Influence of sevoflurane and desflurane on neurological and adaptive capacity scores in newborns

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ABSTRACT

الأهداف: تقييم ومقارنة آثار عقار ديسفلوران وسيفوفلوران على الأم والمولود بعد الخضوع لعملية ولادة قيصرية تحت التخدير العام.

الطريقة: أجريت هذه الدراسة كدراسة عشوائية وصفية في الفترة ما بين يناير 2003م وحتى يناير 2004م، بجامعة هاسيتيب – تركيا. تم وضع 102 مريضة تراوحت أعمارهم ما بين 20–35 عام، عند الأسبوع 37 إلى 42 من الحمل بشكل عشوائي في مجموعتين تم تصنيفهم في المستوى الأول بناء على معايير الجمعية الأمريكية للتخدير (ASA). تلقى جميع المرضى عقار ثيوبنتال وعقار سوكسينلكولين من أجل التحريض. تلقى المريضات في المجموعة الأولى عقار ديسفلوران بمقدار 2.5%، وتلقى المريضات في المجموعة الثانية عقار سيفوفلوران بمقدار 1.5% متحداً مع 50% من أكسيد النتروجين والأكسجين. تم تقييم كمية فقدان الدم لدى الأم، وقيم غازات الدم الشريانية السرية، وتدخلات الولادة، ونقاط أبجار ونقاط (NACS) في الدقيقة 15، والساعة الثانية، والساعة 24 من العمر لتقييم حالة المولود.

النتائج: شملت الدراسة 102 (52 في المجموعة التي تلقت سيفوفلوران، 50 في المجموعة التي تلقت ديسفلوران). في المجموعة التي تلقت ديسفلوران، كانت نقاط (NACS) أفضل بشكل ملحوظ في التقييمات عند الدقيقة 15 والساعة الثانية. لم يكن هنالك اختلافات إحصائية ملحوظة في تقييمات الساعة 24 لنقاط (NACS)، ونقاط أبجار، وقيم غازات الدم الشريانية السرية، وأوقات الولادة، وكمية فقدان الدم بين المجموعتين.

خاتمة: كانت نتائج جهود التخدير بعقار ديسفلوران أكثر إيجابية مقارنة بعقار سيفوفلوران في المواليد الذين تتم ولادتهم بطريقة العملية القيصرية الاختيارية تحت التخدير العام عند الساعات المبكرة بعد الولادة.

Objectives: To evaluate maternal and neonatal effects of desflurane compared with the sevoflurane for general anesthesia for cesarean section.

Methods: The study was conducted as a prospective randomized blind study between January 2003 to January 2004 at the Hacettepe University, Ankara, Turkey. One hundred and two American Society of Anesthesiologists (ASA) I patients aged between 20-35 at 37-42 weeks of pregnancy were randomly allocated into 2 groups. All patients received thiopental and succinylcholine for induction. Patients assigned to the first group received desflurane 2.5%, and the second group sevoflurane 1.5% combined with 50% nitrous oxide and oxygen. Maternal blood loss, umbilical arterial blood gas values, delivery intervals, Apgar scores, and neurologic and adaptive capacity score (NACS) on the fifteenth minute, second hour, and twenty-fourth hour of age were evaluated to assess the neonatal status.

Results: One hundred and two (52 sevoflurane group, 50 desflurane group) parturients were included in the study. In the desflurane group, NACS were significantly better on the fifteenth minute and second hour evaluations. There were no statistically significant differences in twenty-fourth hour NACS evaluations, Apgar scores, umbilical arterial blood gas values, delivery times, and maternal blood loss between the groups.

Conclusion: Desflurane anesthesia offers more favorable results compared to sevoflurane in newborns delivered by elective cesarean section under general anesthesia in the early hours after delivery.

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The potent inhalation anesthetic agents sevoflurane and desflurane were recommended as supplements to nitrous oxide (N_2O) during general anesthesia for cesarean section, but no detailed comparative study of the effects of these agents on the mother and the neonate has been reported.[1,2] Assessments of neonatal result have included Apgar scores, umbilical arterial blood gas values and neurologic and adaptive capacity scores (NACS). The depression of the fetus by general anesthetics might influence the postpartum clinical progress during the newborn period. Various methods such as Brazelton Neonatal Behavioral Assessment Scale (BNBAS), the Scanlon Early Neonatal Neurobehavioral scale (ENNS), the neurological and adaptive capacity scoring system are the methods to evaluate the neonate, have been proposed for the assessment of neonatal neurological status and the influence of different factors and medications, including anesthetics.[3-5] To assess the neonatal effects of various anesthetic techniques NACS has been used. This tool is also useful for differential diagnosis of perinatal asphyxia and primary neurological disorders.[4,6] The aim of the present study was to evaluate maternal and neonatal effects of desflurane compared with sevoflurane for general anesthesia for cesarean section.

Methods. The study was conducted as a prospective randomized blinded study between January 2003 to January 2004 at the Department of Anesthesiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey. After obtaining the University Ethics Committee's approval and written consent, 102 American Society of Anesthesiologists (ASA) I patients aged between 20-35 years at 37-42 weeks of pregnancy scheduled for elective cesarean section were randomly allocated into 2 groups by the random number generation analysis tool of MS Excel 2000 software. Patients with hypertension, diabetes mellitus, preeclampsia, using sedative, hypnotic, or opioid drugs in the 12-hour period before the induction of general anesthesia and age <20 or >35 and gestation <37 weeks and >42 weeks are excluded. None of the patients received any narcotics or sedatives before anesthetic induction. Pre-medication consisted of 10 mg metoclopramide and 50 mg ranitidine intravenous (IV). All patients fasted for 8 hours before cesarean section. After routine monitoring and preoxygenation with 100% oxygen (O_2) with 3 minutes, anesthesia was induced with 4mg/kg^{-1} thiopental sodium followed by 1mg/kg^{-1} succinylcholine and endotracheal intubation. Patients were randomly assigned to receive 2.5% desflurane and 1.5% sevoflurane combined with 50% N_2O and 50% O_2. End tidal carbon dioxide (CO_2) levels were maintained at 30-35 mmHg. Ventilation was controlled mechanically at a tidal volume of 10ml/kg and a rate of 12 breaths/minute ventilation. Succinylcholine 0.15mg/kg^{-1} was administered in increments when needed. The minimal alveolar concentration (MAC) values of both anesthetic agents are determined as a result of bispectral index (BIS) values and awareness reports of previous studies.[1,7] No analgesic supplements were added in the 2 regimens. Both inhalation agents were discontinued following the delivery of the infant and anesthesia was maintained with 67% N_2O and 33% O_2 and a narcotic (1-2 μg/kg fentanyl). Induction to delivery and uterine incision to delivery intervals was noted. Vital signs of the mother (blood pressure, heart rates, and peripheral oxygen saturation) were monitored throughout the operation. Blood loss was estimated by the anesthesiologist. Umbilical blood samples were drawn from the artery of double clamped cord. Immediately after birth, oxytocin 10 IU was administered and was followed by an infusion of another 10 IU in 30 minutes. Apgar scores of the newborn were evaluated at 0, 1, and 5 minutes by a pediatrician who was unaware of the drug given to the mother.[8] Neurologic and adaptive capacity score evaluations were performed with a newborn pediatrician and the anesthesia resident before the beginning of the study and after learning the evaluations, the NACS was performed by the same anesthesia resident who was unaware of the anesthetic method after 15 minutes, 2 hours, and 24 hours. The test is designed as a screening test to detect central nervous system depression from drugs and to differentiate these effects from those found after birth trauma and perinatal asphyxia. This test is based on 20 criteria, each gave a score of 0, 1, or 2. According to this scoring (0) is absent or grossly abnormal response, (1) is mediocre or slightly abnormal response, and (2) is normal response. These criteria assess 5 general areas including adaptive capacity, passive tone, active tone, primary reflexes, and general assessment. The total score of 35 and above indicates neurologically vigorous neonates, whereas scores under 34 might indicate a depressed newborn (**Table 1**).[6]

Power analysis was performed using the PASS 2000 program (NCSS, Kaysville, Utah, USA). Power analysis of Abboud et al's[5] study with NACS as the primary criterion (power (1-β)=0.90, α=0.05, with Fisher's exact test) showed that 50 women were required in each group.[9] Student's t-test was used in statistical analyses of the age of the mother, birth weight of the neonates, blood gas analysis, mean arterial pressures, and NACS evaluations at 15 minutes, 2 hours, and 24 hours. The Mann Whitney U test was used in statistical analyses of Apgar scores, gestational age of the neonates, time periods from induction to delivery, uterine incision to delivery, and total score of NACS. The X^2 test was used for the total scores less than 35 for the 15 minutes

Table 1 - Neurological and adaptive capacity scores.

Neurologic and adaptive capacity scores	0	1	2
Adaptive capacity			
Response to sound	Absent	Mild	Vigorous
Habituation to sound	Absent	7-12 stimuli	<6 stimuli
Response to light	Absent	Mild	Brist blink
Habituation to light	Absent	7-12 stimuli	<6 stimuli
Consolability	Absent	Difficult	Easy
Passive tone			
Scarf sign	Encircles the neck	Elbow slightly passes midline	Elbow does not reach midline
Recoil of elbows	Absent	Slow weak	Brisk reproductible
Popliteal angle	>110	100-110	<90
Recoil of lower limbs	Absent	Slow weak	Brisk reproductible
Active tone			
Active contraction of neck flexors	Absent	Difficult	Good
Active contraction of neck extensors	Absent	Difficult	Good
Palmar grasp	Absent	Weak	Excellent
Response to traction	Absent	Lifts part of the body weight	Lifts all of the body weight
Supporting reaction	Absent	Incomplete	Strong
Primary reflexes			
Automatic walking	Absent	Difficult to obtain	Perfect
Moro reflex	Absent	Weak	Perfect
Sucking	Absent	Weak	Perfect
General assessment			
Alertness	Coma	Lethargy	Normal
Crying	Absent	Weak	Normal
Motor activity	Absent	Diminished	Normal

Table 2 - Mothers age and birth weight, delivery times (mean ± SD) and gestational age (median [range]) between the groups.

Descriptive values of mother and neonate	Sevoflurane (n=52)	Desflurane (n=50)
Age (years)	30.8 ± 4.9	31.8 ± 4.9
Birth weight (g)	3292 ± 404	3201 ± 419
Gestational age (weeks)	38 (37-41)	38 (37-41)
Induction- delivery (min)	5.4 ± 2.7	5.6 ± 2.3
Uterine incision-delivery (sec)	49.3 ± 47.8	44.7 ± 42.6

Table 3 - Apgar scores of the groups (mean ± SD).

Time (minutes)	Sevoflurane (n=52)	Desflurane (n=50)	*P*-value
0	8.44 ± 0.91	8.62 ± 1.15	0.391
1	9.65 ± 0.51	9.76 ± 0.71	0.392
5	10.00 ± 0.00	9.98 ± 0.14	0.310

evaluation and Fisher's exact test were used for the total scores less than 35 for the evaluation of 2 and 24 hours. The data were analyzed with the Statistical Package for the Social Sciences (SPSS) 10.0.5 version for Windows (SPSS Inc., USA). The p values less than 0.05 were considered significant.

Results. There were no significant differences between the groups on maternal age, estimated blood loss, gestational age, birth weight of the neonates, induction to delivery intervals, and uterine incision to delivery intervals (p>0.05) (**Table 2**). There was also no significant difference between apgar scores, or umbilical arterial blood gas values (p>0.05) (**Tables 3 & 4**). Estimated blood loss was >500ml in both groups. Heart rates and peripheral oxygen saturation of the patients did not differ between groups, while mean noninvasive arterial pressure was significantly higher in the desflurane group at most minutes (**Figure 1**). Response to traction and supporting reaction parameters in the active muscle tone subgroup of NACS showed a statistically significant difference in favor of the desflurane group at the 2 hours measurements (p<0.05). Total NACS was also higher in the desflurane group at the 15 minutes and 2 hours scoring. The twenty-fourth hour measurements showed no significant difference between the groups on any

Table 4 - Umbilical arterial blood gas values of groups (mean ± SD).

Umbilical arterial blood gas values	Sevoflurane (n=52)	Desflurane (n=50)	*P*-value
pH	7.31 ± 0.05	7.33 ± 0.05	0.673
pCO_2 (mmHg)	45.44 ± 8.81	45.79 ± 6.47	0.069
PO_2 (mmHg)	42.26 ± 25.81	42.82 ± 26.07	0.697
Percentage O_2	58.24 ± 20.20	58.94 ± 25.10	0.134
BE (mEq/L)	-2.68 ± 4.00	-1.99 ± 2.89	0.289
BEECF (mEq/L)	-2.25 ± 3.26	-1.75 ± 2.85	0.451
HCO_3 (mEq/L)	23.80 ± 5.49	23.60 ± 2.63	0.053
BB	45.54 ± 3.05	44.37 ± 13.04	0.255

pCO_2 - carbon dioxide concentration , PO_2 - oxygen pressure O_2 - oxygen, BE - base excess, BEECF - base excess in extracelluler fluid, HCO_3 - bicarbonate , BB - buffer base

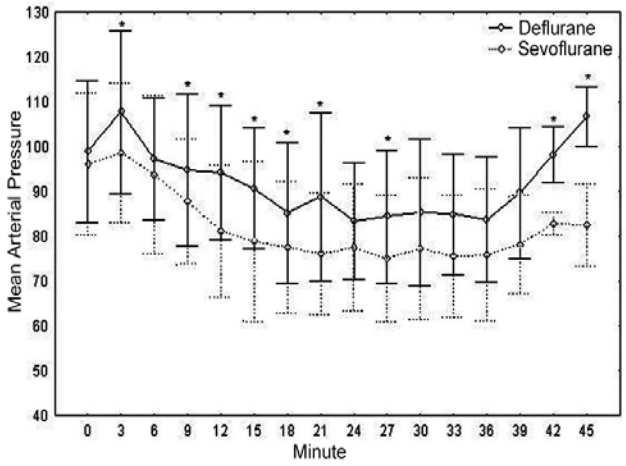

Figure 1 - Mean arterial pressures of desflurane and sevoflurane groups (*p<0.05).

Table 5 - Total neurological and adaptive capacity scores (NACS) of groups (mean ± SD).

NACS values in time	Sevoflurane (n=52)	Desflurane (n=50)
15 minute (total score)	36.60 ± 2.72	38.44 ± 1.21*
2 hour (total score)	37.69 ± 1.98	38.46 ± 1.63†
24 hour (total score)	38.13 ± 1.63	38.66 ± 1.45

* p=0.044 and †p=0.035

Table 6 - Number (%) of neonates with neurological and adaptive capacity scores (NACS) <35.

NACS <35 in time	Sevoflurane (n=52) n (%)	Desflurane(n=50) n (%)
15th minute total score <35	8 (15)	5 (10)
2nd hour Total Score<35	4 (8)	2 (4)
24th hour Total Score<35	2 (4)	1 (2)

NACS parameter. Total NACS of groups are shown in **Table 5** and NACS below 35 are shown in **Table 6**.

Discussion. Many of the drugs newly introduced into anesthetic practice have in common a kinetic profile that permits a more rapid and precise adjustment of effect, including a more rapid recovery of normal function. Sevoflurane and desflurane fit this mold.[10] These inhalational agents can cross the placental barrier easily due to their low blood gas solubility and high lipid solubility and therefore can generally produce fetal depression. Desflurane is a fluronated methyl ether differing from isoflurane only in the substitution of fluorine for chlorine on the alpha-ethyl carbon. It has a pungent odor. The boiling point is 22.8˚C, and the saturated vapor pressure is 664 mm Hg at 20˚C.[11] The use of fluorination rather than chlorination increases vapor pressure. Thus, vapor pressure exceeds isoflurane's by a factor of 3. As the vapor pressure of desflurane exceeds one atmosphere at 22.8˚C, the vaporizer technology designed for delivery of other inhalation agents cannot be applied to desflurane.[12] A new type of vaporizer has been developed in which the anesthetic agent is heated and pressurized and then mixed with the carrier gas or gasses. It has a blood gas partition coefficient of 0.42, the lowest of all of the available volatile agents, which mean equilibration and recovery are likely to occur quickly. Desflurane is 5.2 folds less potent than isoflurane, and 8.1 fold less than halothane.[11] Low potency and solubility, flow rate, and manufacturer determines the price of the agent, which costs higher than the other inhalational agents.[12]

In concentrations of 0.83-1.66 MAC, desflurane causes dose dependent tachycardia in humans, associated with a depression in myocardial contractility and decrease in systemic vascular resistance. As with isoflurane, if the concentration of desflurane is increased rapidly to concentrations exceeding one MAC, then increases in sympathetic activity, heart rates and blood pressure may occur.[11] In distinct contrast to desflurane, sevoflurane has not been associated with tachycardia or hypertension during its initial administration with a mask, or when the inspired concentration is rapidly increased during the intraoperative period.[13] In the present study, mean arterial pressure was significantly higher in the desflurane group than in the sevoflurane group. One of the main concerns associated with the administration of halogenated agents in obstetrics is the resulting decrease in uterine muscle tone, which may be associated with increased bleeding. In vitro studies have shown that sevoflurane and desflurane depress myometrial contraction equally.[14,15] In the present study, blood loss with desflurane or sevoflurane was comparable to each other.

Transient airway irritant effects are the most common adverse events during induction of anesthesia with desflurane, therefore, this agent is not recommended for induction of anesthesia in pediatric patients. Excitatory effects and coughing, breath holding, excessive secretions, and laryngospasms are the most common reported reflexes.[11] Desflurane is 23% (at 40˚C) to 54% (at 0˚C) less absorbed into dry sodalyme, a mixture of calcium oxide (CaO) and sodium hydroxide (NaOH) that is used as a CO_2 adsorbent, compared to isoflurane. It is also less soluble in rubber and plastic components of anesthesia breathing circuit than isoflurane, sevoflurane, or halothane. Desflurane is resistant to in vitro degradation in moist soda lime (containing 15% water) at <60˚C, although there is slight degradation at 80˚C. This compares favorably with the isoflurane and halothane, which degrade to some extent even at 40˚C. The chemical breakdown product of desflurane is a relatively innocuous compound trifluoromethane. Degradation of desflurane (as well as isoflurane and enflurane) can also occur in dry soda lime or 'Baralyme,' which results in carbon monoxide (CO) production. However, this generation of CO can be avoided with the use of soda lime with >4.8% water content or 'Baralyme' with >9.7% water content.[16]

The NACS is more sensitive than the Apgar score for the assessment of newborn adaptivity and for detecting the potential depressive effects of drugs. In the present study, the influence of the anesthetic technique showed better NACS in the desflurane group at 15 minutes and 2 hours. The desflurane group had significantly higher scores in response to traction and supporting reaction in the active muscle tone subgroup of NACS at the 2 hours recording (p<0.05). The pharmacokinetic properties of desflurane, such as low solubility, faster washout, and rapid alveolar equilibration can explain this difference.[12] Clinical studies indicate that emergence from desflurane effect is significantly earlier than that of sevoflurane (5.2 versus 8.8 minutes).[16]

In Chin and Yeo[7] study, bispectral index values less than 60 were consistent with high probability of unconsciousness in cesarean delivery.[7] In the same study, end-tidal concentration of 1% of sevoflurane maintain BIS values more than 60, whereas 1.5% sevoflurane was able to maintain BIS values less than 60 during cesarean delivery without causing any adverse affects due to larger concentrations.[7] In the study by Navarro[1] comparing 0.5% isoflurane, 2.5% desflurane in cesarean section, the patients were interviewed on intraoperative awareness 24 and 48 hours after the operation. With these concentrations, none of the patients reported intraoperative awareness during the operation.[1] The MAC values of both anesthetic agents are determined as a result of BIS values and awareness reports of these previous studies.[1,7] Furthermore in our study, for the determination of MAC values we used the previous studies. If we were able to use BIS for our patients, awareness could have been determined more objectively.

In a study performed by Abboud et al,[9] comparing NACS after epidural, spinal, and 0.5% enflurane anesthesia, neonates delivered with general anesthesia scored significantly lower for adaptive capacity, passive tone, active tone, primary reflexes, and total scores at both 15 minutes and 2 hours of age than those delivered with either spinal or epidural anesthesia. Neonates delivered with epidural anesthesia scored lower than those delivered with spinal anesthesia in supporting reaction and motor activity at 2 hours of age. The smaller amounts of local anesthetics used for spinal anesthesia might have influenced this result. All neonates had high scores at the twenty-fourth hour, at which time there were no significant differences between the 3 groups.[9] In the present study, both the sevoflurane and desflurane groups showed comparable scores to Abboud et al[17] spinal and epidural anesthesia groups. The rapid elimination of desflurane and sevoflurane might be responsible for this outcome. Apgar scores give an indication of the general well-being of the newborn. Previous studies comparing different general anesthetics for cesarean section showed no significant differences of Apgar scores.[5,17,18] In the present study, the Apgar scores with desflurane and sevoflurane were similar.

Studies have demonstrated no significant difference in umbilical cord blood gas and pH measurements in neonates exposed to general anesthesia.[19] In the present study, the umbilical blood values were all within normal limits and there were no significant difference between the groups. In a study, comparing 0.5% isoflurane, 1% isoflurane, and 0.5% halothane on NACS measurements and Apgar scores, no significant differences were found between the groups. The 70-78% of the neonates were found to have a NACS score >35 at 15 minutes.[5] In our study, the 15 minutes total score was 85-90%. Second hour and 24-hour NACS were comparable with the Abboud study.[5] In a study, comparing epidural anesthesia and general anesthesia, 0.5% halothane resulted in lower scores at one minute Apgar scores, however, there was an obvious improvement at 5 minutes in the general anesthetic group. The choice of anesthetic technique did not appear to affect short-term neonatal survival.[20] According to our data, median Apgar scores were 9 at birth and 10 in the following evaluations. The faster clearance of desflurane and sevoflurane might explain the less depressant effects on the neonate.

In conclusion newer inhalational anesthetics, especially desflurane, have a favorable outcome on neonatal NACS at early times of delivery. Thus general anesthesia with desflurane or sevoflurane may be safely used in terms of neonatal outcome in selected cases undergoing elective caesarean section.

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