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Cardiovascular Changes in Preterm Neonates Receiving Isoflurane, Halothane, Fentanyl, and Ketamine

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Hemodynamic changes during four anesthetic techniques were studied in 80 preterm neonates. Atropine, 0.02 mg/kg, and pancuronium, 0.1 mg/kg, were given intravenously to all patients, who were ventilated with oxygen and air. Each group of 20 patients then received 0.75% isoflurane, 0.5% halothane, 20 μg/kg fentanyl, or 2 mg/kg ketamine. Heart rate (HR), systolic blood pressure (SAP), and mean blood pressure (MAP) were recorded at 1-min intervals until surgical stimulation. HR remained at or above control level in all groups. Statistically significant decreases ($P < 0.01$) in SAP and MAP occurred following administration of each anesthetic. SAP decreased 30% during isoflurane administration, 25% during halothane, 21% following fentanyl, and 16% following ketamine. Clinically important decreases (25% or greater) in SAP were observed in some patients in each group, but the incidence was significantly less in patients receiving ketamine ($P < 0.02$). The covariables of conceptual age, postnatal age, weight, urine specific gravity, hematocrit, and presence of patent ductus arteriosus did not have statistically significant effects on SAP and MAP changes. The authors conclude that SAP and MAP decrease significantly during each of the anesthetic techniques studied and that clinically important decreases in SAP occur less frequently during the technique using ketamine. (Key words: Age factors: prematurity. Anesthesia: cardiovascular effects. Anesthesia: pediatric.)

IN HIS EXTENSIVE REVIEW of the physiologic characteristics of the mammalian fetal heart, Friedman demonstrated incomplete cardiac sympathetic innervation, low myocardial norepinephrine stores, and poor ventricular compliance.[1] This cardiovascular immaturity was most marked in the fetus, less marked in the term neonate, and improved postnatally as the animals matured.[1] Because of this cardiovascular immaturity, the preterm neonate may be at greater risk of developing hypotension during general anesthesia than the term neonate or older infant.

A variety of anesthetic techniques for preterm neonates have been described.[2–10] While significant hypotension has been observed in preterm neonates undergoing general anesthesia,[8,10] cardiovascular effects of most techniques remain inadequately documented. Some anesthesiologists emphasize blood pressure maintenance at the expense of adequate anesthesia. Early reports of anesthetic management of preterm neonates undergoing ligation of patent ductus arteriosus (PDA), for example, include techniques using no anesthetic or only local anesthetic infiltration of the chest wall.[4,5] Nitrous oxide, advocated as the main anesthetic for preterm neonates,[6–8] is associated with little cardiovascular depression in newborn rabbits.[11] However, concerns over inadequate anesthetic potency, high inspired oxygen requirements, and diffusion of nitrous oxide into gas containing spaces make it a poor choice for many preterm neonates.

This study was undertaken to document changes in heart rate (HR), systolic blood pressure (SAP), and mean blood pressure (MAP) in preterm neonates during general anesthesia using isoflurane, halothane, fentanyl, and ketamine.

Methods

Eighty preterm neonates (conceptual age < 37 weeks; weight < 2500 g) requiring a variety of surgical procedures were studied prospectively by methods approved by the institutional review board. All patients were of ASA physical status III or IV. None of the patients were given preanesthetic medication or were receiving cardiostimulatory or vasoactive drugs. Characteristics of the patient population are shown in table 1. Conceptual age ranged from 26–36 wk; weight ranged from 560–2400 g. The four groups were similar in all respects except preoperative urine specific gravity (table 1).

The patients required a variety of surgical procedures, the most frequent being insertion of central venous catheters for parenteral nutrition (30 patients), ligation of PDA (26 patients), and laparotomy for various indications (16 patients). No significant differences existed in the incidence of various operations among the four groups. Because data collection ended just after the skin incision, the surgical procedure did not affect the cardiovascular changes observed during the study.

On arrival in the operating room, monitoring devices were applied and atropine, 0.02 mg/kg, was administered intravenously. An orotracheal tube was placed in patients who were not already intubated (table 1). Pancuronium, 0.1 mg/kg, was administered intravenously and ventilation with an air/oxygen mixture appropriate for the patient was controlled manually using a nonrebreathing system (Jackson Rees' modification of Ayre's T-piece).

Using a table of random numbers, the patients were divided into four groups of 20 each. Group 1 received inhalation isoflurane 0.75%. Group 2 received inhalation halothane 0.5%. Group 3 received fentanyl 20 μg/kg in-

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TABLE 1. Patient Population

Covariable	Isoflurane	Halothane	Fentanyl	Ketamine
Postnatal age (day)	16.3 ± 13.0	22.0 ± 19.2	10.3 ± 9.5	16.1 ± 10.4
Conceptual age (week)	32.0 ± 2.7	32.6 ± 3.5	30.9 ± 3.6	31.6 ± 2.5
Weight (g)	1306 ± 537	1471 ± 591	1221 ± 548	1319 ± 471
Urine specific gravity	1.008 ± 0.004	1.009 ± 0.005	1.011 ± 0.008*	1.006 ± 0.003*
Patent ductus arteriosus (no. patients)	5	4	9	8
Hematocrit (%)	43 ± 6	43 ± 6	44 ± 6	42 ± 4
Intravenous fluids (ml/kg)	6.9 ± 3.0	7.9 ± 5.2	6.0 ± 3.7	5.0 ± 2.9
Without prior endotracheal tube (no. patients)	5	6	5	2

Mean ± SD; n = 20 in each group.
* Groups significantly different from each other ($P < 0.05$), but not from the other groups, by multivariate analysis of variance.

travenously. Group 4 received ketamine 2 mg/kg intravenously. The vaporizers used for administration of isoflurane and halothane were agent-specific, variable bypass, flow-over vaporizers (Ohio Medical Products, Madison, WI). The vaporizers were calibrated by the manufacturer prior to the study with an infrared gas analyzer (Foxboro-Wilkes, Foxboro, MA). Analysis of vaporizer output after the conclusion of the study with an interference refractometer gas analyzer (Riken Keiki, Tokyo, Japan) indicated that precision and accuracy were maintained.

Intravenous fluids and infusion rates were maintained at preoperative levels, which varied according to the patients' diseases and preoperative conditions. Normal saline boluses, 0.5 ml, were given to facilitate drug administration. Fluids administered during the study period are indicated in table 1.

HR, SAP, and MAP were measured and recorded using an automated oscillometric technique previously demonstrated to be accurate and precise in infants (Dinamap 847®, Critikon, Tampa, FL).[12,13] These measurements were made at 1-min intervals in the operating room beginning prior to atropine administration and ending with surgical stimulation. The HR, SAP, and MAP determinations subjected to statistical analysis were those obtained at the following times: 1) after arrival in the operating room (control); 2) after atropine and pancuronium administration; 3) the lowest HR, SAP, and MAP occurring between administration of the anesthetic and surgical incision; and 4) immediately after incision. Statistical tests were performed on the mean of absolute values and not on the changes in values. The time intervals between administration of the anesthetic and surgical incision ranged from 15–25 min and were not significantly different among the groups.

The covariables recorded were postnatal age, conceptual age, weight, urine specific gravity, presence of PDA, hematocrit, intravenous fluids administered during the study period, and whether tracheal intubation was performed during the study period. Statistical analysis of the data was carried out using multivariate analysis of variance[14] and the chi-square test. Statistical significance of differences in mean values was defined as $P < 0.05$. A clinically important change in HR, SAP, and MAP was defined as a change from control of 25% or greater.

Results

Results for the HR, SAP, and MAP changes are depicted in figures 1–3. The mean lowest HR, SAP, and MAP for each group following anesthetic administration are shown in Table 2.

Administration of atropine and pancuronium resulted in a statistically significant ($P < 0.01$) increase in HR and insignificant changes in SAP and MAP in each group.

During administration of 0.75% isoflurane, HR decreased to control level, SAP decreased 30% ($P < 0.01$), and MAP decreased 31% ($P < 0.01$) below control levels. Surgical incision did not significantly affect the variables in this group (figs. 1–3).

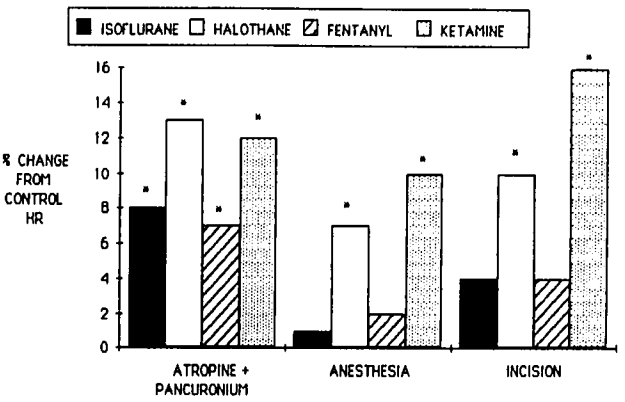

FIG. 1. Changes in heart rate of preterm neonates during anesthetic management. Values are means of each anesthetic group. *Indicates a significant change from control by multivariate analysis of variance ($P < 0.01$).

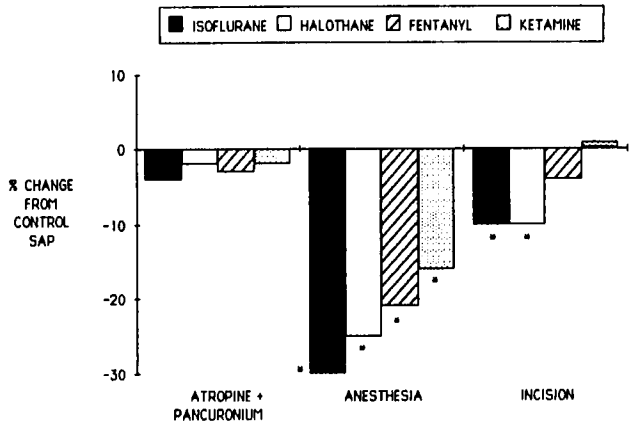

FIG. 2. Changes in systolic blood pressure of preterm neonates during anesthetic management. Values are means of each anesthetic group. *Indicates a significant change from control by multivariate analysis of variance ($P < 0.01$).

During 0.5% halothane administration, HR remained above control ($P < 0.01$), SAP decreased 25% ($P < 0.01$), and MAP decreased 29% ($P < 0.01$). Surgical incision did not significantly alter these changes (figs. 1–3).

Following administration of fentanyl, 20 μg/kg, HR decreased to control level, SAP decreased 21% ($P < 0.01$), and MAP decreased 24% ($P < 0.01$). Following surgical incision, HR remained unchanged, and SAP and MAP returned to control levels (figs. 1–3).

Following administration of ketamine, 2 mg/kg, HR remained above control ($P < 0.01$), SAP decreased 16% ($P < 0.01$), and MAP decreased 19% ($P < 0.01$). Surgical incision did not further alter HR, but SAP and MAP returned to control levels (figs. 1–3).

No statistically significant differences existed among the groups with regard to the SAP and MAP decreases following administration of the anesthetic.

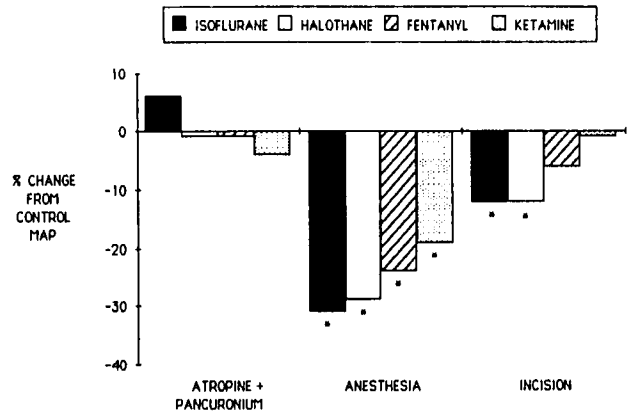

FIG. 3. Changes in mean blood pressure of preterm neonates during anesthetic management. Values are means of each anesthetic group. *Indicates a significant change from control by multivariate analysis of variance ($P < 0.01$).

None of the covariables had significant effects on the SAP and MAP changes observed following anesthetic administration. In the 18 patients who were intubated unanesthetized and unparalyzed in the operating room, mean SAP transiently increased 9.1%. This increase was not statistically significant and abated 1–2 min after intubation.

Clinically important decreases in SAP (25% or greater) occurred in 12 patients receiving isoflurane, 10 receiving halothane, eight receiving fentanyl, and four receiving ketamine. This incidence of hypotension was significantly less in the ketamine group ($\chi^2 = 6.05$, DF = 1, $P < 0.02$).

Discussion

A major factor in choosing an anesthetic technique for the preterm neonate is its effect on HR and SAP. The infant 1–6 months of age displays considerable sensitivity to the cardiovascular depressant effects of halothane[15,16] and isoflurane.[17] This sensitivity appears to be inversely related to age.[18–21] The term neonate has not been as extensively studied as the older infant. A 71% incidence of hypotension associated with halothane was reported to occur in term neonates in a retrospective study.* A prospective study of neonates and infants 1–6 months of age demonstrated significant incidences of hypotension at 1 MAC halothane, which were similar in both groups (33% of neonates and 44% of older infants).[22]

Because of the immaturity of the fetal and neonatal mammalian heart,[1] the preterm neonate may be at greater risk of developing hypotension during general anesthesia than the term neonate or older infant. Gregory reported a 33% decrease in SAP and a 2% decrease in HR in a retrospective study of preterm neonates receiving 0.5–1.0% halothane in air and oxygen.[10] Other studies reporting the use of halothane anesthesia in preterm neonates[2,3] do not discuss changes in SAP or HR.

Robinson and Gregory[9] studied fentanyl, 30–50 μg/kg, as the anesthetic for PDA ligation in preterm neonates. They reported excellent stability of SAP and HR, with decreases of only 5% following administration of the anesthetic.

Ketamine has been found to support cardiovascular function in infants and children with congenital heart disease.[23–25] Ketamine's use in preterm neonates, while reported previously,[3] has not been studied.

Anesthetic Requirement in Preterm Neonates

There is no question that the preterm neonate feels pain and, therefore, requires an anesthetic. While the

* Diaz JH, Lockhart CH: Is halothane really safe in infancy (abstract)? ANESTHESIOLOGY 51:S313, 1979

TABLE 2. Changes in Heart Rate (HR), Systolic Arterial Pressure (SAP), and Mean Arterial Pressure (MAP) during Anesthesia in Preterm Neonates

	Isoflurane	Halothane	Fentanyl	Ketamine
Control HR (beats/min)	164 ± 18	160 ± 13	159 ± 15	161 ± 16
Lowest HR	167 ± 17	171 ± 16*	163 ± 14	177 ± 18*
Percent change	+1	+7	+2	+10
Control SAP (mmHg)	61 ± 18	70 ± 17	61 ± 14	66 ± 10
Lowest SAP	42 ± 11*	52 ± 11*	48 ± 11*	55 ± 8*
Percent change	−30	−25	−21	−16
Control MAP (mmHg)	45 ± 14	54 ± 12	47 ± 13	52 ± 8
Lowest MAP	31 ± 9*	38 ± 8*	35 ± 8*	42 ± 5*
Percent change	−31	−29	−24	−19

Mean ± SD; n = 20 in each group.

* Significantly different ($P < 0.01$) from control by multivariate analysis of variance.

preterm neonate is neurophysiologically immature, his response to pain is specifically present even at 28 weeks of conceptual age.[26]

Anesthetic requirement has not been determined for the human preterm neonate, although available evidence indicates that it is probably lower than that of older infants and children. The MACs of both halothane and isoflurane are significantly lower in term neonates (0.87% halothane, 1.6% isoflurane) than in infants 1–6 months of age (1.2% halothane, 1.87% isoflurane).[22,27] Gregory *et al.*, studying equipotent arterial halothane concentrations, reported that the halothane requirement of the fetal lamb was less than half that of the pregnant ewe, and concluded that fetal MAC for halothane was 0.33%.[28] This suggests a low requirement for the preterm neonate.

The doses and concentrations of anesthetics used in this study were chosen arbitrarily, based on our clinical practice. While we cannot be certain, we think that they were adequate to provide anesthesia, assuming a low anesthetic requirement for the preterm neonate.

We do not know how the selected doses of the anesthetics used in our study compare in potency. Studies in older patients of MAC relationships[29,30] and fentanyl requirements[31,32] suggest that the four techniques we employed are roughly equivalent in anesthetic potency.

CARDIOVASCULAR CHANGES

The cardiovascular changes observed in our study should be viewed as associated with the anesthetic technique as a whole, not the anesthetic agent alone. We believe that atropine is an important component of the anesthetic management of these patients. Because of the neonate's poor ventricular compliance,[1] cardiac output is highly dependent on HR. Maintenance of HR with atropine has been shown to decrease the extent of hypotension in infants 1–6 months of age[15] and children[33] anesthetized with halothane. Our choice of pancuronium for muscle relaxation also was made because of the HR increase associated with its use. In our patients, HR was maintained at or above control levels throughout the study (fig. 1), thus supporting cardiac output and preventing reflex bradycardia often associated with surgical manipulation in the lightly anesthetized neonate.

Statistically significant decreases in SAP and MAP followed administration of the anesthetic agent in each group. The incidence of clinically important decreases (25% or greater) in SAP was lower during ketamine anesthesia than during the other anesthetics. Previously reported clinical experience in preterm neonates with halothane[10] is consistent with our data, while that of fentanyl[9] is not. Different methods in Robinson and Gregory's study of fentanyl[9] and ours may have contributed to the difference in results. They used HR and SAP values from the intensive care nursery as controls, rather than those recorded before surgery in the operating room. Berger *et al.* reported significant increases in HR and SAP from ward values to preinduction operating room values in adults[34]; similar changes may occur in preterm neonates. If the two studies had used the same control point, the results may have been similar. Another difference is that Robinson and Gregory administered a fluid bolus of 10 ml/kg of lactated Ringer's solution in 5% dextrose prior to the fentanyl, while we infused less fluid by maintaining preoperative infusion rates.

We examined preoperative patient factors for correlation with decreases in SAP and MAP using multivariate analysis of variance. Greater decreases in SAP and MAP tended to occur in patients of lower weight and younger postnatal age, but not in those of younger conceptual age. Presence of PDA did not correlate with decreases in blood pressure, despite the potential for cardiovascular instability in those patients. Awake tracheal intubation, performed at the time of induction in the 18 patients who were not already intubated, also did not affect the results. High urine specific gravity, an indirect indicator of hy-

povolemia, was not associated with changes in SAP and MAP. None of these factors had a statistically significant effect on the blood pressure changes observed during anesthesia.

We conclude that, while blood pressure of the preterm neonate decreases significantly during each of the described anesthetic techniques, SAP is better maintained during the technique using ketamine than during those using isoflurane, halothane, and fentanyl.

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