, GOKMEN N, GUNASTI S, GUCLU S,YILMAZ F, ISIK G 2008 The influence of epidural volume extension on spinal block with hyperbaric or plain bupivacaine for Caesarean delivery. *European Journal of Anaesthesiology 25:* 307–313
31. LEW E, YEO SEOW-WOON, EASAW T 2004 Combined spinal--epidural anesthesia using epidural volume extension leads to faster motor recovery after elective cesarean delivery: a prospective, randomized, double-blind study. *Anesth analg 98(3):* 810–814
32. VERCAUTEREN M P, COPPEJANS H C, HOFFMAN V H, MERTENS E, ADRIAENSEN H A 2000 Prevention of hypothension by a single 5-mg dose of ephedrine during small-dose spinal anesthesiain prehidrated cesarean delivery patients. *Anesth Analg 90(2):* 324–7

33. VAN DE VELDE M, VAN SCHOUBROECK D, JANI J, TEUNKENS A, MISSANT C, DEPREST J 2006 Combined Spinal--epidural anesthesia for cesarean delivery: dose-dependent effects of hyperbaric bupivacaine on maternal hemodynamics. *Anesth Analg 103(1):* 187–190

34. PARPIGLIONI R, FRIGO MG, SEBASTIANI M, BARBATI G, CELLENO D 2006 Minimum local anaestheic dose (MLAD) of intrathecal levobupivacaine and ropivacaine for caesarean section. *Anaesthesia 61:* 110–115

35. COPPEJANS H C, VERCAUTEREN M P 2006 Low-dose combined spinal-epidural anesthesia for cesarean delivery: a comparison of three lain local anesthetics. *ActaAnaesth Belg 57:* 39–43

36. VAN DE VELDE M 2006 Spinal anesthesia in the obstetric patient:prevention and treatment of hypothension. *Acta Anaesthe Belg 57:* 383–386

37. NGAN KEE W D, LEE A 2003 Multivariate analysis of factors associated with umbelical arterial pH and standard base excess after caesarean section under spinal anaesthesia.*Anaesthesia 58(2):* 125–30

38. HIGUCHI H, ADACHI Y, KAZAMA T 2005 Effects of epidural saline injection on cerebrospinal fluid volume and velocity waveform: a magnetic resonance imaging study. *Anesthesiology 102:* 285–292