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The outcome of preterm neonates with intraventricular hemorrhage delivered with intravenous meperidine or epidural analgesia

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Abstract
We aimed to study, retrospectively, the neonatal outcome of 45 preterm neonates with intraventricular hemorrhage (IVH) who were delivered vaginally with intravenous meperidine (n = 23) or epidural analgesia (n = 22). Neonates in the epidural group had a better outcome in terms of a first-minute Apgar score of 7 or less, in 31% vs 69% (P = 0.001); 5-min Apgar score of 7 or less, in 18% vs 82% (P = 0.003); a lower incidence of respiratory distress syndrome (RDS; 23% vs 30%; P = 0.03); a lower dopamine requirement during the first neonatal week (13% vs 72%; P = 0.01); and a higher survival rate (91% vs 58%, respectively; P = 0.008). It is concluded that preterm neonates with IVH had a better outcome when delivered to mothers receiving epidural analgesia as compared to those receiving intravenous meperidine.

Key words Intraventricular hemorrhage · Analgesia in labor · Perinatal labor · Neonatal complications

The pathophysiology of intraventricular hemorrhage (IVH) in the preterm infant has been extensively studied, but the exact etiology, as well as the impact of anesthesia and analgesia during labor or for cesarean delivery on the outcome of the preterm infant have not been determined [1–5]. Our aim was to study, retrospectively, the neonatal outcome of preterm neonates with IVH who were delivered vaginally with intravenous meperidine or epidural analgesia.

During the study period, from January 1994 to December 2002, 20768 deliveries were managed at our university hospital. We reviewed the medical records of 75 preterm neonates, less than 37 weeks (completed) gestational age who were diagnosed sonographically as having early (first 72 h) IVH. During this period we used the same protocol for neonatal management. Fetuses under 530 g or those with congenital anomalies and those delivered with cesarean section were excluded from the study. Database analyzed variables included demographics, pregnancy complications, medication used, type of analgesia, outcome of labor and delivery, and neonatal management until discharge from hospital.

Epidural anesthesia was performed for labor pain after prehydration with 10 ml·kg^{-1} normal saline or lactated Ringer's solution. Bupivacaine 0.125%, 6–10 ml·h^{-1} was administered after a test dose of 3 ml lidocaine 1.5%. Intravenous pethidine 75 mg in 100 ml normal saline was administered over 30 min in parturients who refused epidural analgesia or if there were contraindications. Fetal heart rate (FHR) monitoring was assessed throughout labor and delivery by a senior obstetrician who provided the obstetric intervention when necessary. Fetal heart rate was classified according to the National Institute of Child Health and Human Development (NICHD) [6].

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS, Chicago, IL, USA; 1999). For continuous variables such as birth weight and cord pH, descriptive statistics were calculated and reported as means ± SD. Normalcy of distribution of continuous variables was assessed using the Kolmogorov-Smirnov test (cutoff at P = 0.01). Categorical variables such as group and IVH were described using frequency distributions, and are presented as frequencies (%). The t-test for independent samples was used to detect differences in continuous variables by group. Continuous variables with distributions deviating significantly from normal (such as gravidity and parity) were compared by group, using the Mann-Whitney U-test. Categorical variables were compared by group, using the χ^2 test. All tests are two-sided and considered significant at P < 0.05.

The overall incidence of IVH among the 20768 deliveries was 0.36% (75 cases).

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Table 1. Obstetric characteristics and labor outcome

Variable	Meperidine analgesia $n = 23$	Epidural analgesia $n = 22$	P value
Age (years; mean ± SD)	28 ± 5.6	28.9 ± 6.2	0.6
First pregnancy (%)	4	10	0.3
PET/PIH %	3.8	20	0.3
Antepartum bleeding or placental abruption (%)	4.3	4.3	0.6
Premature rupture of membranes (PROM; min; mean ± SD)	1197 ± 909	609 ± 1711	0.46
Maternal fever >37.8°C (%)	14	13	0.4
Medications in pregnancy			
Magnesium sulfate (%)	1	4.5	0.36
Steroids (%)	24	18	0.36
Tocolytics (%)	4	2	0.36
Indomethacin (%)	4	2	0.36
Aspirin/LMWH (%)	8	4.5	0.36
Oxytocin in labor %	64	73	0.3
Abnormal FHR tracing (%)	27	28	0.1
Mode of delivery			
Normal/spontaneous (%)	80	82	0.3
Breech delivery (%)	20	18	0.3
Duration of labor (min; mean ± SD)			
First stage	287 ± 341	253 ± 202	0.7
Second stage	33.4 ± 27	37.6 ± 21	0.69

Out of 75 preterm neonates reviewed, 24 newborns delivered with cesarean delivery under general anesthetic were excluded from the study. Also excluded were 6 other neonates who were delivered with cesarean delivery (3 out of 26 in the meperidine group and 3 out of 25 in the epidural group).

Obstetric characteristics and mode of delivery did not differ significantly (Table 1). The neonatal outcomes of the newborns in the epidural group were significantly better than those from the meperidine group, in terms of first and 5-min Apgar scores, dopamine requirement to stabilize blood pressure, incidence of respiratory distress syndrome, and rate of survival (Table 2).

This retrospective analyisis of early IVH showed better perinatal outcome in preterm neonates delivered with epidural analgesia as compared to those with intravenous meperidine. Among the multiple risk factors for the development of early IVH, the degree of prematurity correlated with a higher rate of occurrence and increased severity of IVH, even with advanced neonatal intensive care unit (ICU) care [7–8]. The association of IVH with fetal asphyxia and acidosis has also been implicated [9]. There were no cord arterial blood pH differences in the two study groups, possibly because both groups included IVH neonates. Other characteristics suggestive for fetal asphyxia, such as the Apgar scores, were found to be better in the group of infants delivered under epidural analgesia.

The early onset of IVH may be correlated with early mechanical ventilation in preterm infants [10]. In our study, 68% in the epidural group were ventilated compared to 84% in the meperidine group ($P = 0.2$). IVH may also be associated with premature rupture of membranes and pregnancy-induced hypertension [11, 12]. Fluctuations in blood pressure and cerebral blood flow may precipitate cerebral hemorrhage in humans and in experimental animal models [13, 14]. Neonates from our study who were delivered under meperidine analgesia had a lower mean arterial blood pressure and more of them required dopamine administration for blood pressure stabilization.

Antenatal steroid administration may reduce by 50% the occurrence of IVH [7]. Instrumental delivery has been implicated in the occurrence of IVH [15, 16], although the introduction of plastic cups has reduced its incidence [16]. Instrumental deliveries were not recorded in our groups. We omitted from our study neonates delivered under general anesthesia, as well as those delivered with cesarean delivery, because cesarean delivery itself may affect the incidence of IVH [4, 5].

The effect of the method of analgesia and anesthesia on the risk of IVH has not been determined, although regional anesthesia was deemed advantageous for the delivery of fullterm and preterm infants with both elective and non-elective cesarean section [5]. In addition, the outcome of neonates who were delivered under

Table 2. Neonatal variable association with mode of analgesia

Variable	Meperidine analgesia $n = 23$	Epidural analgesia $n = 22$	P value
Pregnancy week (mean ± SD)	27.3 ± 3.5	28 ± 3.8	0.8
Birth weight (g; mean ± SD)	1056 ± 547	1162 ± 624	0.07
Apgar score ≤7 (%)			
1 Min	69	31	0.001
5 Min	82	18	0.003
Cord arterial pH (mean ± SD)	7.31 ± 0.12	7.2 ± 0.15	0.10
First arterial PO_2 (mmHg)	50.6 ± 38	47.4 ± 28	0.7
First arterial pH (mean ± SD)	7.2 ± 0.12	7.24 ± 0.13	0.8
Hypoglycemia (%)[a]	28	27	0.9
MAP (mmHg; mean ± SD)	28.5 ± 8.9	35.5 ± 8.1	0.04
Maximal $F_{I_{O_2}}$ (mean ± SD)	0.5 ± 0.36	0.37 ± 0.28	0.06
Dopamine usage (%)	72	13	0.01
Neonatal sepsis (%)	34	32	0.25
Mechanical ventilation (%)	84	68	0.2
Barotrauma (pneumothorax; %)	5	10	0.07
Peak inspiratory pressure (mean ± SD)	12.7 ± 11.5	11.4 ± 10	0.6
RDS (%)	29	23	0.03
Convulsions (%)	12	22	0.3
Thrombocytopenia <150 000 μl^{-1} (%)	64	59	0.4
Survivors (%)	58	91	0.008

[a] Hypoglycemia is defined as <38 $mg \cdot dl^{-1}$

epidural anesthetic was better than that for those delivered under general anesthesia [4, 5].

The possible reason for the somewhat protective effect of epidural analgesia for labor and vaginal delivery on the neonates with IVH stems from the fact that epidural analgesia had a less depressant effect on the fetus and neonate and from the decreased need for mechanical ventilation. Also, epidural analgesia provided more hemodynamic stability to the fetus.

Thus, epidural analgesia may decrease the incidence of IVH among vaginally delivered preterm infants, or it may improve the outcome of those who have already suffered from IVH. Our results show that preterm neonates with early IVH who were delivered with epidural analgesia had better outcomes than those delivered with intravenous meperidine. The inherent limitations of this study are related to the small sample size and that the study was undertaken in a retrospective manner.

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