Respiratory outcome in extremely premature infants following ketamine anaesthesia

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Premature infants are prone to develop postoperative apnoea. The purpose of the present study was to determine if risk factors could be identified to predict which patients would require postoperative tracheal intubation and lung ventilation. Twenty-five extremely premature infants (birth weight: 811 ± 242 g (mean ± SD) and operation weight: 1585 ± 394 g) needing cryotherapy for retinopathy were studied. After surgery the tracheas were extubated if there was no prolonged apnoea, $SaO_2 > 85\%$, and heart rate > 120 bpm. In eight, tracheal extubation in the operating room was unsuccessful. Using multivariate discriminant analysis, four risk factors correlated with the need for pulmonary ventilation – gestational duration, birth weight, postconceptional age, and preoperative amyophylline treatment for seven days. A scoring system using these factors successfully predicted the need for a tracheal tube after surgery in 92% of patients. It is concluded that the system may be clinically useful in the perioperative care of low-birth-weight infants as it identifies important variables for evaluating postoperative prolonged apnoea.

Les prématurés sont susceptibles d'encourir des épisodes d'apnée en période postopératoire. Nous avons voulu en établir les facteurs de risque afin de prédire quels prématurés auraient besoin de ventilation mécanique aprés une anesthésie. Nous avons inclu dans l'étude 24 grands prématurés dont le poids moyen à la naissance était de 811 ± 242 gr et de 1585 ± 394 lors de l'intervention. Après leur anesthésie pour cryothérapie rétinienne, nous avons détubé la trachée de ceux qui n'avaient pas d'apnée prolongée et qui maintenaient leur SaO_2 à plus de 85% et leur pouls à plus de $120 \cdot min^{-1}$. Huit enfants ne purent remplir ces exigences en salle d'opération. L'analyse de multiples variables en a isolé quatre qui corrélait avec le besoin de ventilation mécanique : la durée de la gestation, le poids à la naissance, l'âge postconceptionnel et un traitement à l'aminophylline de plus de sept jours. La combinaison de ces quatre variables permettait de prévoir 92% des cas nécessitant un support ventilatoire en postopératoire et pourrait ainsi devenir un outil clinique fort utile.

Key words
ANAESTHESIA: paediatric;
COMPLICATIONS: apnoea.

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The progressive decrease in the mortality of extremely low-birth-weight (<1000 g) or very low-birth-weight (<1500 g) infants has led to an increase in the number of these babies undergoing general anaesthesia and surgery. Premature infants are more prone to develop prolonged apnoea following general anaesthesia than are full-term infants.[1–5] The risk factors for postoperative apnoea have been identified as follows: postconceptional age of less than 44–46 wk,[3,5] postnatal age,[1,3] history of prolonged apnoea,[3] body weight at operation,[1] and pre-existing diseases.[6] However, these factors were derived from a comparison of premature and full-term infants, and the relative importance of each remains obscure in extremely low-birth-weight infants. In our institution some former or present low-birth-weight infants require early cryotherapy for their retinopathy. Although they possess many of the risk factors described above, in some infants the trachea may be extubated in the operating room, whilst others may require postoperative mechanical ventilation.

The present study applied statistical techniques of linear regression and multivariate discriminant analysis to this clinical situation in order to select those preoperative variables which were most useful in identifying low-birth-weight infants needing postoperative intubation. In particular, we aimed to devise a scoring system for the prediction of postoperative intubation for premature infants with prolonged apnoea that would be both reliable and easy to use in the clinical setting.

Methods

Twenty-five patients undergoing trans-scleral cryotherapy for progressive retinopathy of prematurity were studied. They met the following criteria: (a) weight at operation <2500 g, (b) postconceptional age <41 wk, (c) first operation with ketamine anaesthesia, and (d) no endotracheal tube or mechanical ventilation was used in the seven days before operation. The study was approved by the institutional ethics committee and the patients' parents had all given their informed consent to participate in the study.

Anaesthetic technique

No preanaesthetic medication was administered. Intraoperative monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, rectal thermometer, inspired oxygen analyser and neuromuscular stimulator. Anaesthesia was induced with ketamine 1 $mg \cdot kg^{-1}$, *iv*. Muscle relaxation was obtained with alcuronium 0.4 $mg \cdot kg^{-1}$ in 23 infants and with vecuronium 0.15 $mg \cdot kg^{-1}$ in two infants. After endotracheal intubation, no supplemental dose of ketamine was administered. Topical anaesthesia with 0.4% oxybuprocaine-HCl was performed before the start of cryotherapy. An additional one-third or one quarter of the initial dose of muscle relaxant was given if needed. Manual ventilation of the lungs with air or air/oxygen mixture was maintained to keep SaO_2 85–95%. Room temperature was kept at 30–32° C and the infant was wrapped with cotton bandage and aluminium foil. Rectal temperature was kept at 37–38° C with a radiant warmer and a warming mattress. During operation 5% dextrose was infused at 4 $ml \cdot kg^{-1} \cdot hr^{-1}$. When cryotherapy was finished, the fourth twitch was observed in response to train-of-four stimulation. Muscle relaxation was reversed with 0.04 $mg \cdot kg^{-1}$ atropine and 0.1 $mg \cdot kg^{-1}$ neostigmine.

The criteria for extubation were (1) no prolonged apnoea (<15 sec) without manual stimulation; (2) $SaO_2 > 85\%$ ($FiO_2 = 0.21$), and (3) heart rate >120 bpm. When one or more of these criteria was not met, *iv* aminophylline 3 $mg \cdot kg^{-1}$ was administered. When the criteria were not fulfilled five minutes after aminophylline, arterial blood was drawn, and then calcium gluconate 0.2 $ml \cdot kg^{-1}$ was given when total plasma calcium concentration was <7 $mg \cdot dl^{-1}$ and sodium bicarbonate 0.5 $mEq \cdot kg^{-1}$ when the BE was < -5 $mEq \cdot L^{-1}$. The patients, whose condition matched the criteria and whose tracheas were extubated, were observed in the operating room for 15 min and then were transferred to the neonatal intensive care unit (NICU). When the patient did not fulfil the criteria, artificial ventilation (IMV 3–10 bpm with 3 cmH_2O PEEP) was continued after surgery in the NICU.

Data analysis

The infants were divided into two groups according to postoperative outcome: (1) extubation group: those patients whose tracheas were extubated in the operating room and who required no postoperative intubation. Some showed apnoeic episodes postoperatively and required manual stimulation with or without the administration of aminophylline. (2) Ventilation group; those patients who did not meet the criteria for tracheal extubation and had mechanical ventilation in the NICU, or those who, after initial tracheal extubation in the operating room, subsequently needed reintubation because of prolonged apnoea.

Data are expressed as the mean ± SD. Linear regression was employed for statistical analysis based on infants who required postoperative ventilation were given a value of one and those in whom the trachea was readily extubated were allocated zero. Each preoperative variable significantly related to the respiratory outcome was chosen on the basis of the correlation coefficient ($P < 0.05$). For each continuous variable, chi-square analysis with Yates' correction or Fisher's exact test was used to select a single value that maximized statistical significance while maintaining clinical usefulness. Using the selected value (e.g., birth weight = 800 g), the preoperative variables for each patient were converted to 1 (e.g., birth weight < 800 g) or 0 (birth weight ≥ 800 g) and subjected to multivariate discriminant analysis to predict which would tolerate early tracheal extubation and which would need postoperative intubation. Weighting was based on the following discriminant function that maximized the multivariate F ratio:

$$\text{Discriminant function} = K_1 \cdot X_1 + K_2 \cdot X_2 + \cdots + K_N \cdot X_N$$

where K is the weight and X is the predicting variable (1 or 0 used for each variable).

For clinical purposes, the discriminant function weights were converted to integer "point" values by multiplying them by a constant. The total "preoperative score" for each patient was then used to predict postoperative outcome. Finally, these predictions were compared with actual outcomes.

Results

The patients' mean gestation was 26.3 ± 2.3 (mean ± SD) wk and birth weight 813 ± 242 g. At operation, postconceptional and postnatal ages were 36.4 ± 1.6 wk and 71 ± 15 d, respectively, and body weight was 1585 ± 395 g (Table I). All 25 infants had preanaesthetic histories of apnoea, aminophylline therapy and mechanical ventilation after birth. Twenty infants had episodes of prolonged apnoea and 19 infants had received aminophylline seven days before operation, but without mechanical ventilation, endotracheal intubation or nasal oxygen canula.

Seventeen infants had successful tracheal extubation in the postoperative period, while eight needed postoperative intubation with ventilatory support. Four risk factors had statistically significant correlation with the need for postoperative intubation (Table I). A single value that maximized statistical significance was selected for each variable: gestational period <25 wk, birth weight <800 g, postconceptional age <37 wk, and requirement for aminophylline seven days preoperatively (Table II). Table III lists their discriminant function weights, and their clinical "point" values which were obtained in multiplying each function weight by 5.09. Using these "points," a total score was obtained for each patient. A preoperative score <12 points predicted that tracheal extubation would be readily tolerated. A score ≥12 points predicted the need for ventilatory support.

Comparing the preoperative prediction with the postoperative respiratory outcome for each infant, our model was correct for 92% of the patients (Figure). No infant was predicted incorrectly to be ready for tracheal extubation, and only two, with 14 and 21 points, were predicted to need postoperative intubation but whose tracheas were extubated in the operating room. This zone of 14 to 21 points may be considered a borderline area between those needing and those not needing postoperative ventilatory support.

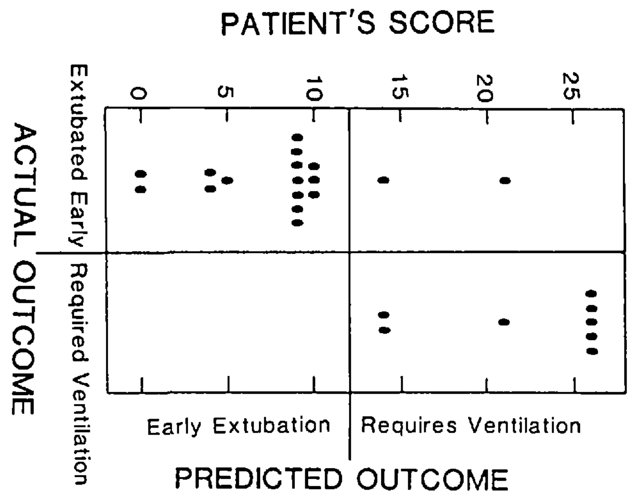

FIGURE Comparison of actual and predicted outcomes for the 25 infants based upon the four risk factors.

There was no correlation in operation times (60 ± 21 min in extubation group, 66 ± 19 min in ventilation group) with outcome (r = 0.198, NS), while anaesthesia time (152 ± 21 min in the extubation group, 93 ± 19 min in the ventilation group) was correlated with outcome (r =

TABLE I Preoperative variables for low-birth-weight infants

Preoperative variables	*Total (n = 25)*	*Outcome* *Trachea extubated (n = 17)*	*Ventilation required (n = 8)*	*Correlation coefficient (r)*
Postnatal age (d)	71 ± 15	68 ± 17	76 ± 8	0.236
Postconception (wk)	36.4 ± 1.6	36.8 ± 1.6	35.5 ± 0.9	−0.382*
Gestation (wk)	26.3 ± 2.4	27.1 ± 2.5	24.6 ± 0.6	−0.482†
Birth weight (g)	811 ± 242	894 ± 263	660 ± 51	−0.453*
Weight at operation (g)	1585 ± 394	1676 ± 408	1393 ± 273	−0.336
Preoperative blood data				
– Haemoglobin ($g \cdot dl^{-1}$)	10.9 ± 1.3	11.0 ± 1.4	10.9 ± 1.2	0.065
– Total protein ($g \cdot dl^{-1}$)	4.5 ± 0.4	4.5 ± 0.4	4.4 ± 0.5	−0.123
– Total calcium ($mg \cdot dl^{-1}$)	9.1 ± 0.4	9.0 ± 0.2	9.1 ± 0.6	0.048
Prolonged apnoea				
– Preop. episode for 7 d	20 (80.0%)	13 (76..5%)	7 (87.5%)	0.185
Aminophylline				
– Preop. therapy for 7 d	19 (76.0%)	11 (64.7%)	8 (100%)	0.385*
History				
– Patent ductus arteriosus	16 (64.9%)	11 (64.7%)	5 (62.5%)	0.021
– Neurological disease	18 (72.0%)	12 (70.6%)	6 (75.0%)	0.046
– Necrotizing enterocolitis	8 (32.0%)	6 (35.3%)	2 (25.0%)	−0.103
– Pulmonary disease	15 (60.0%)	9 (52.9%)	6 (75.0%)	0.090

*$P < 0.05$.
†$P < 0.01$.

TABLE II Univariate relations between the independent risk factors and respiratory outcome

Risk factor	*All patients*	*Outcome* *Trachea extubated*	*Ventilated*	*P**
Postconception				
<37 wk	17	10	7	NS
≥37 wk	8	7	1	
Gestation				
<25 wk	7	1	6	<0.01
≥25 wk	18	16	2	
Birth weight				
<800 g	16	8	8	<0.05
≥800 g	9	9	0	
Aminophylline preop. 7 d				
Yes	19	11	8	NS
No	6	6	0	

*Fisher's exact test.

TABLE IV Predicted respiratory outcome based upon risk factors

Score	*Prediction*
<12	Trachea may be extubated
12–26	Needs ventilation

0.511, $P < 0.001$). Anaesthesia time in the ventilation group was prolonged because of the determination of postoperative ventilatory need. Aminophylline was used in all patients of both groups. Calcium gluconate was administered to one infant in the extubation group and to two in the ventilation group, and sodium bicarbonate was given to two of the ventilation group (one infant in the ventilation group received both agents).

Discussion

It is important to enable to predict the need for postoperative intubation and mechanical ventilation in premature infants needing minor surgery which cannot be postponed until 44–46 wk postconception when the risk of postoperative apnoea is reduced.[3,4] Although several risk factors of postoperative prolonged apnoea have been reported,[1,3–7] the relative importance of each is unclear. In addition, most investigations have been performed to determine the safety limit of infantile characteristics for day-case anaesthesia. Therefore, we applied discriminant analysis to a multitude of preoperative data as Leventhal *et al.*[8] did for the prediction of postoperative ventilatory need in myasthenia gravis.

TABLE III Risk factors predicting the need for mechanical ventilation in low-birth-weight infants following operation

Preoperative factors	*Discriminant function weight*	*"Points"*
Gestation <25 wk	2.341	12
Birth weight <800 g	0.987	5
Postconception <37 wk	0.970	5
Aminophylline preop. 7 d	0.797	4
Maximum total		26

Premature infants require anaesthesia for surgery to reduce pain perception and to prevent hypertension,[7] although the dose of anaesthetic agents should be considerably reduced especially in preterm infants <32 wk gestation.[9,10] Using ketamine anaesthesia supplemented with topical anaesthesia in this study, heart rate and blood pressure showed no remarkable changes during cryotherapy. This may indicate that *iv* ketamine is adequate for premature infants under cryotherapy, while the deleterious effect of the drug was suggested in premature infants undergoing spinal anaesthesia.[11]

The present results indicate that the four risk factors – gestational period, birth weight, postconceptional age and the administration of aminophylline within seven days of surgery – may predict the need for postoperative mechanical ventilation in low-birth-weight infants. Both short gestation and low birth weight may represent prematurity of the respiratory control system at birth. On the other hand, young postconceptional age and preoperative administration of aminophylline within seven days before surgery may indicate delayed development of this system after birth. Kueth *et al.*[5] reported that the risk of postoperative apnoea for preterm infants <60 wk postconception was related to a short duration of postconception and to a history of necrotizing enterocolitis. Other investigators[3-5] also emphasized postconceptional age as a risk factor. In the present study, postconceptional age was less important than the duration of gestation. This may be explained because the postconceptional age of all our infants was less than 41 wk and they were examined in terms of the postoperative need for intubation and ventilatory support rather than postoperative apnoea. Among low-birth-weight infants with a postconception age <41 wk, the prematurity at birth would affect postoperative outcome more than does postnatal development. Thus, gestation <25 wk is the most important risk factor in predicting the need for postoperative ventilatory support. Furthermore, it may be expected that, among infants of the same postconceptional age, those with a lower gestational age have a more premature respiratory control system.

Preoperative administration of aminophylline within seven days of surgery proved to be a risk factor. Aminophylline as well as caffeine is known to stimulate the central nervous system and to prevent prolonged apnoea in preterm infants.[12,13] This administration indicates that the prematurity of the respiratory control system is severe regardless of preoperative prolonged apnoea. That is, infants requiring aminophylline therapy before operation possess a poorer respiratory control system than those requiring no drug therapy for prolonged apnoea so that the former are more susceptible to anaesthetic and surgical stress.

Surprisingly, our analysis found that pre-existing diseases such as intraventricular haemorrhage, patent ductus arteriosus, necrotizing enterocolitis and bronchopulmonary dysplasia, and preoperative laboratory data were unimportant. Such pre-existing diseases experienced by the majority of our infants may only show the presence of many immature organ systems in the past. Preoperative laboratory data had been already corrected to normal limits.

Intraoperative blood sugar concentrate, arterial gas analysis, end–expiratory fraction of carbon dioxide will be important predictors of postoperative outcome. However, blood sampling and capnography is usually difficult in extremely premature infants. The choice of anaesthetic agent, operation time, rectal temperature, etc., may also affect outcome, and the scoring system derived from both pre- and intraoperative factors would afford more accurate prediction. However, preoperative prediction is important for explanation to the patient's doctor and family.

Our scoring system may apply only to selected patients, namely those whose postconceptional age is less than 41 wk, whose weight at operation is <2500 g and who are anaesthetized with ketamine. However, its retrospective application to our infants (weight at operation <2500 g) undergoing herniorrhaphy (three cases) and cryotherapy (eight cases) with nitrous-oxide, oxygen, isoflurane anaesthesia, gave a successful prediction in ten of eleven infants. Postoperative ventilation was required in all four infants (score ≥ 12) and in one of seven infants (score <12).

The decision to extubate the trachea or mechanically ventilate the lungs is multifactorial. Our results identify those preoperative factors that seem to be most important in determining postoperative respiratory outcome. Further prospective study of these factors is necessary for complete evaluation. However, our scoring system can help the clinician focus on preoperative risk factors, and may be useful in the preoperative evaluation and postoperative management of premature infants. It can serve as an aid to the physician to identify those infants who are unable to tolerate early tracheal extubation.

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