Clinical and Biochemical Studies of Cyclopropane Analgesia in Obstetrics

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THE interesting possibility of using cyclopropane in analgesic concentrations for obstetrics arose following the successful administration of another potent anesthetic, chloroform, in a similar manner.[1] Cyclopropane has several advantages: it is a widely used, readily-available agent administered with high concentrations of oxygen; its action is rapid and easily controllable; it is nonirritating in low concentrations; and it does not have the stigma nor inherent dangers associated with chloroform.[2] Although continuous cyclopropane analgesia has been investigated in human volunteers,[3, 4] its safety and effectiveness have not hitherto been evaluated in labor and delivery. In this study, the technique is compared clinically and biochemically with nitrous oxide analgesia given to a similar group of mothers and infants.

Clinical Material and Technique

A total of 718 patients undergoing vaginal delivery was studied; 336 received cyclopropane analgesia and 382 nitrous oxide analgesia. The patients were randomly selected and virtually all were in good health. The two groups were similar in their obstetric and medical histories, duration of administration, incidence of episiotomies (75 per cent), forceps application (12 per cent), local anesthesia, and use of premedication. Usually premedication was light and consisted of 50 to 100 mg. of meperidine intramuscularly. Approximately 20 per cent of the mothers in both groups received no premedication.

Cyclopropane analgesia was administered during the second and third stages of labor and frequently during the repair of the episiotomy. The duration before delivery was in most cases (89 per cent) no more than 15 minutes. The agent was usually started at a 3 per cent concentration (0.2 liter/minute cyclopropane and 6.0 liters/minute oxygen) in a semiclosed carbon dioxide absorption system. The usual rigorous precautions against explosion were taken, since the lower limit of flammability of cyclopropane in oxygen is 2.4 per cent.[5]

The concentration was increased slowly to reach the maximal level at which the patient remained cooperative, oriented, and conversant. Five per cent cyclopropane was the highest as well as the most frequently used concentration. Whenever time permitted, the obstetrician performed a pudendal block or local perineal infiltration with 1 per cent lidocaine. This was true in 75 per cent of the mothers. Conversation was usually maintained in order to provide continuous reassurance and to monitor the patient's sensorium.

Nitrous oxide analgesia was given in a similar manner, with continuous administration of approximately 40 per cent nitrous oxide in oxygen. A preliminary report on the first 200 patients in this series has been published elsewhere.[1]

Method of Study

The degree of analgesia for the birth of the baby was graded as 0 to 4 plus according to the following criteria: 4 plus (excellent), no observable signs of pain; 3 plus (good), slight

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TABLE 1. Distribution of Analgesia Scores

Score	Cyclopropane		Nitrous Oxide	
	Number	Percentage	Number	Percentage
4 plus (excellent)	94	29.5	63	16.5
3 plus (good)	101	31.7	173	45.3
2 plus (fair)	91	28.5	107	28.0
0–1 plus (none-poor)	20	6.3	35	9.2
Abandoned technique	13	4.0	4	1.0
Total	319	100.0	382	100.0

grimace or moan; 2 plus (fair), some movement or complaint at height of contraction; 1 plus (poor), little apparent relief; and 0 (none), no demonstrable analgesia.

Amnesia was considered the inability to recall the birth of the baby. If the patient was uncertain and memory for the event was clouded, it was listed as partial amnesia.

The infants were evaluated clinically 60 seconds after birth by means of the Apgar score.[6] In addition, note was made of the time to sustained respiration, *i.e.*, the time elapsed from birth until the infant established and maintained spontaneous respiration.

In 35 patients, a sample of blood from the maternal brachial artery was drawn at the time of clamping of the umbilical cord. In addititon, control samples were drawn from 11 patients prior to induction of cyclopropane analgesia. Samples were also drawn from the umbilical artery and vein of a doubly-clamped segment of cord. Analysis of the blood for percent oxygen saturation, *p*H, P_{CO_2}, CO_2 content, hematocrit, and buffer base * was performed as soon as possible, usually within one hour. The oxygen saturation was determined by means of the Beckman spectrophotometer [8] and the *p*H by use of either the Astrup Micro-Equipment [9] or Sanz Electrode.[10] The carbon dioxide content was determined with the Kopp-Natelson microgasometer.[11] The P_{CO_2} and buffer base values were calculated using either the Siggaard-Anderson and Engel,[12] or Singer and Hastings [7] nomogram.

* Buffer base defines the total buffering capacity of blood and includes not only the bicarbonate (alkaline reserve) but also plasma and hemoglobin protein components.[7] The value for normal pregnant women is 42 mEq./liter. A depression of the buffer base is a measure of metabolic acidosis.

Results

Maternal. There were no intra- or postpartum complications which could be attributed to the use of either cyclopropane or nitrous oxide analgesia, nor was there any maternal mortality. Serious cardiac arrythmias or hypotension were not seen. Nausea and vomiting were rare in both series. Of the 336 patients who received cyclopropane analgesia, 4 per cent required general anesthesia for the delivery or repair of the episiotomy; this was true of 1 per cent of the nitrous oxide analgesia series. The factors responsible for the substitution included either inadequate analgesia or obstetrical complications requiring surgical levels of anesthesia, such as face presentation or shoulder dystocia. In all such instances cyclopropane anesthesia was administered and the case omitted from statistical analysis.

Fair to excellent (2 to 4 plus) analgesia was noted in approximately 90 per cent of both the cyclopropane and the nitrous oxide series; good to excellent (3 and 4 plus) analgesia was achieved in 61 per cent of both groups (table 1). It thus appears from our studies that 3 to 5 per cent cyclopropane in oxygen achieves approximately the same degree of maternal analgesia as does 40 per cent nitrous oxide in oxygen. Partial or complete amnesia was noted in 50 per cent of the cyclopropane series and in 40 per cent of the nitrous oxide group.

The acid-base status and percentage oxygen saturation of the maternal arterial blood are listed in tables 2 and 3. The control blood samples drawn from the cyclopropane series indicated a mild respiratory alkalosis (average *p*H, 7.46). At birth there was no significant difference between the two analgesia groups in percentage oxygen saturation or P_{CO_2} ($p >$

TABLE 2. Biochemical Analysis of Maternal Arterial Blood Prior to Start of Cyclopropane Analgesia

	*p*H	Percentage of Oxygen Saturation	Carbon Dioxide Pressure (mm. Hg)	Buffer Base (mEq./liter)
Number	11	11	11	11
Average	7.46	100	27.7	44.1
Range	7.38–7.57	100–100	19.2–33.5	40.0–47.3

TABLE 3. Biochemical Analyses of Blood Samples at Birth

Source	*p*H	Percentage of Oxygen Saturation	Carbon Dioxide Pressure (mm. Hg)	Buffer Base (mEq./liter)
(A) *Maternal Artery*				
Cyclopropane				
number	21	21	21	21
average	7.40	100	31.4	43.1
range	7.33–7.50	100–100	22.7–43.0	38.9–49.8
Nitrous Oxide				
number	14	14	13	13
average	7.35	99.8	32.4	39.5
range	7.30–7.39	98.5–100	24.9–40.2	37.0–42.0
(B) *Umbilical Vein*				
Cyclopropane				
number	21	21	21	21
average	7.34	63.0	40.9	43.2
range	7.22–7.41	23.0–95.0	23.0–55.0	38.5–48.6
Nitrous Oxide				
number	26	26	24	24
average	7.29	65.2	41.5	39.6
range	7.06–7.41	16.7–93.2	28.0–63.3	30.7–44.8
(C) *Umbilical Artery*				
Cyclopropane				
number	21	21	21	21
average	7.27	25.3	54.2	42.9
range	7.17–7.38	6.5–55.0	28.5–76.0	38.0–46.5
Nitrous Oxide				
number	26	24	18	18
average	7.20	26.6	53.5	37.1
range	7.02–7.37	0.0–64.5	34.9–84.5	28.0–42.5
Statistical Analysis (according to Student t test)	A, C, $P < 0.01$ B, $P = 0.03$	A, B, C, $P = >0.05$		A, B, C, $P < .01$

0.05, Student *t* test). The *p*H and buffer-base values were significantly lower in the nitrous oxide series ($P < 0.01$).

Infant. There were nine still births in the two groups, none of which were related to the method of analgesia. All were previously known fetal deaths *in utero*. There were six breech presentations and seven premature deliveries. Breech and premature births are associated with an increased percentage of depressed babies, not necessarily related to anesthesia.[13] Therefore, breech presentations, infants with birth weights under 2,500 g., and infants who died *in utero* before the administration of analgesia were excluded from consideration in both series.

The condition of the infants as determined by the Apgar score is shown in figure 1. The over-all distribution of scores in the two series is similar. The babies were further grouped according to the incidence of 0 to 6 and 7 to 10 scores. This division was based on prior analysis of 16,000 scores correlated with mortality which showed that the high score group has a distinctly better prognosis for survival.[13] The infants delivered with the aid of inhalation analgesia were compared to two other groups of full-term vaginal vertex deliveries previously reported by Apgar and co-workers.[13] One group was delivered with the use of regional anesthesia and the other with cyclopropane anesthesia (fig. 2). The incidence of

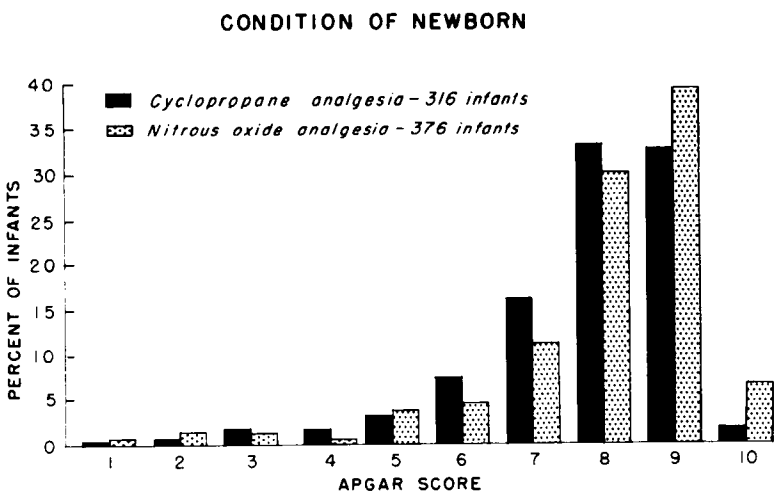

FIG. 1. Condition of the newborn—Apgar scores. Cyclopropane analgesia compared with nitrous oxide analgesia.

babies with low scores in the cyclopropane analgesia series (15.8 per cent) is not significantly different (chi square, $P > 0.05$) from that found in either the nitrous oxide analgesia or regional anesthesia groups. However, the higher percentage (23.8 per cent) of depressed babies born under cyclopropane anesthesia is statistically significant ($P < 0.01$) when compared to those born under cyclopropane analgesia.

To see the effect, if any, of an increasing duration of exposure to cyclopropane analgesia on the condition of the newborn, the incidence of low Apgar scores (0 to 6) was plotted against time (fig. 3). There was no correlation between the status of the infant and the duration of cyclopropane analgesia. This was also true of the nitrous oxide group.

Additional clinical evaluation of the infant using the time to sustained respiration is listed in table 4. The percentage of babies in each time segment is similar: 82.7 per cent of the babies in the cyclopropane series and 81.7 per cent of the nitrous oxide series established

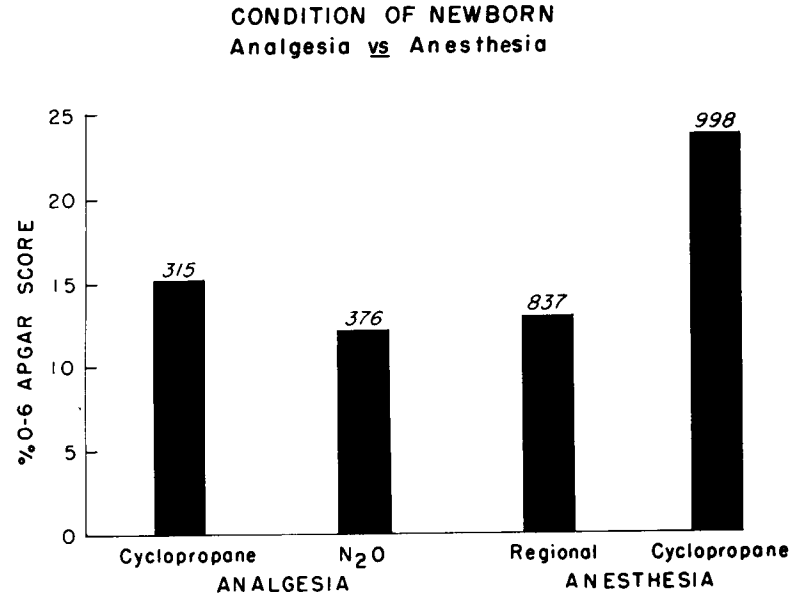

FIG. 2. Condition of the newborn—Apgar scores. Analgesia versus anesthesia.

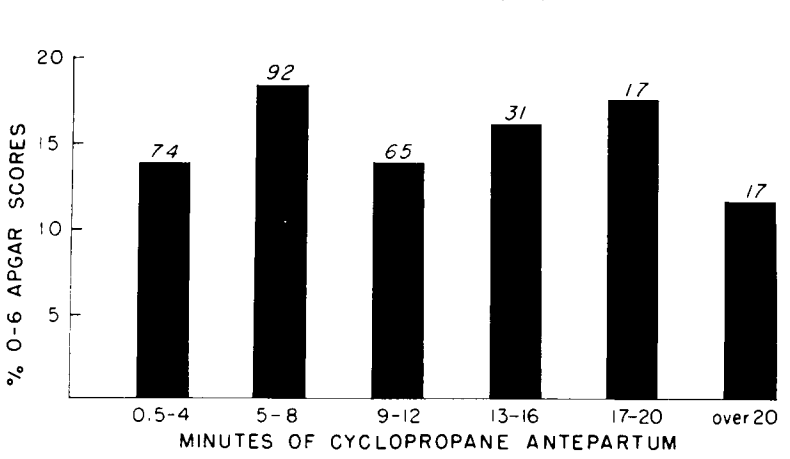

FIG. 3. Condition of the newborn—Apgar scores. Effect of increasing exposure to cyclopropane analgesia.

spontaneous respiration within one minute of birth. There is no significant difference between these two groups.

Acid-base values and percentage oxygen saturation in the cord blood are, together with statistical analysis, presented in table 3. There was no significant difference between the two groups of infants in umbilical venous and arterial percentage oxygen saturation or P_{CO_2}. However, as with the mothers, the *p*H and buffer-base figures in the nitrous oxide series were significantly lower when compared to cyclopropane.

Discussion

The use of an inhalation agent administered continuously in low concentrations to produce analgesia has much to recommend it for vaginal deliveries. The mother obtains pain relief while remaining awake and cooperative during the expulsive stage of labor, and although analgesic concentrations of gases and vapors cross the placenta,[14] their clinical effect on the baby is minimal.[1]

Cyclopropane analgesia was first studied by Seevers *et al.*[3] in ten healthy human volunteers. With continuous inhalation of cyclopropane (4 to 6 per cent), the subjects reported a sensation of impending loss of consciousness or euphoria within one to three minutes and maximal reduction in pain within the first five minutes. In obstetrics, Knight and Urner[15] used anesthetic concentrations of the agent intermittently during labor to relieve the pain of uterine contractions. Their technique has several disadvantages, particularly during the second stage of labor. The short duration of a uterine contraction, combined with breath-holding and bearing down, often renders the intermittent administration of anesthesia ineffective. On the other hand, the use of high concentrations of anesthetic gases with contractions may occasionally result in excitement and unconsciousness at the very moment when the mother's cooperation is most needed.

The use of low concentrations of cyclopropane administered continuously during the second stage has been reported by Bianchetti and Bertoletti.[16] However, unlike the technique described here, the patient was rendered unconscious by cyclopropane anesthesia at the point of maximal perineal distention by the fetus. Surgical planes of cyclopropane anesthesia are not without hazard to both mother

TABLE 4. Time to Sustained Respiration

T.S.R. in seconds	Cyclopropane Analgesia		Nitrous Oxide Analgesia	
	Number	Percentage	Number	Percentage
0–29	192	61.5	222	60.5
30–59	66	21.2	78	21.3
60–89	23	7.4	35	9.5
90–119	13	4.2	11	3.0
120–149	11	3.5	7	1.9
150 plus	7	2.2	14	3.8
Total	312	100.0	367	100.0

and fetus. The possible dangers include aspiration of vomitus, airway obstruction, and respiratory depression. Previous biochemical studies of maternal arterial blood in a group of women delivered with the aid of cyclopropane anesthesia revealed a moderate respiratory and metabolic acidosis [17] possibly related to hypoventilation or airway obstruction during anesthesia or both. With cyclopropane analgesia, on the contrary, analysis of maternal blood revealed a normal acid-base status at the time of delivery.

Our findings indicate an increased incidence of depressed infants with the use of cyclopropane anesthesia when compared to a similar group of mothers delivered with inhalation analgesia. When anesthetic concentrations of the agent are used there is a direct relationship between duration of anesthesia and depression of the newborn.[18, 19, 20] Our study, however, indicates that cyclopropane analgesia may be given as long as fifty minutes with little clinical effect on the newborn.

Analyses of umbilical-cord blood showed no significant difference in oxygen saturation between infants of patients delivered with the use of 95 to 97 per cent oxygen (cyclopropane analgesia) and 60 per cent oxygen (nitrous oxide analgesia), or were these values significantly different from those previously reported on mothers delivered with the use of 20 or 100 per cent oxygen.[1, 21] These data indicate that the administration of increased oxygen concentrations to the mother are not necessarily accompanied by changes in oxygen saturation in the newborn. While there is evidence that increasing the oxygen tension in the maternal arterial blood may result in an increased transfer to the fetus,[21] the maternal-placental-fetal circulation must be intact and functioning efficiently for this to occur.

It has been shown that the delivery process is associated with some degree of asphyxia to the fetus owing to one or more factors: cord compression, changes in uterine blood flow, placental infarction or separation, or reduction in maternal exchange of respiratory gases.[23, 24] Furthermore, *in vivo* [25] and *in vitro* [26] experiments indicate that high oxygen tensions may constrict the fetal vessels in the placenta. These mechanisms offer an explanation for low oxygen levels in the infant despite administration of a mixture rich in oxygen to the mother.

Although there was a statistically significant difference in the average maternal *pH* and buffer-base values in the two analgesia groups, clinically it was considered to be probably unimportant. These values were within the normal range for pregnant women. The acid-base status of the infant reflected that of the mother.

In conclusion, there is little to choose between cyclopropane and nitrous oxide analgesia in so far as maternal pain relief and safety to the infant are concerned. A possible advantage of cyclopropane analgesia is a more rapid establishment of anesthetic levels with the agent when necessary. An inherent disadvantage is its explosiveness and the usual rigorous precautions must always be taken.

Summary

A total of 336 mothers received analgesic concentrations (3–5 per cent) of cyclopropane in oxygen for delivery. Detailed observations of the clinical and biochemical effects on the mothers and infants are presented and compared with those in 382 patients who received 40 per cent nitrous oxide in oxygen.

The analgesic technique described includes vocal encouragement and reassurance by the anesthesiologist and local perineal or pudendal anesthesia when forceps application or episiotomy is required. Both cyclopropane and nitrous oxide analgesia provided the majority of the mothers with good to excellent pain relief for vaginal delivery.

The clinical condition of the infant at birth bore no apparent relation to the type or duration of analgesia. Biochemical analyses of maternal and umbilical cord blood samples showed no clinically significant difference between the two agents.

It was concluded that cyclopropane analgesia is a safe, simple, and effective means of producing maternal pain relief with no apparent depression of the infant.

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