J Anesth (1995) 9:220–223

Journal of
Anesthesia

Comparison of the placental transfer of halothane, enflurane, sevoflurane, and isoflurane during cesarean section

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Abstract: The concentrations of placental transfer of halothane (H), enflurane (E), sevoflurane (S), and isoflurane (I) were measured in 46 patients during cesarean section. The mean inhalation times of H (0.5%), E (1%), S (0.8%), and I (0.6%) were 13 min 27 s, 13 min 49 s, 13 min 20 s, and 8 min 8 s, respectively. The mean concentrations in the maternal artery (MA) were 5.2 mg · dl^{-1} in H, 12.3 mg · dl^{-1} in E, 5.2 mg · dl^{-1} in S, and 2.4 mg · dl^{-1} in I. The concentration ratio between the MA and the fetal umbilical vein (UV) was 0.44 for H, 0.49 for E, and 0.38 for S, and these ratios were not significantly different for these anesthetics. Although the concentration ratio for I (0.27) was significantly lower than those of the other three anesthetics, the UV:MA ratio was calculated to be 0.4 for an inhalation time 13 min. Our result, therefore, suggests that if the inhalation times were equal, the ratios of placental transfer would not differ among these four inhalational anesthetics. The Apgar scores in these four groups were not different from that in the group given only 66% nitrous oxide in oxygen as anesthetic (N_2O group). The cardiovascular changes induced by skin incision were bigger in the N_2O group than in the other groups. The use of a low concentration of H, E, S, or I is, therefore, suggested to be a useful and acceptable anesthetic method for cesarean section.

Key words: Placental transfer, Halothane, Enflurane, Sevoflurane, Isoflurane, Cesarean section

Introduction

The use of low concentrations of volatile agents in combination with a mixture of nitrous oxide in oxygen for cesarean section can prevent awareness without appreciable depression of uterine contractility and undue depression of the fetus. There are only a limited number of reports discussing the placental transfer of halothane (H) and enflurane (E) during cesarean delivery [1–5]. The concentration ratio of H between maternal artery and umbilical vein was reported to be 0.35 for 10.5 min of 0.65% inhalation [5], and that of E was 0.59 for 17 min of 1% inhalation [6]. However, the placental transfer of isoflurane (I) and sevoflurane (S) have not been examined, and furtheremore the comparison between H, E, S, and I has not been made in the same institute under the same conditions. We, therefore, measured the concentration of H, E, S, and I across the placenta and evaluated the usefulness of low concentrations of volatile anestheties for cesarean section.

Address correspondence to: D. Satoh
Received for publication on July 27, 1994; accepted on March 2, 1995

Patients and methods

Forty-six patients (23–41 years old) scheduled for cesarean section were randomly divided into five groups according to the inhalational anesthetic used: eight patients in the H group, ten patients in the E group, ten patients in the S group, ten patients in the I group, and eight patients in the 66% nitrous oxide in oxygen (N_2O) group. Thirty minutes after premedication with 0.5 mg of atropine, anesthesia was induced by thiopental 4 mg · kg^{-1} i.v., followed by succinylcholine 1 mg · kg^{-1} i.v., then the trachea was intubated and respiration was controlled. Anesthesia was maintained with 4 l · min^{-1} of N_2O plus 2 l · min^{-1} of O_2 combined with 0.5% of H in the H group, 1% of E in the E group, 0.8% of S in the S group, 0.6% of I in the I group, or alone in the N_2O group. We used almost half the minimum alveolar concentration (MAC) of volatile anesthesia. Muscle relaxation was maintained with intermittent administration of succinylcholine. Maternal arterial blood, and fetal umbilical venous and arterial blood were simultaneously sampled immediately after the delivery. Form these samples, the plasma concentration of the anesthetics (H, E, S, and I) was measured by gas chromatography. The time from the start of anesthetic inhalation to delivery (I-D time) was recorded, and an Apgar score was assigned by pediatricians. The data are expressed

as the mean ± SEM. Statistical analyses were performed using analysis of variance (ANOVA) and Student's *t*-test. A *P* value less than 0.05 was defined as significant.

Results

Of the 46 patients, there were 4 elective cases in the H group, 1 in the E group, 4 in the S group, 2 in the I group, and 2 in the N_2O group. There were 4 emergency cases in the H group, 9 in the E group, 6 in the S group, 8 in the I group, and 6 in the N_2O group. No statistical differences were seen between the groups with respect to age. The I-D time and Apgar scores are shown in Table 1. There were no significant differences in Apgar scores among the H, E, S, I, and N_2O groups, but the I-D time was significantly shorter in the I group than in the other groups. The plasma concentrations of H, E, S, and I in the maternal artery (MA) were 5.2 mg · dl^{-1}, 12.3 mg · dl^{-1}, 5.2 mg · dl^{-1}, and 2.4 mg · dl^{-1}, respectively. The plasma concentrations of H, E, S, and I in the umbilical vein (UV) were 2.2 mg · dl^{-1}, 6.1 mg · dl^{-1}, 2.0 mg · dl^{-1}, and 0.7 mg · dl^{-1}, respectively. The ratio of the anesthetic concentration between the UV and the MA was 0.44 for H, 0.49 for E, 0.38 for S, and 0.27 for I (Table 2). The plasma concentration of S in umbilical artery (UA) was 0.6 mg · dl^{-1} and that of I was 0.2 mg · dl^{-1}. The ratio of the anesthetic concentration in the UA to that in the MA was 0.1 in S and 0.1 in I (Table 2). No significant differences were seen among the groups with respsect to maternal systolic arterial pressure and heart rate preinduction (Tables 3, 4). Systolic arterial pressure increased after skin incision in N_2O group, but in the other four inhalation anesthetic groups, it did not change significantly (Table 3). The heart rate was not changed by incision in any of the groups (Table 4).

Table 1. Induction to delivery times and Apgar scores

Group	I-D time	Apgar scores 1 min	Apgar scores 5 min
N_2O		6 ± 1	9 ± 0
Halothane	13 min 27 s ± 1 min 25 s	8 ± 1	9 ± 0
Enflurane	13 min 49 s ± 1 min 4 s	7 ± 1	9 ± 0
Sevoflurane	13 min 20 s ± 1 min 55 s	6 ± 3	8 ± 2
Isoflurane	8 min 8 s ± 1 min 0 s*	6 ± 1	8 ± 1

Values are mean ± SEM.
I-D, time from the start of induction to delivery of baby.
* $P < 0.05$ isoflurane group versus other three anesthetic (H, E, S) groups.

Table 2. The ratio of anesthetic concentration in fetal to maternal blood

Group	Anesthetic concentration MA (mg/dl)	UV (mg/dl)	UA (mg/dl)	Concentration ratio UV/MA	UA/MA
Halothane	5.2 ± 0.7	2.2 ± 0.3		0.44 ± 0.05	
Enflurane	12.3 ± 0.8	6.1 ± 0.6		0.49 ± 0.03	
Sevoflurane	5.2 ± 0.6	2.0 ± 0.4	0.6 ± 0.2	0.38 ± 0.07	0.10 ± 0.03
Isoflurane	2.4 ± 0.3	0.7 ± 0.2	0.2 ± 0.1	0.27 ± 0.05	0.10 ± 0.05

Values are mean ± SEM.
MA, maternal artery; UV, umbilical vein; UA, umbilical artery.

Table 3. The changes in maternal systolic arterial pressure

Group	Pre-induction (mmHg)	Incision (mmHg)
N_2O	122 ± 6	134 ± 6*
Halothane	140 ± 6	142 ± 7
Enflurane	137 ± 6	131 ± 5
Sevoflurane	134 ± 7	132 ± 12
Isoflurane	135 ± 6	143 ± 6

Values are mean ± SEM.
* $P < 0.05$ *vs* pre-induction values.

Table 4. The changes in maternal heart rate

Group	Pre-induction (min^{-1})	Incision (min^{-1})
N_2O	110 ± 4	114 ± 1
Halothane	95 ± 2	108 ± 3
Enflurane	88 ± 1	98 ± 5
Sevoflurane	73 ± 7	89 ± 5
Isoflurane	100 ± 2	107 ± 2

Values are mean ± SEM.

Discussion

General anesthesia for cesarean section should fulfill four criteria: no material awareness, no undue depression of the fetus, no significant effect on uterine contractility, and a small change in the cardiovascular system. When N_2O alone is used as the anesthetic for cesarean section, the incidence of intraoperative maternal awareness has been reported to be 8.6% to 26% [7]. Although no awareness has been reported when a low concentration of H, E, or I was added to N_2O [1,4,8,9].

There have been no reports in which the concentrations of H, E, S, and I across the placenta were measured at the same institute. We obtained a UV/MA ratio of 0.44 for H, 0.49 for E, and 0.38 for S, which were almost the equal after about 13 min of inhalation, and the UV/MA ratio for I was 0.27 after about 8 min of inhalation. However, since we found that the UV/MA ratio of I is positively correlated with the inhalation time (Fig. 1), the UV/MA ratio after 13 min of inhalation instead of 8 min was estimated to be about 0.4. This result, therefore, suggests that there is no difference in the UV/MA ratio among volatile anesthetics. Furthermore, because the extent of placental transfer of each anesthetic depends principally upon its physicochemical properties such as molecular weight, lipid solubility, degree of ionization, and spatial configuration, placental transfer might be expected to be similar as long as the concentration (namely, inhalation time) and uterine blood flow are equal. Since the physicochemical properties of these volatile anesthetics are similar, it is not surprising that placental transfer is similar among them. Regarding the time factor, the UV/MA ratio of 0.35 after 10.5 min of H inhalation reported by Latto and Waldron [5], and 0.60 after 17 min of E inhalation reported by Dick et al. [6] are comparable to our results of 0.44 after 13.5 min of H inhalation and 0.49 after 13.8 min of E inhalation.

The disadvantages of general anesthesia for cesarean section compared with local anesthesia is early neonatal depression, even when only N_2O is used [10]. However, it has been reported that neonatal depression, as demonstrated by a low Apgar score at 1 min was improved at 5 min to a level close to the score under local anesthesia [11]. A similar result was also obtained in our study (Table 1). This rapid recovery may be explained by the fact that the newborn can quickly eliminate the inhalational anesthetic if respiratory function is adequate [11]. Moreover, there were no differences in Apgar scores between the N_2O group and the group given potent inhalational anesthetics. This may be explained partly by the finding that the concentration of inhalational anesthetics transferred into neonatal blood is low, more so in arterial blood than in venous blood, which has been mentioned by Latto and Waldron [5] and Dick et al. [6] and was also observed in this study. Furthermore, the difference between arterial and venous concentrations suggests that some of the inhalational anesthetic is eliminated through pulmonary circulation in the fetus.

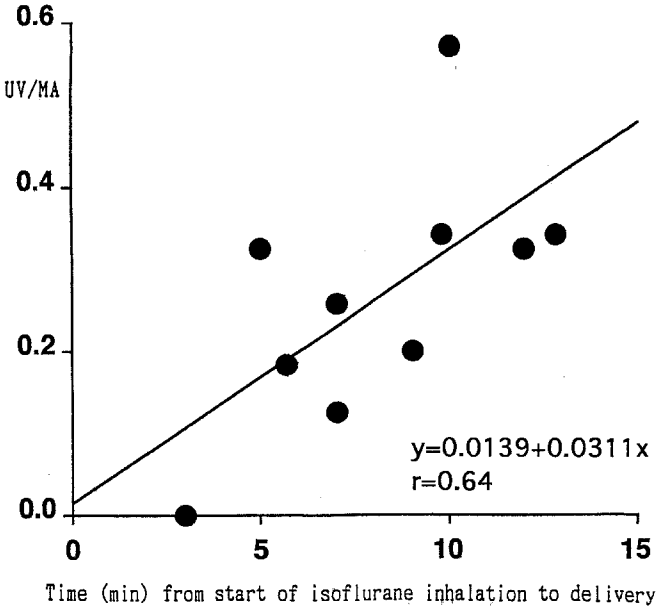

Fig. 1. Correlation between the time of isoflurane inhalation and the concentration ratio of the umbilical vein (*UV*) over the maternal artery (*MA*)

The increase in blood pressure after skin incision was smaller in the group using volatile anesthetics than the group of N_2O in this study, as reported previously [12]. Therefore, a low concentration of a potent inhalational anesthetic may be superior to using N_2O alone because of the prevention of maternal awareness and the circulatory stability. The other concern associated with using a potent volatile anesthetic is the decrease in uterine muscle tone due to increased perioperative blood loss. In this study, there was no evidence of increased perioperative blood loss. Several clinical investigations have also failed to reveal any increase in blood loss when a low concentration of a volatile anesthetic was used during cesarean section [1,2,4,5,9]. Under low concentrations of volatile anesthetics, the uterus in the postpartum period can adequately respond to oxytocin stimulation [13].

In conclusion, the placental transfer ratios of halothane, enflurane, isoflurane, and sevoflurane, namely the concentrations in fetal umbilical venous blood over that in maternal arterial blood, are almost equal when the inhalational time is equal (almost 0.4 for 13 min of inhalation). The use of low concentrations of volatile anesthetics is an acceptable anesthetic method for cesarean section because of the prevention of maternal awareness and the stability of the circulation, and because neonatal depression is small and lasts for only a short time.

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