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Regional *versus* IV analgesics in labor

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Aim. **The aim of this study was to compare combined spinal epidural (CSE), epidural (E) and IV pethidine analgesia and their effects on the mother, fetus, newborn and the labor course.**

Methods. **This is a prospective parallel single blind study, where 60 women in active labor were recruited and were allocated to five subgroups to receive analgesia by different routes. The mother and the fetus were assessed. The results were recorded and compared using Visual Analogue Scale (VAS) and modified Bromage scale for motor block, in addition to other clinical findings.**

Results. **The duration of first stage of labor was significantly longer in the E group, compared with the CSE and IV pethidine groups. When the pain control achieved by CSE bupivacaine and lidocaine was compared with the corresponding epidural, it was found that the first technique achieved better pain control. Women who received pethidine had higher incidence of nausea and vomiting compared to those received CSE or E analgesia. There was no significant difference between the five groups with respect to other side effects.**

Conclusion. **Regional analgesia especially CSE using bupivacaine or lidocaine is a safe effective method for analgesia in labor with relative better efficacy of bupivacaine.**

Key words: **Analgesia, epidural - Labor, obstetric - Delivery, obstetric.**

Labor is one of the experiences which results in severe pain in delivering mothers. Many analgesic techniques are available in a trial to control this pain. The ideal analgesic technique should reduce the labor pain, while allowing the parturient to actively participate in the labor process. In addition, it should have no or minimal effect on the fetus or the progress of labor.[1]

Pethidine IV has the advantage of low cost, ease of administration and familiarity.[2] However, there are considerable doubts about the efficacy of pethidine and concerns about the side effects in mother, fetus, and neonate.[4-7]

Epidural analgesia has become one of the most commonly used methods to alleviate pain during childbirth.[8] However, E labor analgesia is not a generic procedu-

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re and many technical modifications have been invented.[9]

Continuous search for a balanced labor analgesia, which provides relief of pain of labor while preserving motor functions, has lead to the development of the CSE. The CSE technique offers many advantages, and has gained wide spread popularity in obstetric anesthesia worldwide.[9]

This study aims at establishing a comparative study on three different analgesic regimens in normal labor, namely, CSE, E, and IV pethidine in an attempt to select the most appropriate method in sense of pain management; total amount of drug administered, and experienced side effects.

Materials and methods

Study design

This is a prospective parallel single blind study, which was approved by the institutional review board of El-Galaa Teaching Hospital, and the research and ethics committee of Faculty of Pharmacy, Cairo University, which followed the tenets of the Declaration of Helsinki promulgated in 1964.

Sixty full-term, nulliparous women in active labor with cervical dilatation of 5 cm and cephalic presenting fetus were randomly assigned to one of five groups after providing informed epidullary consent:

— Group 1: received CSE analgesia, where 25 μg fentanyl were injected intrathecally and a bolus dose of 10 mL of 0.5% lidocaine were injected epidurally. Top-ups of 5-10 mL of 0.5-0.8% of lidocaine were then injected epidurally upon request;

— Group 2: received CSE analgesia, where 25 μg fentanyl were injected intrathecally and a bolus dose of 10 mL 0.0625% bupivacaine rinjected epidurally. Top-ups of 5-10 mL 0.0625-0.25% bupivacaine were then injected epidurally upon request;

— Group 3: received epidurally analgesia, where 50 μg of fentanyl were injected epidullary together with a bolus dose of 10 mL of 0.5% lidocaine. Top-ups of 5-10 mL of 0.5-0.8% lidocaine where then injected epidurally upon request;

— Group 4: received epidurally analgesia, where 50 μg of fentanyl were injected epidurally together with a bolus dose of 10 mL of 0.125% bupivacaine. Top-ups of 5-10 mL of 0.125-0.25% bupivacaine were then injected epidurally upon request;

— Group 5: 50 mg of IV pethidine were administered as a loading dose, followed by 0.5 mg/kg, with a maximum limit of 130 mg.

Study population

Women who had diabetes, neurological disease, pre-eclampsia, or subjects who had received parenteral analgesics or subjects with contraindication to E or spinal analgesia, or subjects with sensitivity to local anesthetics or opioids were excluded.

Study method

All the recruited subjects were screened before the administration of any analgesia. Blood pressures, heart rate and oxygen saturation (SpO_2) were monitored.

The degree of motor block was assessed according to a modified Bromage scale before analgesic administration, 10 and 30 minutes after the first dose. The duration of analgesia was taken as the time from the beginning of analgesic injection to the time of request for additional analgesia.

The number of top-ups, the intervals between each top-up and the duration of each stage of labor together with the mode of delivery were recorded.

The Visual Analogue Scale (VAS) (0=no pain, 10=worst pain) was measured before administration of analgesia, 10 and 30 minutes after administration of each dose until the delivery.

Maternal arterial pressures, heart rate, SpO_2, and FHR were noted before the analgesia was given, and afterwards every 30 minutes until delivery. Maternal temperature was recorded before starting the analgesia and thereafter every hour till the end of labor. Fever was defined as temperature of ≥38 °C.

Fetal heart rate (FHR) was monitored. The 1-min and 5-min APGAR scores, weight of the neonate were also recorded.

Any experienced adverse drug reactions by any of the recruited subjects were recorded.

Statistical analysis

Descriptive statistics were generated, specifically means, standard deviations and ranges. To minimize type I error, a p value equal to or less than 0.05 was taken as cut-off level for the level of significance. The main tests being used to analyze data extracted from this study are the t-test and ANOVA for nominal continuous data.

The χ^2 test for categorical data used to identify by how much the two observations differ. Statistical Package for Social Science (SPSS) was used for analysis.

Results

Sixty pregnant women were recruited according to the previously set inclusion and exclusion criteria during the period between January 2008 and January 2009.

When the subjects in the 5 groups were compared with respect to their demographic data, it was found that the demographic variables were comparable between the groups. Hemodynamic changes did not differ among the groups (Table I).

The duration of first stage of labor was significantly longer in E group (236.25 112.79) minutes), compared with the 162.50 (97.41) minutes and 150.75 (84.36) minutes in the CSE and IV pethidine groups, respectively (P=0.033, P=0.010, respectively).

Epidural lidocaine prolonged the first stage significantly when compared with the IV group. A significant difference was observed between women who received CSE lidocaine and those who received E lidocaine with respect to the duration of the first stage where women who received CSE experienced a shorter duration of the first stage than those received E (107.5 minutes *vs.* 268.50 minutes).

The duration of second stage of labor was significantly longer in the CSE group (65.50 [40.36] minutes) in comparison with 41.31 (32.74) minutes and 26.84 (11.21) minutes in the E group and IV pethidine group (Table II).

CSE bupivacaine group showed longer second stage: 77.00 (47.80) minutes when compared with 26.84 (11.21) in the IV pethidine group, where P=0.001.

When the pain control achieved by CSE bupivacaine was compared with the corresponding E group, it was found that the first achieved better pain control with a lower VAS, but this difference was not statistically significant. Same outcomes were reported with lidocaine groups.

There was a significant difference between CSE (both bupivacaine and lidocaine) and IV pethidine. On comparing E with IV

TABLE I.—*Number and distribution of the recruited patients, demographic data and baseline data for the recruited patients.*

Parameters	CSE		E		IV	P
	Bupivacaine	Lidocaine	Bupivacaine	Lidocaine	Pethidine	
	N.=10	N.=10	N.=10	N.=10	N.=20	
Average age/years (SD)	20.90 (2.60)	22.80 (3.94)	22.80 (3.33)	22.30 (4.55)	23.05 (2.84)	0.577*
Median age in years	20.5	21	22.5	21	23	
Age range in years	17.00-27.00	19.00-30.00	17.00-28.00	18.00-32.00	18.00-28.00	
Average weight/kg (SD)	76.80 (4.61)	74.80 (8.04)	69.70 (16.98)	70.10 (11.96)	73.10 (8.15)	0.494*
Weight range in kg	68-85	65-90	50-110	60-100	60-85	
Average height/cm (SD)	160.40 (3.50)	164.9 (3.21)	162.1 (5.42)	161.00 (3.40)	163.45 (3.63)	0.061*
Average gestational age/weeks (SD)	39.90 (1.96)	39.60 (1.35)	39.40 (1.78)	40.20 (1.13)	39.20 (1.40)	0.491*
Baseline pain score (VAS) mean	8	6.1	6.3	5.6	6.95	0.056*

CSE: combined spinal epidural; E: epidural; IV: intravenous; SD: standard deviation. *Statistical significance level at P<0.05, using ANOVA test.

TABLE II.—*The duration of first and second stages of labor among different analgesic groups.*

	CSE			E			IV	
	Bupivacaine	Lidocaine		Bupivacaine	Lidocaine		Pethidine	P*
	N.=10	N.=10	N.=20	N.=10	N.=10	N.=19	N.=20	
Average duration of first stage (SD) in min.	217.50 (111.51)	107.50 (29.56)	162.5 (97.41)	204 (102.44)	268.5 (118.53)	236.25 (112.79)	150.75 (84.36)	0.002*
Average duration of second stage (SD) in min.	77 (47.80)	54 (29.33)	65.5 (40.36)	43.89 (35.78)	39 (31.52)	41.31 (32.74)	26.84 (11.21)	0.003*

CSE: combined spinal epidural; E: epidural; IV: intravenous; SD: standard deviation. *Statistical significance level at P<0.05, using ANOVA test.

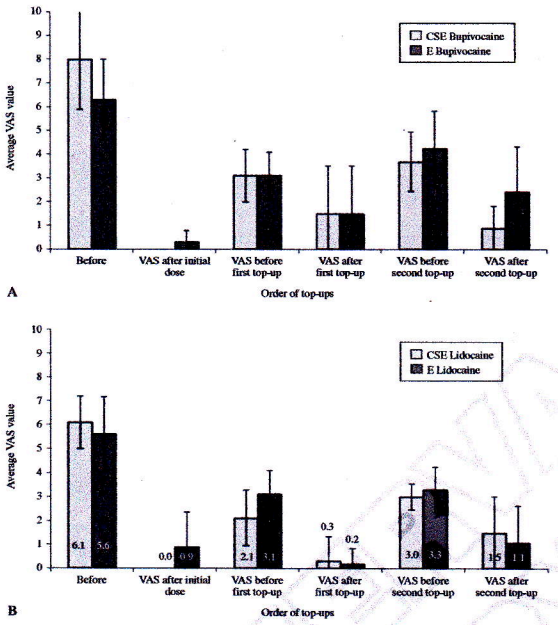

Figure 1.—Average VAS before and after the starting dose, the first and second top-ups with CSE and E (A) bupivacaine and (B) lidocaine.

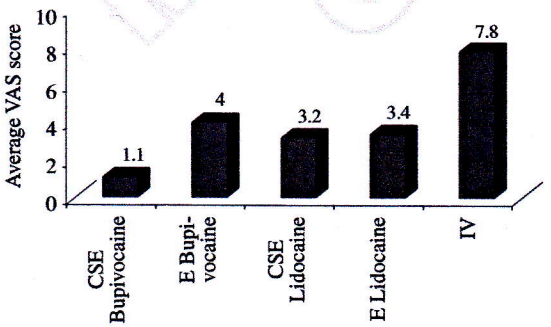

Figure 2.—Average VAS at time of delivery among the five analgesic regimens tested.

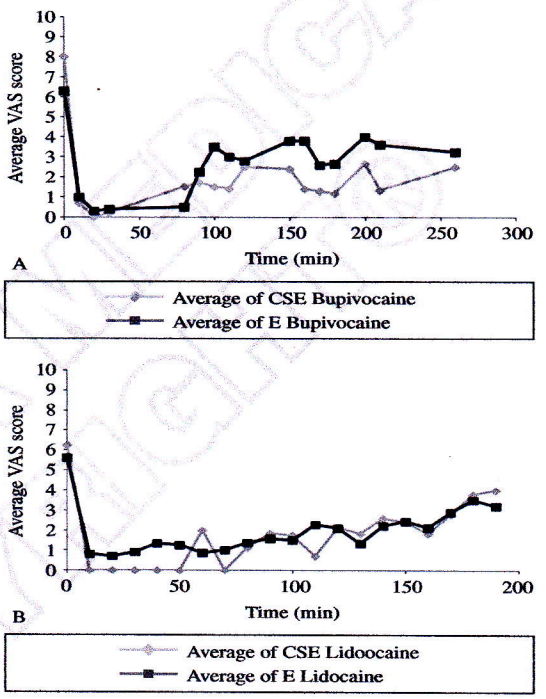

Figure 3.—Average VAS of both CSE and E from Time 0 (just before receiving the initial dose) till the end of labor (A) bupivacaine and (B) lidocaine.

pethidine, a significant difference was detected (P=0.000).

When the effect of bupivacaine using either CSE or E technique was compared over the whole delivery period it was found that, CSE bupivacaine showed lower VAS throughout the labor process as compared to E bupivacaine (Figures 1-3).

It can be noticed that throughout the labor process, the average VAS score was between 0 and 2, and only increased near the delivery to reach 4. Throughout the

TABLE III.—*The different modes of deliveries among the different analgesic regimens and side effects reported by the recruited patients in the five analgesia groups.*

Parameter	CSE		E		IV	Total	P
	Bupivacaine	Lidocaine	Bupivacaine	Lidocaine	Pethidine		
	N.=10	N.=10	N.=10	N.=10	N.=20	N.=60	
Average APGAR score at 1 minute (SD)	6.70 (0.95)	6.20 (1.03)	6.70 (0.67)	6.50 (1.18)	5.85 (0.93)		0.094*
Average APGAR score at 5 minutes (SD)	9.30 (0.82)	9.00 (0.66)	9.30 (0.67)	9.10 (0.87)	8.45 (0.69)		0.013*
Mode of delivery							
Spontaneous (%)	6 (60)	5 (50)	7 (70)	8 (80)	7 (85)	43	0.278**
Ventouse or forceps (%)	4 (40)	5 (50)	2 (20)	2 (20)	2 (10)	15	0.126**
Cesarean section (%)	0	0	1(10)	0	1 (5)	2	0.629**
Experienced side effects							
Number (%) of patients with nausea and vomiting	1 (10)	1 (10)	0 (0)	4 (40)	15 (75)	21	0.000**
Number (%) of patients with hypotension	1 (10)	3 (30)	2 (20)	3 (30)	0 (0)	9	0.114**
Number (%) of patients with light sedation and drowsiness	5 (50)	5 (50)	5 (50)	4 (40)	13 (65)	32	0.746**
Number (%) of patients with pruritus	3 (30)	4 (40)	0 (0)	0 (0)	0 (0)	7	0.003**
Number (%) of patients with fever	1 (10)	6 (60)	0 (0)	4 (40)	0 (0)	11	0.000**

CSE: combined spinal epidural; E: epidural; IV: intravenous. *Statistical level of significance at $P<0.05$ using ANOVA. ** Statistical level of significance at $P<0.05$ using χ^2 test.

labor process, the average VAS score was most of the time higher in the E lidocaine group than the CSE lidocaine group.

The five groups were compared with respect to the incidence of instrumental or cesarean deliveries. There was no significant difference between the groups in the incidence of instrumental or cesarean deliveries (Table III).

When the recruited subjects were screened for the experienced side effects, it was found that, women who received IV pethidine had a significantly higher incidence of nausea and vomiting (75%) in comparison to those received CSE or E analgesia (10%, and 20%, respectively).

There was no significant difference between the five analgesic groups with respect to hypotension, sedation or drowsiness effect as a side effect. Pruritus was observed only in women received CSE analgesia.

Maternal fever was detected in women received CSE analgesia (35%) and those received E (20%) analgesia. None of those received pethidine experienced maternal fever.

Within the same group, maternal fever was significantly lower (P=0.019) in CSE bupivacaine group than CSE lidocaine group and also significantly lower in E bupivacaine (P=0.025) than E lidocaine.

A significant difference was observed in the average number of top-ups between CSE group and E group, with the CSE group having lower number of top-ups (P=0.002). Another significant difference was observed between E bupivacaine and E lidocaine, with the E lidocaine showing less number of top-ups.

Although there was no significant (P=0.094) difference among the analgesic groups in the fetal APGAR scores at 1 minute, a significant difference was observed among the five analgesic groups in the fetal APGAR scores at five minutes (P=0.013) as shown in Table III, with the IV group showing the significantly lowest score.

Discussion

Many authors have studied E and CSE techniques separately but few have com-

pared them with each other and compared both of them with IV pethidine, which was the aim of the current study.

The study is based on trying different techniques of analgesia during the labor process. When the different analgesic groups were compared for their effects on the duration of labor, it was found that, women received IV pethidine showed the shortest duration of first stage of labor. This could be explained by the fact that pethidine can induce stronger contractions and increase the cervical dilatation.[10]

Pain relief may increase uterine contractility, as reported in Yilmaz *et al.* study in which 50mg of pethidine was administered and was associated with a significant reduction in the duration of the first stage of labor.[11]

A Meta-analysis reviewing the experience of 2400 women randomly assigned to receive either E analgesia or parenteral opioid analgesia came with the conclusion that, E analgesia was associated with a prolongation of the first stage of labor.[12]

Alexander et al. found that the rate of cervical dilatation was significantly slower in women received E analgesia, resulting in a longer active labor.[13] One hypothesis is that E analgesia results in suppression of prostaglandin release, leading to diminished uterine contractility and prolongation of the active phase of labor.[14]

The present study supports these findings as the duration of first stage was the longest in women received E analgesia.

Bupivacaine has been found to decrease the rate and strength of uterine contractions this could be attributed to the rapid establishment of analgesia decreased maternal catecholamine levels that have been found to be tocolytic.[15] That is why women received E bupivacaine showed longer first stage of labor when compared to those received pethidine. This goes with a study done by Jain *et al.*,[16] and another study conducted by Mansoori *et al.*[17] However, this increase was not statistically significant. This goes with the NICE Guidelines on intrapartum care, which indicates that E analgesia is not associated with a longer first stage of labor.[18]

An explanation of why CSE lidocaine is associated with shorter first stage of labor than E lidocaine is that intrathecal fentanyl may cause more rapid cervical dilatation and shortens the first stage of labor.[19] This goes with a study conducted by Tsen *et al.*[20]

When comparing the duration of the second stage among the five analgesic groups, it was found that, no significant difference between both CSE bupivacaine and E bupivacaine groups or between CSE lidocaine and E lidocaine. This means that CSE affects only the duration of first stage by reducing the time to full cervical dilatation, with no effect on the duration of the second stage of labor.[20]

In the present study the quality of analgesia was better in the CSE group. Evidence suggests that the analgesic quality is better with the CSE. This is one of the main advantages of the CSE technique.[21, 22]

Retrospective study by Thallon and Shennan, involving comparisons of women requesting E analgesia with those who did not, suggested an increased cesarean delivery rate with E usage. This is opposing the results of the present study in which E analgesia has no effect on the rate of cesarean delivery. This controversy in the results could be explained by the fact that the formal study suffers from significant distortion due to selection bias as the request for E analgesia is in itself a marker of a more painful, prolonged and difficult labor, which may be in turn related to increased intervention. In addition, retrospective studied are unable to prove causation, merely demonstrating the association between various factors.[23]

On the other hand, a study of painless labor and instrumentation in Taiwan, found that, E analgesia decreased the rate of cesarean section but increased the frequency of instrumental delivery.[24] Two meta-analyses systemically and independently reviewed the previous literature, drawing similar conclusions, that E analgesia did not increase rates of instrumental vaginal delivery or cesarean section, which again supports the results of the current study.[12, 25]

A study by O'Sullivan, found that E analgesia was not associated with an increased

risk of caesarean birth rates.[26] Same results were confirmed by Kukulu and Demirok.[27]

Although Nageotte *et al.*, suggested that CSE analgesia may be associated with a reduction in instrumental vaginal delivery compared with E alone,[28] other investigators have found no difference in this aspect.[20, 21, 29-32] This goes with the results of the current study as it was observed that CSE was not associated with lower number of instrumental deliveries compared to the E technique.

When comparing E with IV pethidine regarding the mode of delivery, a large meta-analysis by Leighton and Halpern (2002), exploring the effects of E analgesia on labor, maternal and neonatal outcomes, found no difference in C-section rate between women who received parenteral opioids versus E analgesia.[33] This goes with the results of the current study, where there was no difference in C-section rates between those who received parenteral opioids *versus* E analgesia.

Another study in which 459 nulliparous women in active labor were randomly assigned to receive either E analgesia or IV pethidine, found no significant difference in the rate of cesarean deliveries performed.[34]

The use of fentanyl via both CSE and E routes may induce nausea and vomiting. The literature reports a broad range of incidences associated with E analgesia ranging from 10-50%. In the present study, nausea was more common in the E group. This could be explained by the fact that women in the E group received more fentanyl. This goes with what was proposed by Miro *et al.*[35]

Pethidine is well known to cause nausea and vomiting, which is common with all opioids thus, the rate of nausea and vomiting in women received IV pethidine was higher than the other modes of analgesia.[36]

For unknown reasons, the E administration of opioids may decrease the incidence of nausea and vomiting in comparison to the IV administration.[37] That is evident in this study as the incidence of nausea and vomiting was less in women received E analgesia compared to those received pethidine.

Although the use of E analgesia was usually thought to cause maternal hypotension, in present study there was no significant difference in the incidence of hypotension among women in all study groups. This goes with what was reported by Newman *et al.*[38]

Pruritus is the most common side effect of spinal opioids, and a frequent problem in the obstetric population. In the present study, pruritus was found to be more likely localized to the face, neck, or upper thorax. This goes with Cousins and Mather,[39] and Morgan.[40]

Various non-randomized and retrospective cohort studies have confirmed the association of labor E with intrapartum pyrexia, including overt clinical fever, with an incidence varied from 1% to 36%.[41-43]

Other studies also identified nulliparity, prolonged rupture of membranes, prolonged duration of labor, high maternal temperature on admission, early chorioamnionitis, and frequent cervical examinations as risk factors for maternal pyrexia.[44, 45]

Fetal APGAR scores at five minutes were significantly lower in the IV pethidine group. This may be due to placental transfer of pethidine. Pethidine is metabolized to norpethidine. Pethidine and its metabolites decrease fetal respiratory movements causing low APGAR scores.[36, 46]

A meta-analysis of randomized controlled trials showed that there were significantly fewer lower APGAR scores at five minutes with E than with systemic opioid analgesia.[12] This goes with the results of the current study.

APGAR scores associated with E bupivacaine were normal. This goes with Abboud *et al.*,[47, 48] who examined how E analgesia determines the various factors of fetal well-being.

Bupivacaine was shown to give better APGAR scores than lidocaine. A possible explanation for this is that lidocaine, because of its low pKa, could be sequestered into the fetus in its ionic form.[49] This may help to explain the lower APGAR scores experienced in women receiving lidocaine than those receiving bupivacaine.

It has become clear that CSE provides better analgesia throughout the course of labor, thus reducing the request for additional doses for recurrent breakthrough pain.[50, 51] Why CSE analgesia should be associated with fewer requests for additional analgesia remains

unclear. This could be due to several mechanisms including the effect of E injections on spinal analgesia level, or an intrinsic superior efficacy of spinal versus E analgesia.[52]

Study limitations

The study experienced several limitations. The first limitation was the small sample size recruited. This could be attributed to the nature of the study, which is a self-funded study. To overcome this point a well-designed set of inclusion and exclusion criteria was designed and the study was conducted in a randomized manner. Second weak point was heterogeneity of the professionals performing the techniques, as the hospital at which the study was conducted is a teaching hospital with vast range of experiences. Finally, subjects' satisfaction with the screened techniques was not performed in the present study.

These limitations are partly compensated by designing a prospective study, excluding women with major complications to prevent confounding factors, the obstetric population recruited from the same area, with a limited team of people using standard procedure and materials, and involving a statistical analysis of data designed to identify and eliminate possible confounding factors.

Conclusions

It can be concluded that CSE analgesia provide highly efficient labor pain control compared to E and IV analgesia. The CSE group showed a significantly lower number of top-ups among all studied groups. CSE bupivacaine showed better pain control over CSE lidocaine. CSE and E analgesia were not associated with increased rates of C-section or instrumental deliveries.

Riassunto

Analgesici IV versus *analgesici regionali nel travaglio di parto*

Obiettivo. Obiettivo del presente studio è stato quello di confrontare l'analgesia combinata spinale-epidurale (CSE), epidurale (E) ed endovenosa (IV) con petidina e i loro effetti su madre, feto, neonato e andamento del travaglio di parto.

Metodi. Si tratta di uno studio prospettico, a gruppi paralleli e in cieco singolo, nel quale sono state arruolate 60 donne in travaglio attivo, collocate in cinque sottogruppi al fine ricevere l'analgesia mediante vie diverse. La madre e il feto sono stati valutati. I risultati sono stati registrati e confrontati usando la scala analogica visiva (VAS) e la scala di Bromage modificata per il blocco motorio, oltre ad altre scoperte cliniche.

Risultati. La durata della prima fase del travaglio di parto è stata significativamente più lunga nel gruppo con petidina E, rispetto ai gruppi con petidina CSE ed IV. Quando il controllo del dolore raggiunto da bupivacaina e lidocaina CSE è stato paragonato alla relativa epidurale, è stato rilevato che la prima tecnica aveva ottenuto un migliore controllo del dolore. Le donne che avevano ricevuto petidina avevano una maggiore incidenza di nausea e vomito rispetto a quelle che avevano ricevuto analgesia CSE o E. Non vi era una differenza significativa tra i cinque gruppi rispetto ad altri effetti collaterali.

Conclusioni. L'analgesia regionale, soprattutto quella CSE con bupivacaina o lidocaina, è un metodo sicuro ed efficace per l'analgesia nel travaglio di parto con un'efficacia relativamente migliore della bupivacaina.

Parole chiave: Analgesia, epidurale - Travaglio - Parto.

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