Comparison between 0.08% Ropivacaine and 0.06% Levobupivacaine for Epidural Analgesia during Nulliparous Labor: A Retrospective Study in A Single Center

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Background: Levobupivacaine and ropivacaine are new local anesthetics that have effects similar to bupivacaine. However, the relative potency of these two drugs is controversial. The purpose of this retrospective study was to assess whether a combination of 0.06% levobupivacaine and 0.0002% fentanyl had the same effects as 0.08% ropivacaine and 0.0002% fentanyl on the mode of delivery and other obstetric outcomes when used for epidural analgesia of labor in nulliparous women.

Methods: Computer records of 392 Asian nulliparous parturients, who had presented with spontaneous labor or spontaneous rupture of the membranes, and had received epidural analgesia were retrospectively reviewed. Of these, 193 received 0.08% ropivacaine and 199 received 0.06% levobupivacaine. Fentanyl (0.0002%) was used in both regimens.

Results: There were no significant differences in the mode of delivery, duration of labor, or neonatal outcome between the two groups. In the levobupivacaine group, the parturients required top-up boluses of local anesthetics more frequently (1.4 $\pm$ 1.6 vs. 0.9 $\pm$ 1.3, $p < 0.0001$), and the incidence of temporary maternal fever (25% vs. 15%, $p = 0.024$) and the cost of local anesthetic were higher (292 $\pm$ 183 NTD vs. 146 $\pm$ 104 NTD, $p < 0.0001$). However, the amount of local anesthetic administered during labor was lower (79 $\pm$ 49 mg vs. 114 $\pm$ 81 mg, $p < 0.0001$) than for the ropivacaine group.

Conclusions: 0.06% levobupivacaine was as effective as 0.08% ropivacaine, when both were used with 0.0002% fentanyl for labor epidural analgesia of nulliparous women.

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Key words: epidural analgesia, ropivacaine, levobupivacaine

Although epidural bupivacaine is highly effective in providing pain relief, its use is limited because of side effects including motor blockade and cardiovascular toxicity.[1] Levobupivacaine and ropivacaine are new local anesthetics that have effects similar to bupivacaine. They are believed to be less

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toxic to the central nervous system and cardiovascular system. They have also been reported to cause less motor blockade.[2-4] However, the relative potency of the two drugs is controversial. While some researchers have found a similar potency for levobupivacaine and ropivacaine,[5] while others have observed that levobupivacaine is more potent than ropivacaine.[6,7] These possible differences in potency may be masked by the presence of opiates.[8] Until May 2007, epidural analgesia was administered to parturients admitted to our hospital with a regimen of 0.08% ropivacaine and 0.0002% fentanyl. Subsequently, due to an unavailability of ropivacaine, the regimen in our hospital was changed to 0.06% levobupivacaine and 0.0002% fentanyl. The purpose of this retrospective study was to assess whether there are differences in the mode of delivery and other obstetric outcomes between the two regimens when administered for epidural analgesia during labor among nulliparous women.

METHODS

This study was approved by the ethics committee of our university hospital. There were a total 1544 of parturients admitted to the labor and delivery room between January 2007 and October 2007 at our institution. The computer records of 858 parturients who had received epidural analgesia were retrospectively reviewed. We sequentially excluded the following parturients: (1) those with incomplete data records (n = 6), (2) multiparas participants (n = 266), (3) those to whom a regimen other than 0.08% ropivacaine or 0.06% levobupivacaine was administered (n = 11), (4) those who underwent preterm labor or termination (n = 19), (5) those with a twin pregnancy (n = 2), (6) those with failed or replaced epidural catheterization during epidural analgesia (n = 13), (7) those admitted for induction of labor (n = 133), (8) those with pregnancy-induced hypertension (n = 8), and (9) those with gestational diabetes mellitus (n = 8). Finally, there were 392 healthy nulliparous parturients who underwent spontaneous labor or experienced spontaneous rupture of the membranes with a singleton fetus presenting by the vertex and who had received epidural analgesia with 0.08% ropivacaine or 0.06% levobupivacaine in combination with 0.0002% fentanyl; these were then included in this study.

Epidural insertion was performed after hydration with intravenous 500 ml to 1,000 ml of lactated Ringer's solution. The lower lumbar epidural space was identified by the loss-of-resistance technique with an 18-gauge Tuohy needle. The parturients were in the lateral position and an epidural catheter was inserted into the epidural space. If no sign of an intravascular or subarachnoid puncture was observed, the catheter was secured and the parturient was placed in the supine position with left uterine displacement. A standardized epidural protocol was followed during the administration of analgesia to all parturients; it consisted of a 10-ml initial loading dose of ropivacaine (1 mg/ml) or levobupivacaine (0.5 mg/ml) in combination with fentanyl (7.5 μg/ml). In addition, a continuous maintenance dose of ropivacaine (0.8 mg/ml) or levobupivacaine (0.6 mg/ml) combined with fentanyl (2 μg/ml) was administered at a rate of 10 ml/h after the various standard recordings (electrocardiography, automated noninvasive blood pressure, and fetal heart rate monitoring) had been normal for 15 min. An additional 10 ml of the drug was administered on the patients' request as a top-up bolus. When cervical dilatation was less than 5 cm, we used 2 mg/ml ropivacaine or 1 mg/ml levobupivacaine for this purpose. When the cervical dilatation was more than 5 cm, we used 3 mg/ml ropivacaine or 1.5 mg/ml levobupivacaine. Epidural analgesia was continued through the second stage of labor. Decisions concerning obstetrical management were made by the attending obstetrician.

Maternal age, height, body weight, presence or absence of spontaneous rupture of membranes at admission, admission white blood cell count, and time interval from admission to initiation of epidural analgesia were recorded as the pre-labor characteristics. The following were recorded as labor characteristics: time interval from admission to delivery, duration of the epidural analgesia, duration of the second stage, total amount of local anesthetic uses as top-up bolus doses and their frequency of administration, and the parturients' complaints after epidural anesthesia (including nausea, vomiting, and fever). The definition of maternal fever for this study was an ear temperature > 38°C. Mode of delivery, Apgar scores of the newborn, body weight of the newborn, temperature of the newborn, whether antibiotics were administered to the parturients during the peripartum period, the presence of postpartum hemorrhage, and

the total amount and cost of local anesthetics were recorded as the labor outcome characteristics.

Data are presented as mean ± standard deviation. Differences in the continuous variables were analyzed by the Mann-Whitney U test. Differences in categorical variables were analyzed by the chi-square and Fisher's exact test, where appropriate. A p value of less than 0.05 was considered statistically significant.

RESULTS

Information on the 392 parturients was collected. A sample size of 392 will have a power of 99.6% when detecting differences and the alpha is equal to 0.05. Of these parturients, 193 belonged to the ropivacaine group and 199 to the levobupivacaine group. No differences were observed in the pre-labor characteristics between the two groups (Table 1). The parturients in the levobupivacaine group required top-up boluses of local anesthetics for adequate pain relief more frequently (1.4 ± 1.6 vs. 0.9 ± 1.3; $p < 0.0001$), and the rate of temporary maternal fever during the peripartum period was also higher in this group (25% vs. 15%, $p = 0.024$) than in the ropivacaine group. No differences were observed for the time interval from admission to delivery, the duration of epidural analgesia, the duration of the second stage, the total in milligrams of the bolus doses, and frequency of nausea and vomiting (Table 2).

With regard to the labor outcome characteristics, no differences were observed in the mode of delivery, Apgar score of the newborn, newborn weight of the newborn, frequency of fever in the newborn, antibiotic administration to parturients during the peripartum period, and the occurrence of postpartum hemorrhage. More local anesthetic (114 ± 81 mg vs. 79 ± 49 mg; $p < 0.0001$) was administered during labor in the ropivacaine group, but the expenditure on local anesthetics (292 ± 183 new Taiwan dollars (NTD) vs. 146 ± 104 NTD; $p < 0.0001$) was higher in the case of the levobupivacaine group (Table 3).

Table 1. Pre-labor Characteristics

Descriptor	Ropivacaine group (n = 193)	Levobupivacaine group (n = 199)	p value
Age (years)	31 ± 4	31 ± 3	0.363
Height (cm)	160 ± 5	160 ± 5	0.097
Weight (kg)	69 ± 9	67 ± 8	0.081
Spontaneous rupture of membranes	76 (39%)	72 (36%)	0.583
Admission white blood cell count (1000/uL)	10.6 ± 3.4	10.5 ± 2.9	0.750
Time interval from admission to initiation of epidural analgesia (min)	297 ± 380	241 ± 280	0.207

Table 2. Labor Characteristics

Descriptor	Ropivacaine group (n = 193)	Levobupivacaine group (n = 199)	p value
Time interval from admission to delivery (min)	911 ± 598	810 ± 456	0.270
Duration of epidural analgesia (min)	599 ± 410	556 ± 349	0.609
Duration of second stage (min)	86 ± 56	95 ± 61	0.194
Frequency of top-up boluses	0.9 ± 1.3	1.4 ± 1.6	< 0.0001
Total boluses dose (mg)	24 ± 35	18 ± 21	0.984
Frequency of nausea and vomiting	23 (12%)	17 (9%)	0.349
Frequency of maternal fever	29 (15%)	49 (25%)	0.024

Table 3. Labor Outcomes

Descriptor	Ropivacaine group (n = 193)	Levobupivacaine group (n = 199)	*p* value
Vaginal delivery	135 (70%)	149 (75%)	0.269
Instrumental delivery	39 (20%)	28 (14%)	
Cesarean delivery	19 (10%)	22 (11%)	
Apgar Score of newborn < 8 at 1 min	12 (6%)	12 (6%)	> 0.99
Newborn weight (g)	3191 ± 381	3207 ± 345	0.501
Frequency of newborn fever	31 (16%)	31 (16%)	> 0.99
Antibiotic use	99 (51%)	96 (48%)	0.615
Total use of local anesthetics (mg)	114 ± 81	79 ± 49	< 0.0001
Local anesthetic cost (NTD)	146 ± 104	292 ± 183	< 0.0001
PPH	1 (1%)	2 (1%)	> 0.99

Abbreviations: NTD: new Taiwan dollars; PPH: postpartum hemorrhage.

DISCUSSION

The results of our study demonstrated that there was no significant difference in the mode of delivery, duration of labor, or neonatal outcome between the two drugs when used with the above regimens. The use of levobupivacaine in labor analgesia has been previously compared with that of ropivacaine at similar or different concentrations.[9-12] Beilin et al. demonstrated that there was no significant difference in the total dose of local anesthetic administered per hour or the number of top-up doses required per hour during labor when 0.0625% ropivacaine or 0.0625% levobupivacaine were used with 0.0002% fentanyl.[11] Further, Purdie et al. found that 0.1% ropivacaine or 0.1% levobupivacaine, both administered with 0.0002% fentanyl, necessitated the administration of the same number of rescue top-up doses, and, hence, seemed pharmacologically equipotent.[9] Atiénzar et al. found that there were no significant differences in the total dose of local anesthetic and the number of rescue boluses when 0.2% ropivacaine or 0.125% levobupivacaine was used with 0.0001% fentanyl.[12] In contrast, Smet et al. in their article compared 0.165% ropivacaine and 0.125% levobupivacaine, both administered with 0.0001% sufentanil, for patient-controlled epidural analgesia for 24 h after orthopedic surgery. They found that even at a 25% weaker concentration, a lower amount of levobupivacaine was required, which may be explained by a difference in potency of or the duration of action of the levobupivacaine.[13] In this study, even if our data showed that the total doses of local anesthetic were significantly higher in the 0.08% ropivacaine group than in the 0.06% levobupivacaine group, it is difficult to evaluate the relative potency of the two drugs in this type of retrospective study. Furthermore, the inclusion of fentanyl might also influence the quality of analgesia.[14] A more frequent use of a top-up bolus was noted with levobupivacaine and therefore daily practice can be improved by increasing the top-up bolus dose, which will then decrease frequency of use when levobupivacaine is used.

The incidence of fever in nulliparous women continuously receiving analgesics varies from 14.5% to 33% and increases with the duration of epidural use.[15-17] The rise in temperature is often temporary, and the temperature may normalize at or soon after delivery.[18] In some parturients, the fever is caused by infection, usually chorioamnionitis, but in most cases, the origin of the fever is unknown.[18] Intermittent epidural injections as against continuous analgesic infusion appear to prevent intrapartum fever during the first 4 h of labor analgesia.[19] Several theories have been proposed as to the mechanism of epidural fever, and they largely emphasize the changes in maternal thermoregulation. Goetzl et al. found that epidural fever is associated with an elevated maternal serum IL-6 level, which supports an inflammatory basis for epidural fever.[20]

On the basis of our results, there were no significant differences in the incidence of spontaneous rupture of membranes at admission, admission white blood cell count, and the duration of epidural analgesia between the two groups. Nonetheless, the rate of temporary maternal fever was higher in levobupivacaine group (n = 49, 25%) than in the ropivacaine group (n = 29, 15%) (p = 0.024). All the 78 fever parturients had a normal temperature before epidural analgesia. The CRP and the WBC counts were checked in the parturients that fever was suspected to pinpoint any possible infection. In the Ropivacaine group, there were 21 out of 29 (72%) parturients who had an elevated CRP value or WBC count. In the Levobupivacaine group, there were 31 of 49 (63%) parturients who had an elevated CRP value or WBC count. The temperatures of these mothers recovered to the normal range within 24 h after delivery in 76 of 78 parturients. Only two participants showed persistent fever for > 24 h after delivery and both belonged to the levobupivacaine group. One parturient had chorioamnionitis, while the other had a fever of unknown origin. We do not know the exact mechanisms by which the levobupivacaine group seemed to cause a higher percentage of maternal fever. Even so, although the rates of maternal fever between the groups were different, no significant differences were observed in antibiotic use and neonatal outcome. No difference between the two drugs with respect to maternal fever could be found in any recent publications and therefore more research is required in this area.[9-12]

Levobupivacaine and ropivacaine are more expensive than racemic bupivacaine.[21] In our hospital, 20 ml of 1% ropivacaine (Naropin, Astrazeneca) costs 256 NTD, and 10 ml of 0.5% levobupivacaine (Chirocaine, Abbott) costs 186 NTD. As per the current pricing, levobupivacaine is more than 2.9 times expensive than ropivacaine. Therefore, in our study, expenditure on local anesthetic was higher in the levobupivacaine group.

On the basis of the currently available data, it can be concluded that 0.06% levobupivacaine is as effective as 0.08% ropivacaine when both are used with 0.0002% fentanyl during labor epidural analgesia of nulliparous women.

Limitations

This study has some limitations. Firstly, since we did not record the dosage of augmentation drugs, we were unable to compare them. Second, in a retrospective study, it is difficult to assess the subjective sensations of the parturients and therefore evaluating motor blockade and pain is equally difficult.

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比較 0.08% 耐樂品 (Ropivacaine) 與 0.06% 開洛凱因 (Levobupivacaine)，合併使用 0.0002% 吩坦尼 (fentanyl) 在初產婦硬脊膜外之止痛：單一醫院之回溯性研究

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背 景： 開洛凱因 (levobupivacaine) 與耐樂品 (ropivacaine) 是新的局部麻醉藥品，與麻佳因 (bupivacaine) 有相似的效用。然而，此兩種藥物的相對效力仍有爭議。此一回溯性研究旨在比較初產婦以此兩種不同藥物施打硬脊膜外止痛，對剖腹產率及各項產科因子的影響。

方 法： 回溯性分析 392 位自發性陣痛或破水且接受硬脊膜外止痛之初產婦的護理紀錄，其中有 193 位使用 0.08% 耐樂品 (ropivacaine)，有 199 位使用 0.06% 開洛凱因 (levobupivacaine)，兩者皆合併使用 0.0002% 吩坦尼 (fentanyl)。

結 果： 無論是生產方式、產程、或新生兒結果在兩組之間並無明顯差異。在開洛凱因 (levobupivacaine) 組，產程進展期間使用加強劑量麻醉藥物的頻率較高 (1.4 ± 1.6 vs. 0.9 ± 1.3, $p < 0.0001$)。產婦暫時性的發熱比例 (25% vs. 15%, $p = 0.024$) 與局部麻醉藥物費用 (292 ± 183 NTD vs. 146 ± 104 NTD, $p < 0.0001$) 也較高。而局部麻醉藥物的使用總量較耐樂品 (ropivacaine) 組低 (79 ± 49 mg vs. 114 ± 81 mg, $p < 0.0001$)。

結 論： 0.06% 開洛凱因 (levobupivacaine)，合併使用 0.0002% 吩坦尼 (fentanyl) 在初產婦硬脊膜外之止痛與 0.08% 耐樂品 (ropivacaine)，合併使用 0.0002% 吩坦尼 (fentanyl) 一樣有效。

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關鍵詞： 硬脊膜外止痛，耐樂品 (ropivacaine)，開洛凱因 (levobupivacaine)

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