Pulmonary Function in Infants Exposed to Pethidine

THRATHIP KOLATAT, M.D.*, SUPATTRA JARUNGPHAN, B.N.S.**,
CHANTIMA CHARASTONG, M.N.S.**, YUPIN JUNDEEWONG, B.N.S.**

Abstract

Objective : To investigate the effects of maternal pethidine administration on pulmonary function tests in newborn infants.

Patients and Method : The study was carried out in the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. The study group consisted of 20 infants exposed to pethidine within 4 hours prior to delivery. Twenty infants whose mothers received no analgesic drug or regional anesthesia were randomly selected as the controls. Narcotic related respiratory depression was determined by Apgar scores, the need for ventilatory support in the delivery room and abnormal pulmonary function measurements.

Results : There was no difference in birth weight and gestational age between the two groups of infants. Pethidine was given to mothers at a dose of 72.5 $\pm$ 7.6 mg/kg with a mean drug-delivery interval of 152 $\pm$ 61 minutes. One infant in each group had a 1-minute Apgar score less than 7, but there was no statistical difference in the mean Apgar score between the two groups. None of the infants whose mothers received pethidine required ventilatory support, but oxygen was provided to eight infants who were apparently cyanosed at birth. Pulmonary function measurements were performed at the age of 7.4 $\pm$ 2.3 hours in the controls and 6.0 $\pm$ 2.5 hours in the study group. There was no significant difference in respiratory rate, tidal volume, inspiratory time, functional residual capacity, compliance and resistance between the two groups of infants.

Conclusion : Severe narcotic related respiratory depression was uncommon in this study. In the first 12 hours of life, there was no significant difference in pulmonary function of the infants exposed to pethidine. It is quite safe to allow the baby to room-in with the mother if respiratory depression is not presented at birth.

Key word : Pethidine, Meperidine, Pulmonary Function Testing, Neonate

**KOLATAT T, JARUNGPHAN S,
CHARASTONG C, JUNDEEWONG Y
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* Department of Pediatrics,
** Department of Nursing, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Despite the well-known placental transfer of pethidine (meperidine) and the long neonatal half-life of both meperidine and its active metabolite normeperidine, it is the most widely used drug to control labor pain. The results of the National Birthday Trust Survey in 1990 demonstrated that 26.6 per cent of the infants exposed to pethidine during labor received resuscitation at birth; 17.7 per cent with oxygen tubing, 7.7 per cent with bag and mask, 1.2 per cent with endotracheal intubation[1]. In the past, most investigators have used Apgar scores as one of the measures of pethidine effect on newborn. Previous studies have documented the respiratory effects of meperidine on newborn infants in the first hour of life; a decreased SaO_2[2], lower VE[3], increased $PaCO_2$ levels,[4] and a reduced ventilatory response to CO_2[5] have been demonstrated. In addition, the effects on neonatal behavior[6], breathing pattern[7], breast-feeding behavior[8], and electroencephalogram[9] have been reported in infants exposed to pethidine during labor. The effects may be detectable hours, days and possibly even weeks after birth with diminished alertness, reduced muscle tone and alteration in behavior and motor function [10]. In infants, these effects depend on the drug level of pethidine and it's highly active metabolite, normeperidine. It has been reported that total elimination of the drug takes place 3 to 6 days postnatally [11]. The objective of this study was to evaluate pulmonary function tests in newborn infants whose mothers receive pethidine during labor and delivery, within the first 12 hours of life.

PATIENTS AND METHOD

The study was carried out in the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital from January to December 2001. Forty full-term neonates born to mothers with an uncomplicated pregnancy were recruited after obtaining informed consent. The study group consisted of 20 infants whose mothers received pethidine within 4 hours prior to delivery. Twenty infants, whose mothers received no analgesic drugs or regional anesthesia (spinal or epidural) were randomly selected as the control group. Obstetric histories, mode of delivery, complications, anesthetic and analgesic methods were recorded. The clinical data including maternal weight, amount of pethidine used, drug-delivery interval, gestational age, birth weight, length and Apgar scores including methods of resuscitation needed are shown in Tables 1-2.

Method

Assessment of narcotic related respiratory depression on newborn infants including Apgar scores and the need for ventilatory support in the delivery room and pulmonary function were recorded. Pulmonary function measurements were determined by using the Pediatric Pulmonary Function Laboratory 2600 (SensorMedics, USA). Before performing each measurement, the pneumotachograph and equipment for measuring the functional residual capacity (FRC) were calibrated according to laboratory instructions. All the measurements were performed during quiet sleep with infants in the supine position. The infant's sleep state was determined by observing muscle tone, infant activity, eye movements and breathing pattern. No sedation was used and the infant breathed air during the measurement. The pneumotachometer (dead space 0.5 ml, resistance 0.05 $cmH_2O/L/s$) was attached to a neonatal facemask and placed gently over the baby's nose and mouth. Care was taken to avoid neck flexion and digital pressure on the submental region that

Table 1. Maternal and infant clinical data.

	Pethidine group (n=20) (Mean ± SD)	Control group (n=20) (Mean ± SD)	P-value
Maternal age, g	24.9 ± 4.8	27.3 ± 6.8	NS
Maternal weight, kg	61.9 ± 9.8	59.9 ± 8.7	NS
Gestational age, wk	39.0 ± 1.0	39.1 ± 1.7	NS
Birth weight, g	3,138 ± 478	3,173 ± 225	NS
Length, cm	50.0 ± 1.7	49.3 ± 1.59	NS
Apgar score at 1 min	8.6 ± 1.2	9.0 ± 1.2	NS
Apgar score at 5 min	9.9 ± 0.3	9.9 ± 0.4	NS

Table 2. Obstetric information.

	Pethidine group (n=20)	Control group (n=20)
Mode of delivery		
Vaginal delivery	16	11
Cesarean section	3	8
Vacuum extraction	1	1
Male : Female	10 : 10	11 : 9
Type of resuscitation		
Tactile stimulation	-	1
Oxygen administration	8	-
Bag and mask ventilation	-	1

may have caused airway obstruction. Sleep stage and transcutaneous oxygen saturation were closely monitored. Flow-volume loops were selected to determine the inspiratory volume and expiratory volume, inspiratory and expiratory time and time constant. A single-breath occlusion technique was used to determine lung compliance and resistance[12]. The FRC was measured using the Nitrogen washout technique[13].

Statistical analysis

Pulmonary function data were calculated by a computer and printed out after each measurement. The authors compared the results of pulmonary function testing between the two groups of infants. Data were reported as mean ± SD. Statistical comparisons involved a two-tailed Student *t* test or χ^2 test. A p value of <0.05 was considered statistically significant.

RESULTS

There was no significant difference in birth weight and gestational age between the two groups of infants. Pethidine was given to mothers at a dose (mean ± SD) of 72.5 ± 7.6 mg/kg (range 50-75) with a mean drug-delivery interval of 152 ± 61 minutes (range 66-240). One infant in each group had a 1-minute Apgar score less than 7, but the mean Apgar score was not statistically different between the groups (Table 1). None of the infants whose mothers received pethidine required bag and mask ventilation. Oxygen was provided to eight infants in the pethidine group who were apparently cyanosed at birth. Narcan was given to 11 infants, of whom, eight required resuscitation at birth. Pulmonary function measurements were performed at the age (mean ± SD) of 7.4 ± 2.3 hours in the control group and 6.0 ± 2.5 hours in the study group. Pulmonary function tests of the infants exposed to pethidine was not statistically different when compared to the control group (Table 3). In addition, pulmonary function tests were not affected by the administration of a narcotic antagonist (Table 4).

DISCUSSION

Pethidine is widely used as an analgesic during labor and delivery, and has been shown to cross the placental barrier. Its contribution to respiratory depression and neurobehavioral changes in neonates has been studied by several investigators [6-9]. Following 50 mg of meperidine administered intravenously, fetal exposure to meperidine is highest two to three hours after maternal medication while fetal exposure to normeperidine is highest four hours

Table 3. Results of the pulmonary function testing.

	Pethidine group (Mean ± SD)	Control group (Mean ± SD)	P-value
Age at examination (h)	6.0 ± 2.5	7.4 ± 2.3	NS
Respiratory rate (bpm)	56 ± 11	54 ± 7	NS
Inspiratory volume (ml)	16.6 ± 2.4	17.5 ± 2.0	NS
Inspiratory time (sec)	0.50 ± 0.09	0.53 ± 0.08	NS
Expiratory volume (ml)	16.9 ± 2.4	17.5 ± 2.0	NS
Expiratory time (sec)	0.59 ± 0.14	0.58 ± 0.09	NS
Functional residual capacity, FRC (ml)	62.4 ± 13.5	66.7 ± 9.6	NS
FRC/kg (ml)	20.1 ± 4.3	20.9 ± 2.4	NS
Compliance, mean (ml/cmH_2O)	3.5 ± 0.7	3.3 ± 0.9	NS
Resistance (cmH_2O/l/s)	0.05 ± 0.01	0.06 ± 0.04	NS

Table 4. Effects of narcotic antagonist on pulmonary function testing.

	Narcotic antagonist		P-value
	Yes (Mean ± SD)	No (Mean ± SD)	
Age at examination (h)	6.0 ± 2.5	7.4 ± 2.3	NS
Respiratory rate (bpm)	55 ± 11	58 ± 12	NS
Inspiratory volume (ml)	17.0 ± 2.2	16.2 ± 2.7	NS
Inspiratory time (sec)	0.52 ± 0.10	0.47 ± 0.08	NS
Expiratory volume (ml)	17.1 ± 2.1	16.6 ± 2.9	NS
Expiratory time (sec)	0.59 ± 0.13	0.59 ± 0.15	NS
Functional residual capacity, FRC (ml)	59.6 ± 15.5	65.8 ± 10.3	NS
FRC/kg (ml)	20.2 ± 5.4	19.9 ± 2.8	NS
Compliance, mean (ml/cmH_2O)	3.7 ± 0.6	3.4 ± 0.8	NS
Resistance (cmH_2O/l/s)	0.05 ± 0.01	0.05 ± 0.01	NS

or more after medication[14]. It has been shown that respiratory depression from pethidine occurs more frequently with drug-delivery intervals of longer than one hour, however, there was a significant increase in the percentage of babies with respiratory depression born during the second hour after drug administration[15,16]. Gerhardt et al found meperidine in a dose of 1 to 1.5 mg/kg given to the mothers once or twice within 3 hours prior to delivery caused neonatal respiratory depression as demonstrated by a decreased ventilatory response to CO_2[5]. In the present study, although most of the infants were exposed to pethidine for 1 hour prior to delivery, none of the infants required ventilatory support. Eight (40%) infants whose mothers received pethidine required oxygen in the delivery room. However, the mean Apgar score between the two groups of infants was not statistically different. The fact that infants with mild to moderate narcotic depression are born with 1-minute Apgar score close to normal is not surprising, because most of the clinical findings included in the score are mainly altered by fetal hypoxia and not by the narcotics alone. A decrease in respiration, tone and reflex activity is commonly seen in infants whose mothers received narcotics, but the multiple stimuli that occur at birth are sufficient to establish respiration unless the depression is severe or concomitant depressing factors are present.

Late effects of pethidine on newborn infants have been documented by several investigators. Longer drug-delivery intervals have resulted in lower psychophysiologic test scores in neonates even though they were not depressed at birth[17]. In addition, intermittent EEG changes which lasted for 3 days have been observed in neonates[18]. It has been concluded that the effects of meperidine on the neonate are limited to the first 3 days following birth[11]. Objective evidence suggests that the elimination half-life of pethidine is about 23 h in the neonate compared to 3-5 h in the adult[19], and almost total elimination of meperidine, and it's active metabolite, normeperidine, takes place within 3 to 6 days[20]. Evidence of narcotic related respiratory depression has never been obtained in infants who were admitted to the nursery. Since only mild respiratory depression at birth was observed in this study, the authors did not expect any narcotic related respiratory depression after this period. Results of the pulmonary function measurements performed in the first 12 hours of life confirmed that the respiratory rate, tidal volume, inspiratory time, functional residual capacity, compliance and resistance of infants exposed to pethidine were not different from the control group. Administration of a narcotic antagonist did not have any effects on pulmonary function of the infants exposed to pethidine.

SUMMARY

Severe narcotic related respiratory depression in the first 12 hours of life was not seen in the present study. The obstetric analgesic practice in our hospital is quite safe for the newborn. Mild respiratory depression only was observed in the delivery room. Administration of a narcotic antagonist (Naloxone) should be limited to infants who show

respiratory depression at birth. All infants who do not show severe respiratory depression at birth or infants who receive a narcotic antagonist should be allowed to room-in with their mothers as soon as possible in order to encourage successful breast-feeding.

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การทดสอบสมรรถภาพปอดในทารกซึ่งคลอดจากมารดาที่ได้รับยาระงับความเจ็บปวด

ธราธิป โคละทัต, พ.บ., สุพัฒตรา จรุงพันธุ์, พย.บ.**, จันทิมา จรัสทอง, พย.ม**, ยุพิน จันดีวงษ์, พย.บ.***

วัตถุประสงค์ : เพื่อศึกษาผลของยาระงับความเจ็บปวด (pethidine) ต่อระบบหายใจของทารกแรกเกิด

ผู้ป่วยและวิธีการศึกษา : คณะผู้วิจัยได้ทำการศึกษาผลของยาระงับความเจ็บปวดต่อระบบหายใจโดยการประเมินคะแนนแอพการ์ อุบัติการณ์การช่วยหายใจในห้องคลอด และการทดสอบสมรรถภาพปอด (pulmonary function test) ในทารกแรกเกิดจำนวน 40 รายที่คลอดในภาควิชาสูติศาสตร์-นรีเวชวิทยา โรงพยาบาลศิริราช โดยเป็นทารกที่มารดามีประวัติการได้รับยาระงับความเจ็บปวดภายใน 4 ชั่วโมงก่อนคลอด 20 ราย (กลุ่มทดลอง) และเป็นทารกซึ่งมารดาไม่มีประวัติการใช้ยาระงับความเจ็บปวดหรือมีประวัติการได้รับยาชาเฉพาะที่ (regional anesthesia) 20 ราย (กลุ่มควบคุม)

ผลการศึกษา : มารดาของทารกกลุ่มที่นำมาศึกษาได้รับยาระงับความเจ็บปวดในขนาดเฉลี่ย 72.5 $\pm$ 7.6 มก/กก และได้รับยาก่อนคลอด 152 $\pm$ 61 นาที ทารกกลุ่มทดลองและกลุ่มควบคุม มีน้ำหนักแรกเกิดและอายุครรภ์เฉลี่ยไม่แตกต่างกัน คณะผู้วิจัยพบอุบัติการณ์ของทารกที่มีคะแนนแอพการ์ที่ 1 นาที น้อยกว่า 7 กลุ่มละ 1 ราย แต่ทารกทั้ง 2 กลุ่มมีคะแนนแอพการ์เฉลี่ยที่ 1 และ 5 นาทีไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ไม่พบทารกที่ต้องได้รับการรักษาโดยการช่วยหายใจในห้องคลอด แต่มีทารกซึ่งคลอดจากมารดาที่ได้รับยาระงับความเจ็บปวด 8 รายที่มีอาการเขียวและต้องได้รับการรักษาด้วยออกซิเจน การตรวจสมรรถภาพปอดในระยะหลังคลอด พบว่า อัตราหายใจ tidal volume, inspiratory time, expiratory time, functional residual capacity, compliance และ resistance ของทารกทั้ง 2 กลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ

สรุป : คณะผู้วิจัยไม่พบผลกระทบจากยาระงับความเจ็บปวดที่มีต่อระบบหายใจของทารกแรกเกิด และไม่พบความผิดปกติจากการทดสอบสมรรถภาพปอดเมื่อเปรียบเทียบกับกลุ่มทารกซึ่งคลอดจากมารดาที่ได้รับยาระงับความเจ็บปวดภายใน 4 ชั่วโมงก่อนคลอด ดังนั้นการนำทารกซึ่งระบบหายใจไม่ถูกกด (respiratory depression) โดยยาระงับความเจ็บปวดไปอยู่กับมารดาในหอผู้ป่วยหลังคลอด จะไม่ทำให้เกิดผลเสียต่อทารก นอกจากนี้ยังช่วยส่งเสริมการเลี้ยงลูกด้วยนมแม่และสนับสนุนให้เกิดความสัมพันธ์ระหว่างมารดาและทารก (maternal-infant bonding) ให้ดียิ่งขึ้น

คำสำคัญ : ยาระงับความเจ็บปวด, การทดสอบสมรรถภาพปอด, การเลี้ยงลูกด้วยนมแม่, ความสัมพันธ์ระหว่างมารดาและทารก

ธราธิป โคละทัต, สุพัฒตรา จรุงพันธุ์, จันทิมา จรัสทอง, ยุพิน จันดีวงษ์
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* ภาควิชากุมารเวชศาสตร์,

** งานการพยาบาลกุมารเวชศาสตร์, ฝ่ายการพยาบาลโรงพยาบาลศิริราช, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700