Plasma Hemoglobin in Rectal or Intravenous Hydrogen Peroxide for Extrapulmonary Oxygenation

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To study plasma hemoglobin cats were given serial enemas of 0.5 and 0.25% H₂O₂ with human whole blood, single enemas of 0.5% H₂O₂ and single intravenous administration of 0.5% H₂O₂. Plasma hemoglobin levels were abnormally high in both the serial enema group and the intravenous group, while the plasma hemoglobin level was within normal range in the single enema group. Therefore a single enema of 0.5% H₂O₂ with human whole blood can be utilized with safety clinically for 60 to 75 minutes to relieve hypoxia.

At times the effective administration of oxygen to patients by inhalation methods is impossible. To combat oxygen want under these circumstances, resort to other methods of administration has been attempted. Since Oliver and Murphy (1920) first tried to treat influenza pneumonia by intravenous infusions of 0.6% H₂O₂ for the purpose of extrapulmonary oxygenation, animal studies of intravenous infusion (Lorincz, et al. 1948, Feldman, et al. 1966, Fuson, et al. 1967), intraarterial infusion (Sera, and Brennock, 1967, Urschel, et al. 1966), epicardial perfusion (Urschel, et al. 1966) and peritoneal perfusion (Urschel, et al. 1966, Morgan, et al. 1968) have been made to develop the practical use of hydrogen peroxide. However further study appears to have been abandoned, because of the formation of intravascular gas emboli in many animals and methemoglobin formation in animals having a low catalase level in their blood. Olim and Ciuti (1954) reported that a 0.75% H₂O₂ enema caused successful elimination of meconium without untoward reactions in the treatment of neonatal meconium ileus. After that the H₂O₂ enema was utilized for the treatment of meconium ileus until 1967 when Ellis and Clatworthy (1966), Shaw and Danis (1967), Danis et al. (1967), and Shaw et al. (1967) emphasized the hazardous effects such as intestinal perforation and gas bubbles in the portal vein when a H₂O₂ enema higher than 0.75% was used. Since 1969 Yun and his colleagues (Yun, 1969, Baik 1970, Kim, 1971 Lee, 1972, Chun, 1973, Kim, 1975, Lee and Yun, 1976) have attempted to determine the safe margins for a H₂O₂ enema to increase maximal arterial oxygen tension without forming portal vein gas emboli, methemoglobinemia or other harmful effects in various animals and human beings. They found that a single enema of 0.5% H₂O₂ (10 ml/kg) with

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human whole blood (1 ml/kg) could be used to increase the arterial oxygen partial pressure with safety in both animals and human beings.

We therefore have also studied the effect of giving serially $\text{H}_2\text{O}_2$ enemas with human whole blood to discover a possible safe prolonged utilization of this procedure.

**MATERIALS AND METHODS**

Cats were selected for this study because the amount of cat blood catalase was closest to although slightly less than that of human whole blood.

**Group 1.**

Ten adult cats of either sex, fasted for more than 12 hours, were given glycerin enemas. Under general anesthesia by seconal (30 mg/kg) intraperitoneally, the right femoral artery was exposed and a polyethylene tube was inserted and fixed by suture for easy blood sampling. A long rectal tube was inserted for exchanging enemas and another long rectal tube having a balloon tip was also inserted in order to check the bowel pressure (Deller, and Wangel, 1964). This also was sutured at the anus to prevent leakage after enemas. Tracheostomy was performed and a cannula was connected to a respirator (Model 607, Harvard Apparatus Co.) to control the respiratory rate and tidal volume. Respiration was made with room air first, and then with hypoxic gas of 10% oxygen in 90% nitrogen, continued until the termination of the experiments. Blood samples were drawn from a femoral artery during room air breathing, hypoxic gas breathing, 10 minutes after the first enema, (1 ml/kg of human whole blood followed by 0.5% $\text{H}_2\text{O}_2$ saline solution, 10 ml/kg) and 1 hour after the first enema. At this time intestinal contents were evacuated by a syringe and a new enema of the same content was given. After this blood samples were done with exchange enemas of new blood and $\text{H}_2\text{O}_2$ every 1 hour for 8 hours. The pH, $\text{P}_2$ and $\text{Pco}_2$ of the arterial blood were measured with Astrup’s Radiometer (Astrup, et al. 1960), bowel pressure was checked at the same time by the Deller and Wangel method (Deller, and Wangel, 1964), and plasma hemoglobin with the Crosby and Furth method (Crosby, and Furth, 1956).

**Group 2.**

Five adult cats of either sex were used. The procedure was the same as in group 1 except 0.25% $\text{H}_2\text{O}_2$ was used instead of 0.5% $\text{H}_2\text{O}_2$. In this group, only $\text{PO}_2$ and plasma hemoglobin of arterial blood were measured.

**Group 3.**

Five adult cats of either sex were used. Under general anesthesia as described in group 1, a single enema of 0.5% $\text{H}_2\text{O}_2$ solution with human whole blood was given. Intravenous blood sampling was done every hour to check the plasma hemoglobin level only.

**Group 4.**

Five adult cats of either sex were used. 0.5% $\text{H}_2\text{O}_2$ saline (10 ml/kg) was given intravenously to each cat for 75 minutes. Venous blood samplings were done at room air respiration, 10 minutes, 1 hour, 2, 3, 4, 5, 6, 7 and 8 hours after starting the I.V. injection to check only the plasma hemoglobin level.
Group 5.
RBC fragility tests with human, RBC and cat RBC in H$_2$O$_2$ saline solution were performed. Five blood samples of different humans and cats were used for this study.

RESULTS

Group 1.
0.5% H$_2$O$_2$ serial administration group. The results are summarized in Fig. 1. Arterial oxygen pressure returned to normal 5 hours after the procedure Visible redness of plasma was noted in 2~4 hours. Measured plasma hemoglobin, shown in Fig. 1, ranged from 8 mg/dl with the room air respiration to 170 mg/dl after 7 exchanges of enema. Plasma hemoglobin rapidly increased 2 hours after the procedure. Bowel pressure was increased after the H$_2$O$_2$ enema up to 2 to 3 times normal, but did not increase when the exchanging enema was repeated. Pco$_2$ and pH were both within normal limits up to 8 hours in this study. Observation in one cat for 24 hours with this repeated procedure revealed pH to be below 7.0, Pco$_2$ 36~50 mmHg, Po$_2$ 120 mmHg, plasma hemoglobin 378 mg/dl and bowel pressure 2 mmHg at the end.

Group 2.
0.25% H$_2$O$_2$ serial administration group. The Po$_2$ level in this group was restored to normal 6 hours after the procedure and then was maintained above normal (Fig. 2). Plasma hemoglobin in this study was also increased from 7 mg/dl with room air respiration to 82 mg/dl 8 hours after the procedure. Plasma hemoglobin in this study was about one half of that in group 1.

Fig. 1. Changes of Po$_2$, plasma hemoglobin, bowel pressure, Pco$_2$ and pH in arterial blood following the serial enema of 0.5% hydrogen peroxide solution with human whole blood.

Fig. 2. Changes of Po$_2$ and plasma hemoglobin in arterial blood following the serial enema of 0.25% hydrogen peroxide solution with human whole blood.
Group 3.

0.5% \( \text{H}_2\text{O}_2 \), single enema group. Plasma hemoglobin levels in this study revealed a rather constant curve below 15 mg/dl without showing redness of plasma in any.

Group 4.

0.5% \( \text{H}_2\text{O}_2 \) solution, single intravenous administration group. As shown in Fig. 4, plasma hemoglobin levels in this study gave a straight line increase up to 180 mg/dl in 8 hours, showing redness of plasma 1 hour after injection.

Group 5.

RBC fragility test with \( \text{H}_2\text{O}_2 \) saline solution. In cats, hemolysis began with a 0.025% \(-0.0375\% \text{H}_2\text{O}_2 \) solution and was completed with a 0.1125% \(-0.125\% \text{ solution. In human whole blood, hemolysis began at 0.05\% \(-0.06\% \) and was completed a 0.1125\(-0.135\% \.}

**DISCUSSION**

In cyanotic congenital heart diseases, hyaline membrane disease in the newborn and other pulmonary insufficiencies, gas exchange may be almost impossible in the alveola. It was our desire to find an effective, safe and simple procedure for extrapulmonary oxygenation. The use of \( \text{H}_2\text{O}_2 \) enema has been promising in spite of the hazards with high concentrations reported by some (Lorincz, et al. 1948, Olin, and Ciuti, 1954, Feldman, et al. 1966, Urschel, et al. 1966, Ellis, and Clatworthy, 1966, Fuson, et al. 1967, Stern, and Brennock, 1967, Morgan, et al. 1968). Yun (1969) attempted intestinal perfusion of 0.4% \( \text{H}_2\text{O}_2 \) solution with a preceding enema of human whole blood in dogs and found maximum oxygenation in both the portal vein and inferior vena cava without formation of gas emboli. Human whole blood is a good source of catalase and peroxidase. Therefore, Painker and Iyer (1965) stated that there should
be no problem of causing methemoglobinemia by giving H₂O₂ solution to human beings. The authors first observed that this procedure could be used for the treatment of asphyxia neonatorum. Newborn babies do not have bacteria which contain catalase in their intestines, so an enema of human whole blood is essential to decompose H₂O₂. Baik (1970) proved that a single enema of 0.75% H₂O₂ did not produce any microscopic change of the liver and intestine in rabbits. Kim (1971) found marked increase of P₀₂ in arterial blood in artificially hypoxic cats when a human whole blood enema was followed by a single enema of 0.5% H₂O₂ solution for 85 minutes. Lee (1972) has indicated that intravenous H₂O₂ injection was dangerous, due to the formation of oxygen emboli, but an enema with H₂O₂, especially with human whole blood, could be used safely with little effect on methemoglobin formation. He also observed marked elevation of methemoglobin in dogs and a slight elevation in cats and rabbits after intravenous H₂O₂ injection, but not after H₂O₂ enema. There was slight elevation of methemoglobin in dogs after H₂O₂ enema only, but not after an enema of H₂O₂ with human whole blood. Chun (1973) studied various catalyst materials and found that human whole blood was superior in raising the P₀₂ level in arterial blood. Lee and Yun (1976) studied the change of oxygenation and bowel pressure from H₂O₂ enema in cats and found that a single enema of 0.5% H₂O₂ solution with human whole blood was most adequate for practical use. Bowel pressures when using 3~4% H₂O₂ solution were over 200 mmHg, which could be the explanation of intestinal necrosis or perforation due to disturbance of blood circulation observed by Ellis and Clatworthy (1966), Danis et al. (1967), Shaw and Danis (1967). Kim (1975) has investigated a single enema of 0.5% H₂O₂, with a preceding enema of human whole blood, using a specific balloon catheter (Fig. 5) on 18 cases of cyanotic congenital heart diseases and 2 cases of overwhelming staphylococcal pneumonia in coma while on oxygen inhalation. He noted lips, finger tips and toes tips of all cases became red and the comatose-pneumonia cases became clear mentally and could talk for a few hours after the enema, with adequate raising of arterial P₀₂ in all cases.

The present investigation studied the effect of 0.5% H₂O₂ by serial enemas in hypoxic cats to find the possibility of prolonged use of this procedure. The authors found visible hemolysis after 3 hours in the first cat. Therefore the plasma hemoglobin was measured, and it became gradually higher as the experiment proceeded. The group 2 study was attempted using a 0.25% H₂O₂ solution. In spite of satisfactory elevation of arterial P₀₂, plasma hemoglobin level was still high after 3 hours of the procedure. To see if a single enema of 0.5% H₂O₂ with human whole blood would cause increase in plasma hemoglobin,
the group 3 investigation was performed. There was slight elevation of plasma hemoglobin 1 hour after the enema, still within normal limits (<15 mg/dl). With a single intravenous infusion of 0.5% H$_2$O$_2$ for 75 minutes, in group 4 plasma hemoglobin increased rapidly up to 186 mg/dl after 8 hours.

Thus it is tentatively indicated that serial enemas of H$_2$O$_2$ solution either 0.5% or 0.25% and intravenous infusions of 0.5% H$_2$O$_2$ solution can not be used clinically because of hemolysis, whether this hemolysis is due to absorbed H$_2$O$_2$ or to absorbed nascent oxygen. What lower concentration of H$_2$O$_2$ solution serial enema would not increase plasma hemoglobin in spite of raising arterial P$_O_2$ for clinical use is still not solved. It is suggested that a single preceding enema of human whole blood (1 ml/kg) followed by a 0.5% H$_2$O$_2$ solution (10 ml/kg) enema can be used clinically for the treatment of apneumia neonatorum in the countryside of underdeveloped countries where oxygen inhalation is not available, for cyanotic attacks in congenital heart diseases and for pulmonary insufficiency when oxygen inhalation will not relieve cyanosis and during cardiac surgery with temporary extrapulmonary oxygenation.

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REFERENCES


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