Selected Summaries

Nebulized Epinephrine (Adrenaline) for Postextubation Stridor

*[Nutman J, Brooks LJ, Deakins KM, et al.Race*ic *versus epinerphrine aerosol in the treatment of postextubation laryngeal edema Results from a prospective, randomized, double-blind study.* Crit Care Med 1994, 22: 1591-1594.]

To determine whether there is any advantage of using racemic epinephrine instead of the more potent and less expensive levo(l)-epinephrine (usual adrenaline solution) in the treatment of postextubation laryngeal edema, the authors conducted a prospective, dpouble-blind, randomized study, in the Pediatric Intensive Care Unit. Twenty-eight patients with stridor during the immediate postextubation period were enrolled. After extubation, patients demonstrating clinically important stridor were randomized in a double-blind fashion to receive an aerosol containing either 2.25% racemic or 1% 1-epineph-rine. Heart rate, respiratory rate, blood pressure, and stridor score were deter-mined at 20, 40 and 60 min and 4 and 6 h after the initial aerosol administration, Patients in both groups demonstrated significant reductions in stridor score after aerosol administration. No significant differences were observed between the treatment groups in improvement in stridor score or the number of subsequent aerosols required. Respiratory rate decreased significantly 40 and 60 min after 1-epinephrine but not after racemic epinephrine ($p<0.05$). No significant change in heart rate or blood pressure was observed in either group. Authors conclude that aerosolized 1-epinephrine is as effective as aerosolized racemic epinephrine in the treatment of postextubation laryngeal edema and is without additional adverse side effects.

Comments

Postextubation stridor is a common complication of endotracheal intubation. It is believed to be caused by edema of the subglottic portion of the trachea and may rapidly progress to asphyxia by obstructing the upper airway especially in small children. In 1966, Jordan(l) suggested the use of aerosolized racemic epinephrine as a treatment for patients with postextubation laryngeal edema. Commerical nonavailability of the drug however, precluded its use in many countries including ours. Commonly availabe 1-epinepherine which is 15-30 times more potent was not used due to the belief that it may cause tachycardia, hypertension, tremor and rebound vasodilatation when administered as aerosol. Now, this simple and well designed study following on the heels of a double-blind study(2) comparing use of 1-epinephrine and racemic epinephrine aerosol in treatment of laryngotracheitis (croup), clearly establishes that 1-epinephrine can be used with equal efficacy in place of racemic epinephrine without

any apprehension of significant cardiovascular side effects. In fact, 1-epinepherine aerosol administration had an added advantage in' form of a more rapid decline in respiratory rate during the first hour of study. It is noteworthy that the authors selected the doses of racemic (2.25%) and 1-epinephrine (1%) solutions to reflect the same relative potency of 1-epinephrine.

Considering that 1-epinephrine is less expensive, readily available and clinically as effective and safe as racemic epinephrine, aerosolized 1-epinephrine can be used without hesitation in the treatment of postextubation stridor.

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Recombinant Human Erythropoietin and Anemia of Prematurity

[Shannon KM, Keith JF, Mentzer VJC, Ehrenkranz RA, Brown MS, WidnessJA, et al. Recombinant human erythropoietin use in preterm infants stimulates erythropoiesis and reduces erythrocyte transfusions in very low weight. Pediatrics 1995, 95:1-8].

A multicentric randomized placebo controlled double blinded trial was designed to examine the effect of subcutaneous administration of 500 IU/kg/week of recombinant human erythropoietin (r-HuEPO) in reducing the need for erythrocyte transfusions in preterm infants. Seventy seven out of 157 randomized infants (mean gestational age at birth 26.8 ±1.6 weeks, mean birth weight 923 + 184 g, mean age at study entry 22.9 ± 10.1 days, weight at study entry 981 ± 201 g) received r-Hu Epo as scheduled for a period of 6 weeks, the treatment being initiated when their hematocrit fell below 40%. Even ventilated infants at an $Fi0_2$of <30% and a mean airway pressure of 8 cm of H_2O or less were included in the study. The other 80 preterm infants received indistinguishable placebo injection, and they were comparable to the study group in all aspects at study entry. Transfusions were given according to rigid previously set guidelines.

Overall, 43% of the treated group (33 to *77)* received no transfusions versus 31% (25 of 80) of the placebo group (p=0.18). When phlebotomy losses over

the study period did not exceed 30 ml, 58.9% (33 of 56) of the treated group were not transfused versus only 38.5% (25 of 65) in the placebo group (p=0.04). With phlebotomy losses more than 30 ml, there was a significant reduction in the number of transfusions per infant (2.6 ± 2 *vs* 4 ± 1.7, p=0.007) and in the volume of packed erythrocytes transfused (36.8 ± 31.4 ml us 53.7 ± 30 ml, p=0.01). The hematocrit at the end of study period (6 weeks) in the treated group was 32 ± 5.5 as compared to 27.3 ± 4.9% in the placebo group (p=0.0001). , Reticulocyte counts were higher at the end of study period in the study group (p=0.0001). There were no significant differences between the groups with respect to platelet counts, total or differential white cell counts. All infants had received 3 mg/kg/day oral iron from study entry. Iron levels had decreased over the study period in the treated group, the difference being more marked during the first 3 weeks of treatment. There were no significant adverse effects noticed in the treated infants during follow-up for a minimum period of 6 months.

Comments

Preterm infants of less than 1500 g birth weight are often in need of transfusions (mean=4) either to replace the blood loss occurring due to intrapartum causes and iatrogenic loss due to frequent sampling or as part of managing anemia of prematurity(l). Anemia of prematurity is characterized by low, erythropoietin levels and erythropoietin responsive circulating erythroid progenitor cells(2). Thus with the cloning of erythropoietin gene in 1985, it became a logical therapeutic option in the management of anemia of prematurity. It was believed that erythropoietin would reduce the number of transfusions and multiple donor exposure thereby bringing about a decline in the trasnfusion associated risks, in particular, the risk of transmission of viruses including non-A non-B hepatitis, hepatitis B, human immunodeficiency virus and cytomegalovirus.

The earlier studies on human erythropoietin widely differed in their study design and had smaller number of study patients and hence no conclusion could be drawn as to the optimal dose of r-Hu EPO, the age at the first dose, the frequency of administration and the length of the treatment phase(l). Before the present study there have been two large studies addressing the issue of r-Hu Epo use in the anemia of prematurity. In the multicentric non-placebo controlled blinded study by Maier *et al.,* 120 very low birth weight neonates (median age 29 weeks, median birth weight 1150 g) received subcutaneous r-Hu Epo 250 IU three times a week from day-3 onwards for a total of 17 doses(3). Oral iron supplementation (2 mg/kg/day) was administered to all the infants in the study and control groups from day-14. The study group had a reduced need for transfusion and a higher success rate (defined as absence of need for transfusion and a hematocrit that never fell below 32%), a difference that was noticed after 2 weeks of the study period. Control infants needed a mean of 1.25 transfusions each as compared with 0.87 transfusion for study infants (p=0.013). The rate of a successful outcome as defined before was 27.5% in the study group *vs* 4.1% in the control group

(p=0.008). r-Hu Epo was most beneficial in boys with birth weights of 1200 g or more and their baseline hematocrit of 48% or more. The adverse events noted with r-Hu Epo use were an increased incidence of septicemia and reduced weight gain.

In a double-blind, placebo-controlled study by Meyer *et al,* 40 very low birth weight neonates (age 30.4 ± 1.5, birth weight 1059 ± 1430 g, weight at study entry 1259 ± 168 g) received subcutane ous r-Hu Epo 200 IU/kg/dose three times a week, starting when their hematocrit fell below 35% (2-8 weeks postnatal age(4). Therefore, the study population consisted of larger growing preterm neonates in a stable condition. Study group required fewer transfusion (7 *vs* 21, p=0.002) and also had a higher mean hematocrit (32.3 *vs* 29.3, p=0.014) and absolute reticulocyte count (223 x 10^9/L vs 124.9 x $l0^9$/L; p<0.01) at the end of the study. No significant adverse events were noted except for a case of sudden infant death syndrome in the study group at 4 months of age.

The salient features in the present study are the strict transfusion guidelines that were followed and the restricted use of blood transfusions. Even the infants in the placebo group had a transfusion rate lower than that of similar infants who were not included in the study because Of parental refusal. Thus as authors point out, this study is the first rigorous demonstration that erythropoietin reduces the need for transfusion even in infants managed according to strict transfusion guidelines. Apart from erythropoietin use, the study also identified concurrent phlebotomy losses, ventilatory support, hematocrit less than 35% and birth weight less than 750g, as having an independent effect on the volume of transfusion required. Hence the authors rightly conclude that strict transfusion guidelines, minimizing phlebotomy losses and treatment with r-Hu Epo are complementary strategies for reducing the number of transfusions in very low birth weight infants. It should, however, be noted that the differences in the volume and frequency of transfusions achieved with r-Hu Epo use in this study are small and hence we may not be able to entirely avoid transfusions in small sick infants.

The questions regarding erythroppietin use that persist even after this present study are whether it will achieve the set objective of minimizing the transfusion risk (given that the risk ,of hepatitis-C and hepatitis-B following transfusion is 1 in 3300 and l in 2,00,000(5) and the cost effectiveness and risk benefit ratio; In a previous study the calculated cost of treatment was $1203 for a control infant and $1262 for a r-Hu Epo treated infant(3). However, costs and rates of complications very from country to country and in India where routine screening for cytomegalovirus and hepatitis in the donated blood is not practiced, cost-benefit ratio of r-Hu Epo remains to be evaluated.

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