

## Neonatal Neurobehavioral Effects of Inhalation Analgesia for Vaginal Delivery

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The authors studied the neonatal neurobehavioral effects of nitrous oxide:oxygen and enflurane:oxygen inhalation analgesia for vaginal delivery. Parturients were assigned randomly to receive no inhalation agent (Group 1, n = 21); enflurane, 0.3 to 0.8 per cent, and oxygen (Group 2, n = 22); or nitrous oxide, 30 to 50 per cent, and oxygen (Group 3, n = 18). Infants were tested at 15 min, 2 h, and 24 h of age using the Neurologic and Adaptive Capacity Score (NACS); and at 2 and 24 h using the Early Neonatal Neurobehavioral Scale (ENNS). No significant differences in neurobehavioral status occurred. For all groups, scores tended to be lowest at two hours of age. We conclude that neither enflurane nor nitrous oxide analgesia adversely affects neonatal neurobehavioral status at 15 min, 2 h, or 24 h of age. (Key words: Anesthesia: obstetric. Anesthetics, gases: nitrous oxide. Anesthetics, volatile: enflurane. Neurobehavior: neonatal.)

SUBANESTHETIC DOSES of most of the inhalation anesthetics have long been used to provide analgesia during the second stage of labor.<sup>1-7</sup> We previously reported that when compared with nitrous oxide, enflurane provides excellent analgesia, has a high degree of patient acceptance, and induces minimal maternal amnesia for delivery. Also, enflurane does not increase uterine bleeding or significantly elevate maternal or neonatal serum or inorganic fluoride levels in the urine or blood serum of

the mother or neonate. No biochemical evidence of renal toxicity has been demonstrated.<sup>8</sup> Furthermore, no differences in neonatal acid-base status or clinical condition at birth, as ascertained by Apgar scores or time-to-sustained respiration, are detectable. However, *anesthetic* doses of inhalation agents have been reported to depress the neurobehavioral condition of the neonate.<sup>9,10</sup> Therefore, we evaluated the possible neurobehavioral effects of subanesthetic concentrations of nitrous oxide and enflurane. We used two tests of neonatal neurobehavioral status, the Early Neonatal Neurobehavioral Scale (ENNS), described by Scanlon,<sup>11</sup> and the Neurologic and Adaptive Capacity Score (NACS), which was developed by Amiel-Tison, Barrier, and Shnider.<sup>12</sup> In contrast to the Apgar score, both examinations detect subtle neurobehavioral changes in the neonate. Indeed, many babies with normal Apgar scores have demonstrable neurobehavioral changes within the first few hours of life.<sup>13</sup>

### Methods

After receiving informed consent and approval from the Committee on Human Research, we studied 61 healthy, full-term parturients who were assigned randomly to one of three groups. Group 1 (n = 21) received no inhalation analgesia. Group 2 (n = 22) received enflurane, 0.3 to 0.8 per cent, in oxygen. Group 3 (n = 18) received nitrous oxide, 30 to 50 per cent, in oxygen. An anesthesiologist administered the analgesic mixture during the second stage of labor. We adjusted the concentration of each agent to provide optimal analgesia while keeping the patient awake, cooperative, and oriented. Blood pressure was measured every 2 min, and maternal EKG was monitored continuously. At the moment of birth, the analgesic mixture was discontinued and the mother's attention directed toward her infant. Effectiveness of inhalation analgesia was evaluated by the mother and the anesthesiologist, who gave it a score of 0 (no relief) to 4+ (excellent pain relief).<sup>1</sup> Umbilical arterial and venous blood samples were obtained from a doubly clamped segment of cord for determination of fetal oxygenation and acid-base status. The pediatrician or obstetrician determined time-to-sustained respiration and Apgar scores at 1 and 5 min. The patient's age, parity, method of delivery, dose of narcotic, time of administration of narcotic during labor, and the local anesthetic technique used for delivery were noted. Two

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TABLE 1. Comparison of Patients Who Received Nitrous Oxide or Enflurane Analgesia for Vaginal Delivery, or No Inhalation Analgesia (Controls)

	Controls (n = 20)	N <sub>2</sub> O:O <sub>2</sub> (n = 18)	Enflurane:O <sub>2</sub> (n = 22)
Method of delivery (per cent)			
Spontaneous	90	95	83
Outlet forceps	10	0	13
Mid-forceps	0	5	0
Vacuum	0	0	4
Narcotic administration during labor (per cent)			
None	70	50	59
Within 1 hour of delivery	15	6	14
1-2 hours of delivery	10	22	9
≥2 hours of delivery	5	22	18
Local anesthesia for delivery (per cent)			
None	40	28	43
Local infiltration and/or pudendal block	60	72	57
Duration of inhalation analgesia antepartum (per cent)			
<5 min		11	14
6-10 min		39	28
11-20 min		22	36
21-39 min		22	28
>40 min		6	5
MEAN (±SE) duration of antepartum inhalation analgesia (min)		14.8 ± 2.4	16.5 ± 4.1
Satisfactory (3+ and 4+) analgesia scores (per cent)			
Mother		73	91
Doctor		66	82

examiners, "blind" to both the nature and duration of the analgesia, simultaneously evaluated and scored the neurobehavioral status of the infants. The examinations were performed at 15 min in the delivery room using the NACS, and at 2 and 24 h using the NACS and the ENNS. The examiners were either anesthesiologists or

staff research associates trained to perform their respective examinations by Amiel-Tison (NACS) or Scanlon (ENNS), or persons trained by these pediatricians. The NACS, unlike the ENNS, gives a total score, the maximum being 40. Arbitrarily choosing 35 to 40 as the score denoting a vigorous baby,<sup>12</sup> we determined the percentages of infants scoring 35 or higher and compared these in each study group at 15 min, 2 h, and 24 h. For both the NACS and the ENNS, we also determined the percentages of infants having high scores on each of the individual test items (*i.e.*, for the NACS, those having a score of 2, and for the ENNS, those having a score of 2 or 3). The results were analyzed using a two- or three-way chi-square test, where appropriate, or a Student *t* test for unpaired data (blood gases). A *P* value of less than 0.05 was considered significant.

### Results

Each group was similar with respect to method of delivery, administration of narcotics during labor, administration of local anesthetics for delivery, and, in the groups receiving inhalation analgesic, the duration and effectiveness of analgesia prior to birth (table 1). Over 80 per cent of the parturients in each group delivered spontaneously; 50 to 70 per cent received no narcotics during labor. The remainder received small doses of either meperidine (50 mg) or alphaprodine (20 to 30 mg).

TABLE 2. Comparison of Neonates Whose Mothers Received Nitrous Oxide or Enflurane Analgesia for Vaginal Delivery, or No Inhalation Analgesia (Controls)\*

	Controls (n = 20)	N <sub>2</sub> O:O <sub>2</sub> (n = 18)	Enflurane:O <sub>2</sub> (n = 22)
Mean (±SE) birth weight (g)	3,312 ± 120	3,321 ± 67.7	3,436 ± 85.9
Time-to-sustained respiration (per cent)			
<90 s	100	100	100
>90 s	0	0	0
Apgar scores			
At 1 min (per cent)			
0-4	13	0	4
5-7	9	21	21
8-10	78	79	75
At 5 min (per cent)			
0-4	0	0	0
5-7	0	0	0
8-10	100	100	100

\* No significant differences.

TABLE 3. Blood-Gas Data for Neonates Whose Mothers Received Nitrous Oxide or Enflurane Analgesia for Vaginal Delivery, or No Inhalation Analgesia (Controls)\*

	Controls (n = 20)	N <sub>2</sub> O:O <sub>2</sub> (n = 18)	Enflurane:O <sub>2</sub> (n = 22)
Umbilical vein			
pH	7.36 ± 0.01	7.33 ± 0.01	7.36 ± 0.01
P <sub>CO<sub>2</sub></sub> (mmHg)	35.0 ± 1.5	37.3 ± 1.0	36.1 ± 1.3
Base excess (mEq/l)	-5.2 ± 0.3	-5.6 ± 0.6	-4.8 ± 0.5
P <sub>O<sub>2</sub></sub> (mmHg)	29.4 ± 1.1	30.6 ± 1.5	30.0 ± 1.1
Umbilical artery			
pH	7.28 ± 0.01	7.26 ± 0.02	7.30 ± 0.01
P <sub>CO<sub>2</sub></sub> (mmHg)	42.5 ± 2.2	45.3 ± 1.6	44.4 ± 1.5
Base excess (mEq/l)	-6.1 ± 0.7	-7.2 ± 0.7	-4.4 ± 0.5
P <sub>O<sub>2</sub></sub> (mmHg)	18.9 ± 1.0	18.9 ± 1.0	19.6 ± 1.0

\* No significant differences.

Approximately two-thirds of the patients received a pudendal block and/or infiltration of local anesthetic at the time of delivery. The weight and clinical condition of neonates at birth were similar in all three groups (table 2). All babies established sustained respirations within 90 s and had Apgar scores of 8 or higher at 5 min. Results of analysis of umbilical venous and arterial blood samples for blood gases and acid-base status were also similar for the three groups (table 3).

The testing of neurobehavioral status revealed no statistically significant differences in test scores for any test item on either the NACS (table 4) or the ENNS (table 5) at any of the times of testing. The percentages of infants who scored 35 to 40 on the NACS were not significantly different in the three groups (fig. 1). High scores were found at 15 min after birth in 78 per cent of the infants in the control group, in 77 per cent of the infants whose mothers had received nitrous oxide, and in 83 per cent of the infants whose mothers had received enflurane. Although infants scored significantly lower at 2 h than at 24 h, there were no statistically significant differences between the scores of the three groups. At 24 h, approximately 90 per cent of the infants in all three groups had high scores. The ENNS, using the mean of the percentages of good scores on all test items, also showed that infants in all three groups had similar neurobehavioral status at 2 and 24 h (fig. 2). As with the NACS, infants scored lower at 2 h than at 24 h.

The scores of those infants whose mothers had received systemic narcotics within six hours of delivery were then compared with scores for infants whose mothers had received no narcotic. No individual test item on either the NACS or ENNS was found to be statistically different at any of the times of testing. The percentages of infants

TABLE 4. Percentages of Infants Who Scored 2 for Each Test Item of the Neurologic and Adaptive Capacity Score (NACS)\* and Whose Mothers Had Received N<sub>2</sub>O or Enflurane Analgesia for Vaginal Delivery, or No Inhalation Analgesia (Controls)

	15 min			2 h			24 h		
	Control	N <sub>2</sub> O	Enflurane	Control	N <sub>2</sub> O	Enflurane	Control	N <sub>2</sub> O	Enflurane
Adaptive capacity									
Sound	65	74	91	38	37	44	45	68	46
Habituation to sound	82	68	91	57	74	65	70	78	71
Light	90	84	96	65	68	55	86	84	63
Habituation to light	70	63	88	55	74	71	68	84	75
Consolability	90	95	100	95	95	96	77	94	92
Passive tone									
Scarf sign	86	90	91	81	84	96	96	100	100
Elbow recoil	82	79	96	91	84	96	100	100	100
Lower limb recoil	86	95	96	86	90	100	100	100	100
Popliteal angle	82	84	83	81	84	78	91	94	92
Active tone									
Neck flexors	77	68	88	71	63	70	91	94	88
Neck extensors	73	74	88	62	63	74	86	94	92
Palmar traction	86	90	96	67	68	87	82	94	96
Support reaction	91	74	83	81	63	78	100	100	79
Primary reflexes									
Palmar grasp	86	95	96	81	79	78	91	89	100
Automatic walking	64	90	83	57	47	65	77	73	67
Sucking	36	47	50	67	79	92	96	89	96
Moro response	90	90	96	95	90	96	100	94	96
General assessment									
Alertness	91	90	96	76	84	96	96	100	100
Crying	91	100	91	91	94	96	96	95	100
Motor activity	86	95	91	91	90	100	100	100	100

\* No significant differences.

TABLE 5. Percentages of Good Scores for Each Test Item of the Early Neonatal Neurobehavioral Scale (ENNS)\* for Infants Whose Mothers Had Received N<sub>2</sub>O or Enflurane Analgesia for Vaginal Delivery, or No Inhalation Analgesia (Controls)

	2 h			24 h		
	Control	N <sub>2</sub> O	Enflurane	Control	N <sub>2</sub> O	Enflurane
Pinprick	71	72	82	81	78	77
Sitting	71	56	64	90	100	95
Arm recoil	67	78	82	95	94	100
Truncal tone	71	88	86	100	88	95
General tone	81	88	91	100	100	95
Rooting	48	56	50	71	78	77
Sucking	81	88	91	90	100	95
Moro reflex	76	88	86	90	88	86
Sound	24	22	41	57	67	55
Placing	81	78	82	100	88	73
Alertness	76	50	45	86	94	86
Decrement response						
Pinprick	95	100	91	100	100	91
Moro response	100	100	100	95	94	100
Light	100	94	95	95	100	95
Percentages of good scores on all test items	75.5	76.4	78.4	90.0	90.4	88.0

\* No significant differences.

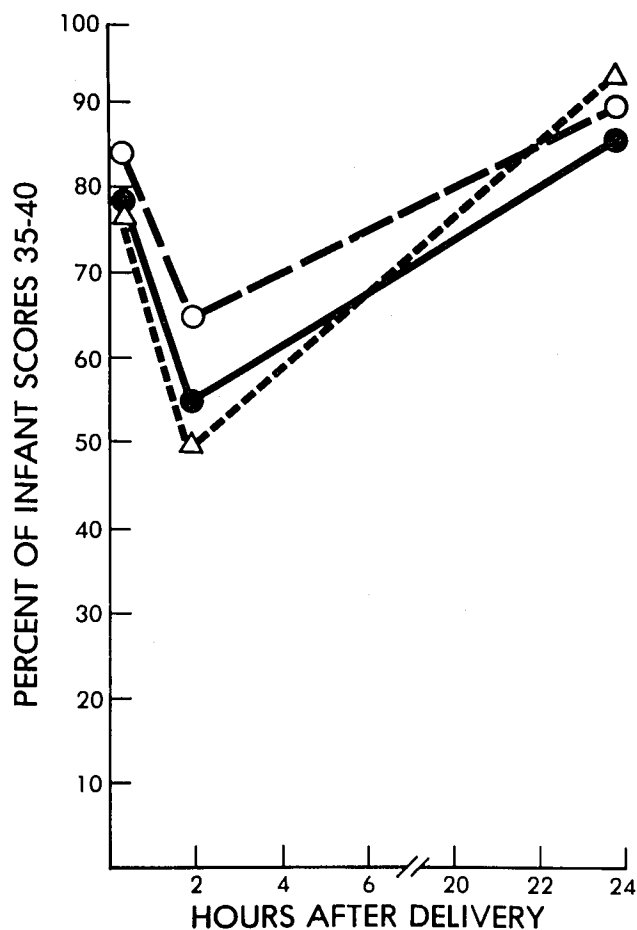


FIG. 1. Percentage of NACS scores of 35 to 40 for infants whose mothers had received nitrous oxide (Δ) or enflurane (O) analgesia for vaginal delivery, or no inhalation analgesia (controls [●]).

who scored 35 to 40 on the NACS and the percentage of infants with an overall good ENNS evaluation were similar in both groups (table 6).

### Discussion

When properly administered, inhalation analgesia with agents such as nitrous oxide or enflurane is effective and does not produce depression of the newborn at birth.<sup>8</sup> However, infants of mothers receiving thiopental/nitrous oxide general anesthesia for vaginal delivery or cesarean section have global depression of neurobehavioral performance when compared to those born after regional anesthesia.<sup>9</sup> This difference in neurobehavioral function occurred despite similar Apgar scores for the two anesthetic groups.<sup>9</sup> Our study confirms the safety and effectiveness of inhalation analgesia for vaginal delivery and also demonstrates no adverse neurobehavioral effects on the neonate at 15 min, 2 h, and 24 h after birth. The inspired concentrations of nitrous oxide or enflurane that produce maternal analgesia but not loss of consciousness or surgical anesthesia are probably too low to depress neurobehavioral function in the neonate. We found no apparent synergism between inhalation analgesics and systemic medication administered to the mother. Babies from mothers receiving narcotics within six hours of birth and either nitrous oxide or enflurane for delivery did not have lower scores than those whose mothers had received narcotics without inhalation analgesia. Because our study used small doses of narcotics, our results should not be interpreted as suggesting that using larger doses would have had little effect on neurobehavioral status.

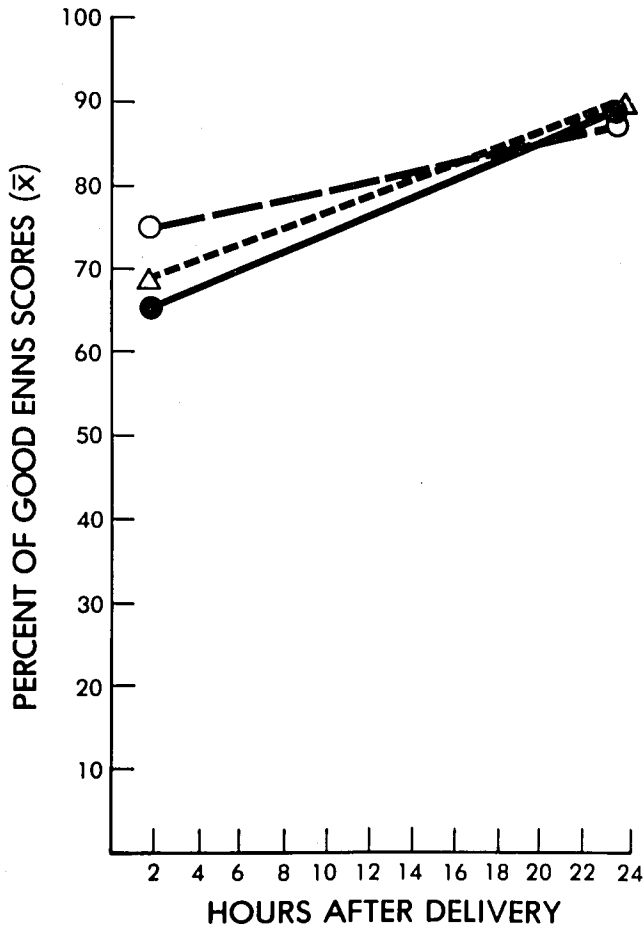


FIG. 2. Mean percentage of good ENNS scores in infants whose mothers received nitrous oxide (Δ) or enflurane (○) analgesia for vaginal delivery, or no inhalation analgesia (controls [●]).

In all three study groups, test performance decreased on both examinations at 2 h compared with 24 h of age. This depression was not greater in infants whose mothers received narcotics alone or in conjunction with inhalation analgesia, but instead, appeared to be relatively uniform in all groups. Similar findings have been reported by McGuinness *et al.*<sup>14</sup> In their study, the neurobehavioral status of infants whose mothers had received bupivacaine epidural anesthesia for cesarean section was compared with that of a control group whose mothers had received tetracaine spinal anesthesia. Although no significant dif-

ferences in neurobehavioral status occurred between the two groups, in both groups infants had decreased tone at 4 h but not at 24 h of age. Klaus and Kennell<sup>15</sup> and Desmond and co-workers<sup>16</sup> report that after birth there is a 45- to 60-min period of infant alertness or "reactivity" that is followed by a three- or four-hour interval of deep sleep and poor responsiveness. Another period of alertness then occurs. Therefore, any test of neurobehavioral status performed two to four hours after birth probably would find the infant less responsive and would reveal decreased neonatal performance.

We conclude that neither enflurane nor nitrous oxide inhalation analgesia adversely affects the neurobehavioral status of the neonate at 15 min, 2 h, or 24 h of age.

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TABLE 6. Percentages of Infants with Good Neurobehavioral Status: Effects of Narcotic Administration during Labor\*

	15 min NACS	2 h		24 h	
		NACS	ENNS	NACS	ENNS
No narcotics	71	53	69	90	88
Narcotics	89	55	72	90	85

\* No significant differences.