TITLE: THE USE OF CAFFEINE IN THE PREVENTION OF POSTANESTHETIC APNEA IN PREMATURE INFANTS

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It has been well established that premature infants are at high risk for developing postoperative ventilatory dysfunction.[1] The incidence of apneic episodes is inversely correlated with gestational age and weight. Caffeine has been widely used as a respiratory stimulant in premature infants and has gained acceptance in the management of neonatal apnea.[2] This double blind, randomized, prospective study examines the possible effectiveness of caffeine in the prevention of postoperative apnea in premature infants.

Methods: Informed consent and institutional approval for the study were obtained. Premature infants (≤37 weeks gestational age) undergoing general anesthesia for minor surgery were studied. All were ≤44 weeks conceptual age at the time of surgery. Infants with cardiac, neurologic, endocrine or metabolic diseases, and patients already receiving methylxanthines were excluded. After preoperative assessment, general endotracheal inhalational anesthesia with neuromuscular blockade was administered. No barbiturates or narcotics were given. Heart rate and sounds, blood pressure, electrocardiogram, temperature, respiration and oxygen saturation were monitored. Infants were randomly divided into two groups. Group 1 received iv caffeine 5 mg/kg over a two minute period. The drug was administered immediately following induction so that its peak effect was manifested at the end of surgery. Group 2 received iv saline (controls). The solutions were supplied by the hospital pharmacy. At the completion of surgery, a venous blood sample was taken to measure caffeine level. The patient's trachea was extubated in the operating room when he was fully awake. The pattern of respiration and heart rate were monitored and recorded using a pneumogram with a magnetic tape recorder for at least 12 hours postoperatively. The recorded data was analyzed by the pulmonologists for evidence of apnea, periodic breathing and bradycardia. Brief apnea was defined as a respiratory pause < 15 seconds; prolonged (life threatening) apnea was respiratory pause ≥15 seconds or < 15 seconds if accompanied by bradycardia (40 bpm below baseline); bradycardia: Heart rate < 100 bpm for at least 5 seconds; periodic Breathing (PB): three or more periods of apnea 3-15 seconds separated by < 20 seconds of normal respiration. The difference in the incidence of apnea and/or PB between the two groups was compared using Fisher's exact test.

Results: Twenty premature infants were studied. Nine received caffeine, and 11 received saline (Table). There were no significant differences between the two groups for gestational or conceptual ages. Eight of the patients in Group 2 developed life threatening apnea and bradycardia 4-6 hrs. postoperatively. Two of these developed PB (14.5% and 24%) as well. Five of those patients had no history of apnea or bradycardia. None of the patients in Group 1 developed life threatening apnea, periodic breathing or bradycardia even though eight of them had a history of apnea. Eight patients in Group 1 had brief apnea <15 secs. None of the patients in either group required endotracheal intubation or controlled ventilation postoperatively. The difference in the incidence of life-threatening apnea with bradycardia between the two groups is statistically significant ($p < 0.002$).

Discussion: Drugs such as theophylline and caffeine have been used for the therapy of neonatal apnea.[2] We chose to use caffeine because of wider therapeutic index, ease of administration, less need for therapeutic drug monitoring, less fluctuation in plasma concentrations, and fewer peripheral effects.[2] Our data suggest that caffeine is a potentially useful drug in the prevention of postanesthetic apnea in premature infants. Although a significant reduction in the severity of apnea was noted in our study, complete abolition of apnea did not occur in all infants following caffeine treatment. It is, therefore,still recommended that all infants at risk be monitored for apnea and/or bradycardia following general anesthesia. The caffeine level achieved in this study was on the lower end of therapeutic range. Since caffeine toxicity is negligible at plasma concentrations up to 50 mg/L,[2] further studies with a higher dose of caffeine are planned to conclusively establish its efficacy.

Age, Number of Infants with Apnea, Periodic Breathing (PB) and Postoperative Ventilation in Groups 1 and 2

	Group 1 Caffeine n = 9	Group 2 Control n = 11
Gestational age wk. (mean ± SD)	29.8 ± 3	31.6 ± 3
Conceptual age wk. (mean ± SD)	40.6 ± 2	40.6 ± 2
History of pre-op apnea	8 (89%)	5 (45%)
Post-op apnea <15 sec (no bradycardia)	8 (89%)*	1 (9%)
Post-op prolonged apnea with bradycardia	none**	8 (73%)
Post-op PB >1%	none	2 (18%)
Post-op intubation or ventilation	none	none
Post-op caffeine level mg/L (range)	5-8.6	zero

*$p < 0.001$; **$p < 0.002$ (Fisher's exact test)

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1. Welborn LG, Ramirez N et al: Postanesthetic apnea and periodic breathing in infants. Anesthesiology 65:658-661, 1986.
2. Arranda JV, Grondin D et al. Pharmacologic considerations in the therapy of Neonatal apnea: Pediat Clin North Amer 28:113-133, 1981.