Extrapulmonary Oxygenation by Giving Hydrogen Peroxide by Enema

Duk Jin Yun

Department of Pediatrics
Yonsei University College of Medicine, Seoul, Korea

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ABSTRACT

An investigation of extrapulmonary oxygenation was made in dogs, rabbits and, finally, in a case of Tetralogy of Fallot using an intestinal perfusion of hydrogen peroxide (H₂O₂).

For a single administration, 0.4 per cent H₂O₂ can be given safely by enema, in doses of 10 ml./Kg. of body weight, this would give maximum oxygenation in both the portal vein and inferior vena cava without the formation of gas emboli. Concentrations higher than this caused gas bubbles in the portal vein. For serial administrations, 0.2 per cent H₂O₂ can be given by enema exchanging the intestinal contents at 10 to 15 minutes intervals. When given concomitantly with human whole blood, 1.0 ml./Kg. of body weight, there is a prolonged higher oxygenation in the portal vein, inferior vena cava and femoral artery. This concentration of H₂O₂ would not cause gas emboli in the portal vein. Although extrapulmonary oxygenation is possible by giving oxygen by enema, this method would cause too much abdominal distension. In experiments of death by suffocation, the group given H₂O₂ had doubled the duration of E.K.G. activity when compared with controls.

One patient with Tetralogy of Fallot, confirmed by clinical findings, X-ray studies, E.K.G. and cardiac catheterization, who was not suitable for cardiac surgery because of low mentality, was selected for this study. 0.2 per cent H₂O₂, 10 ml. per Kg. of body weight by enema, exchanging intestinal contents at 30 minutes intervals, resulted in a marked elevation of the pO₂ in the venous blood and in the inferior vena cava. There was a disappearance of finger tip and toe tip cyanosis and flushing of the soles and palms was noted during the procedure.

INTRODUCTION

Since Oliver and Murphy (1920) first administered H₂O₂ intravenously for the treatment of influenza pneumonia, attempts have been made to use parenterally administered hydrogen peroxide (H₂O₂) as a source of oxygen both in humans and in animals. Lorincz et al. (1948), investigating the therapeutic value of H₂O₂ given in dilute solution and infused in the veins of laboratory animals, concluded it was of little therapeutic value because of the formation of oxygen emboli. Cats with ventilatory arrest have been maintained up to one hour with an intra-arterial infusion of 3 per cent H₂O₂ (1966). Stern et al. (1967) have investigated the effect of the continuous intravenous H₂O₂ infusion using concentration of 6, 3 and 1.5 per cent H₂O₂ with either 6 per cent Dextran in saline or 5 per cent glucose as the diluent. In dogs there were massive emboli during the course of the infusion.
but not so in cats. Since Olim et al. (1964) described its use in two cases of meconium ileus, H₂O₂ has been used for the treatment of neonatal intestinal obstruction due to inspissated meconium. Shaw et al. (1967), however, observed intestinal gangrene in a newborn infant following colonic lavage with H₂O₂ during the surgical treatment of meconium ileus. They emphasized that this potentially dangerous practice should be abandoned. Although intravenous H₂O₂ has been demonstrated to supply up to 50 per cent of the oxygen consumption in pigs, this method produced a severe methemoglobinemia in all animals (1967 Fuson, et al.). H₂O₂ has been used as an adjunct for cardiac resuscitation and was reported to be somewhat effective by Ushel et al. (1966). Recently, Morgan et al. (1968) have investigated the effectiveness of the intraperitoneal administration of 0.5 per cent H₂O₂ in hypoxic rabbits as a possible method of oxygen supplementation in respiratory distress syndrome or in the postoperative cardiac patient. Although initially H₂O₂ caused a slight increase in arterial oxygen saturation, this increase was brief and was followed by a marked fall in arterial oxygen saturation. Hypotension was also observed in all rabbits, therefore they suggested that the intra-peritoneal administration of H₂O₂ for the purpose of extrapulmonary oxygenation was ineffective and hazardous and emphasized that it should not be attempted in the human subject.

We have investigated the effect of giving H₂O₂ enemas in various concentrations to find out the highest concentration not producing gas emboli in the portal vein and yet giving the highest oxygen concentration in both the portal vein and the inferior vena cava in dogs. The result of our finding was utilized to increase the oxygen in a patient Tetralogy of Fallot.

MATERIALS AND METHODS

Adult dogs of either sex were used and fasted for more than 12 hours prior to the administration of a glycerin enema. Under general anesthesia with intravenous seconal (30 mg./Kg. of body weight), the abdomen was opened and a polyethylene tube (Gauge No. 18) was inserted into the inferior vena cava so that the tip was placed beyond the hepatic vein and close to the right atrium, another polyethylene tube was inserted into the portal vein and both tubes were fixed with purse-string suture for easy blood sampling. As an anticoagulant heparin was injected into the inferior vena cava (IVC) in dose of 2,000 units per Kg. of body weight. Heparinized syringes were used for drawing blood.

A long rectal tube was inserted until the tip entered the small intestine. The tube was clamped and fixed at the anus using a purse-string suture to prevent the leakage from the rectum of the diluted H₂O₂ solution or of physiologic saline solution. H₂O₂ was diluted with physiologic saline solution. After removal of the blood sample a piece of gum or soft plastic was put on the tip of the needle to prevent any contact of the drawn blood with air. pO₂, pCO₂ and pH were measured with Astrup's "Radiometer" (1960) and hematocrit was measured in each sample. Pulse rate and respiration rate were also checked at the time of each sampling.

The following steps were taken in this experiment:

1. Single administration group; used a single dose of 10 ml./Kg. of body weight in various concentrations of H₂O₂. Two control dogs received the same amount of physiologic saline solution only. Blood sampling was done once before the first enema and at 10 to 15 minute intervals after the enema for 100 to 110 minutes.

2. Serial administration group; Used multiple doses of 10 ml./Kg. of body weight in various concentrations of H₂O₂ solution by exchanging intestinal content mixture with a new enema at 10 to 15 minutes intervals. Two control dogs were given only normal saline solution using the same method.

3. Serial administration group-H₂O₂ plus human whole blood; used dosed 10 ml./Kg. of body weight (0.2 per cent H₂O₂ solution) followed by whole
blood enema (1.0 ml./Kg. of body weight) by the same method as described above. (Step 2). In this study, three dogs were used for the regular experiment and two dogs were used for the study of methaemoglobin in the blood after elevation of the pO₂ in the portal vein (PV), IVC and femoral artery (FA). The first sample was the control.

4. Oxygen administration group: oxygen was given single time in one sampling and several times in another. Two control dogs were given air only in approximately same amount as the oxygen. Blood sampling was done at the same intervals and for the same period as described above.

5. Experiment on the duration of suffocation death: rabbits were used without regard of sex, and were divided into two groups: Group I: 10 rabbits were given 0.4 per cent solution, 10 ml./Kg. of body weight, under general anesthesia with secunal. A single administration of H₂O₂ was given by enema into the small intestine. The animals were sacrificed 5 minutes after giving H₂O₂. Group II: 10 rabbits were used as untreated controls. The above two groups were observed until the heart sounds were inaudible to a stethoscope, and until complete E.K.G. death had occurred. The duration of suffocation was noted. For this experiment, the rabbits were placed on an "X" board. By puncturing needles E.K.G. electrodes were placed on the extremities. Suffocation was carried out by putting the rabbit's nose and mouth into a bowl of water.

6. A case study using a patient with Tetralogy of Fallot; exercise test, pO₂, pCO₂, pH and hematocrit (Hct.) were measured before and after giving 0.2 per cent H₂O₂ solution by enema with a dose of 10 ml./Kg. of body weight, exchanging the intestinal contents at 30 minutes intervals. Whole blood (1.0 ml./Kg. of body weight) was given prior to the administration of H₂O₂ solution by enema.

RESULTS

1. Single administration group:
In two control dogs, there was no change in pO₂ level in any blood sampling from the portal vein (PV), inferior vena cava (IVC) or from a mesenteric artery (MA) before and after giving normal

![Graph showing blood pressure changes](image)

**Fig. 1.** No gas bubbles were observed in the portal vein. A marked decrease of pO₂ in both portal vein and inferior vena cava is noted following the remarkable elevation of pO₂ in this dog which evacuated the large intestinal contents after the preoperative glycerin enema.
saline solution. However, a slight decrease in pCO₂ in both PV and IVC at the end of the experiment, and a little increase in Hct. was noted as the time passed. The following concentrations of 0.005 per cent, 0.025 per cent 0.05 per cent, 0.1 per cent, 0.2 per cent, 0.3 per cent, 0.4 per cent and 0.5 per cent H₂O₂ solution were used in experiments on two dogs. In the 0.005 per cent group, there was no difference between this group and controls. It was noted that pO₂ was increased in both PV and IVC from 20 to 90 minutes after the administration of 0.025 per cent to 0.5 per cent H₂O₂ solution. The lower the concentrations of hydrogen peroxide, the shorter was the duration of elevation in pO₂ above the control (the value of pO₂ before giving the H₂O₂ solution). It was also noted that dogs which did not pass a stool after the preoperative glycerin enema maintained higher pO₂ levels for a longer period than dogs which passed a stool after the glycerin enema. The latter dogs had a tendency to rapid decrease of the pO₂ in both PV and IVC, or a remarkable decrease of pO₂ at the end period of the experiment irrespective of concentrations of H₂O₂ used. These are illustrated in Fig. 1 and 2. It was also noted that even though the pO₂ in both PV and IVC declined with time, the pO₂ in mesenteric arterial blood (MAB) increased. It was noted that pCO₂ in PV, IVC and MAB were generally decreased slightly with time. However, the pH were stable through the whole experiment and Hct. were slightly increased with time. It was also noted that gas bubbles were not observed using the concentrations of H₂O₂ less than 0.4 per cent in PV. Gas bubbles were observed in 0.5 per cent H₂O₂ solution in PV even though the pO₂ in PV had dropped below the control level (Fig. 2).

2. Serial administration group:

In two control dogs, there were no changes in pO₂ in PV, IVC and femoral artery (FAB) blood samples before and after giving normal saline solution by enema. However a slight decrease in pCO₂ in PV, IVC and FAB a little increase in Hct. were noted as time passed. These results were not related to having the dogs evacuate their enemas. In this experiment, the following concentrations, 0.4 per cent, 0.3 per cent, 0.2 per cent, 0.1 per cent and 0.25 per cent H₂O₂ solution, were used. Two dogs were experimental subjects. This study demonstrated that the pO₂ level in PV and IVC was constantly elevated. Concentrations of H₂O₂ higher than 0.25 per cent caused microgas bubbles in the PV after the several exchanges regardless.

Fig. 2. Microbubbles were observed in the portal vein. The pO₂ became even lower than that of the control. This is the dog which passed the stool well after the glycerin enema. Small circles above the PV line denote the presence of gas bubbles.
of the level of pO₂ in PV. There were no microgas-bubbles in the PV with concentrations of H₂O₂ 0.2 per cent and 0.1 per cent regardless of the level of pO₂ in the PV. (Fig. 3 and 4). The common findings observed in this study were that pCO₂ values in PV, IVC and FAB were mildly decreased in all cases, pH were not changed and the Hct. were slightly increased as time passed. pO₂ levels in PV and IVC were not constantly higher than those of the controls, a finding which had been expected. In many cases elevated pO₂ level in the first part of experiment decreased and then sometimes dropped lower than the control level. This occurred in spite of giving fresh H₂O₂ solutions continuously at 10 to 15 minutes intervals by exchanging the intestinal contents. In this experiment, the intestinal contents become clearer as the exchange of the contents had been repeated. Elevation of the pO₂ was not expected in PV and IVC. However in all cases, pO₂ in FAB was steadily increased with time.

3. Serial administration of 0.2 per cent H₂O₂ solution plus the addition of human whole blood:

Three dogs were used. The results are summarized in Fig. 5. Line curves were made using the arithmetic average of data from 3 dogs over the same sampling period. However, the curves were smooth showing higher levels of pO₂ in the test dogs than the control blood samples from PV, IVC and FAB. No microbubbles of gas were observed in the PV in any of the three dogs used for these experiment. pCO₂ in PV, IVC and FAB declined somewhat as time passed; Hct. appeared unchanged.

Methaemoglobin was measured from the blood of IVC in two dogs given 0.2 per cent H₂O₂ solution with human whole blood and in one dog given only normal saline solution in the same manner for controls. Blood sampling were performed before the enema, and 45 and 90 minutes after the enema. The results are shown in Table 1.

Table 1. Methaemoglobin level by giving 0.2 per cent H₂O₂ solution with human whole blood by enema with control dog

<table>
<thead>
<tr>
<th>Sort of solution given</th>
<th>Met Hb level before enema (mgm/dl)</th>
<th>45 minutes after enema (mgm/dl)</th>
<th>90 minutes after enema (mgm/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.85% NaCl solution</td>
<td>0</td>
<td>60</td>
<td>600</td>
</tr>
<tr>
<td>Human blood plus 0.2% H₂O₂ solution</td>
<td>780</td>
<td>660</td>
<td>500</td>
</tr>
<tr>
<td>Human blood plus 0.2% H₂O₂ solution</td>
<td>640</td>
<td>555</td>
<td>530</td>
</tr>
</tbody>
</table>
4. Oxygen administration group:

In two control dogs given air, there was no change in pO₂ in PV, IVC and FAB before or after giving air enemas. There were decreases in pCO₂ in PV, IVC and FAB and a little increase in Hct. were noted as time passed. In this experiment, two dogs were used—one for a single and the other for multiple administrations of oxygen. Since the exact amount of oxygen given could not be measured with our equipment, oxygen was given so that the distended intestines were easily visible above the abdominal wall. In the single dose group pO₂ in PV and IVC maintained higher levels than the controls for a long periods ranging from 50 to 60 minutes and from 75 to 90 minutes respectively. One of the examples is shown in Fig. 6. The highest pO₂ was reached 20 minutes after giving oxygen. pO₂ in FAB showed slight higher level than the control. In the multiple administration group, it was noted that pO₂ in PV and IVC were increased as the 2nd and 3rd administration were done. Common findings observed in this study were that there were no gas microbubbles seen in any dogs in PV. pCO₂ in PV, IVC and FAB steadily decreased and the Hct. were mildly increased with time. The pH was unchanged, and pO₂ in FAB was mildly increased with time. However, these changes were not as much as those seen in dogs receiving with H₂O₂ solution.

5. Study on suffocation death:

The group I: The average time from suffocation until the absence of an audible heart beat by the stethoscope was 4 minutes and 36 seconds ranging from 3 minutes 50 seconds to 5 minutes 10 seconds. The time from suffocation to electrocardiographic death was 21 minutes and 35 seconds ranged from 12 minutes 30 seconds to 28 minutes 10 seconds. One of the examples is illustrated in Fig. 7.

The group II: control group: the average interval to the disappearance of the heart beat was 4 minutes and 9 seconds ranging from 3 minutes 20 seconds to 4 minutes 50 seconds; and to E.K.G. death was 10 minutes and 9 seconds, ranging from 7 minutes 20 seconds to 11 minutes 10 seconds. One of the control group is illustrated in Fig. 8.

6. A case study using a patient with Tetralogy of Fallot:

This seven year old male orphan (Y.I.B.) was admitted to the pediatric ward of Severance Hospital with the chief complaints of exertional dyspnea, clubbing of the fingers and toes, and marked cyanosis since infancy. He had frequent upper respiratory
Fig. 5. No gas bubbles were observed in the portal vein in any dog at this concentration of hydrogen peroxide even though the levels of pO₂ remained higher than those of any other experiment.

infections. No other history was available. Physical examination revealed that a poorly developed child with a body weight of 15.8 Kg, height 106.5 cm. These are on the tenth percentile of the Korean standard growth curve (1967 Korean Pediatric Association). His skin was dusky, lips were cyanotic and eyelids were puffy. There was no distention of neck veins, lungs were clear. A grade three harsh systolic murmur was heard in the third and fourth intercostal spaces along the left sternal border. The murmur was transmitted to the pulmonary area. The pulmonary second sound was single. The abdomen was slightly distended. The liver was palpable 2 cm. below the right costal margin. The spleen was not palpable and the femoral pulses were present. There was no pitting edema on the legs, and the neurological examination was normal except for a marked mental retardation. Blood pressure on admission was 110/95. Laboratory examination revealed a hemoglobin of 16.8 Gm/dl. The erythrocyte count was 6.5 million/ cumm., white blood cell 9,500/Cu.mm. with segmented neutrophiles 45 per cent, lymphocytes 46 per cent, monocytes 6 per cent, eosinophils 3 per cent, hematocrit 58 per cent. Urinalysis was normal. Bleeding and coagulation times were within normal limits. Prothrombin time was 14 seconds or 100 per cent. Platelet count was 220,000/cu.mm. Chest X-ray and cardiac series showed a boot shaped heart with a markedly concave pulmonary conus and decreased lung markings. E.K.G. showed a right axis deviation with right ventricular hypertrophy. Cardiac catheterization confirmed the diagnosis of Tetralogy of Fallot with high pressure in the right ventricle (119/0/8.9), right atrium (15.6/8), fairly low pressure in the pulmonary artery (22.1/14.2) and low oxygen saturation in the femoral artery (8.44 vol. per cent). Blood flow was calculated at 9.75 L./minute in systemic flow; pulmonary flow 2.91 L./minute; shunt flow: right to left 75.6 per cent of systemic flow; left to right 15.1 per cent of pulmonary flow. It was decided, because of his poor mentality, he was not suitable for cardiac surgery. The following tests were performed.

A) Exercise test:
The following exercise tests were done. He ran a 550 meter distance while being supported by an assistant. The pulse rate, respiration rate and E.K.G.
Fig. 6. A single administration of oxygen showing higher level in $pO_2$ in both the portal vein and inferior vena cava lasting over a period of time.

were measured before and after the exercise. Three exercise tests were done. Two times of three were done in ordinarly states and once of three was done with putting in 0.2 per cent $H_2O_2$ solution, 10 ml/Kg of body weight by enema in five minutes before the exercise test. The results revealed no differences between the both tests.

B) Control blood sampling at 15 minutes interval:

Under sedation with sodium phenobarital 100 mg, demerol 50 mg and sodium amytal 300 mg intramuscularly, blood samples were removed from the left branchial artery and the left branchial vein at 15 minutes intervals. $pO_2$, $pCO_2$, pH and Hct. were measured. The results are shown in Table 2 and Fig. 9. There were no specific differences in $pO_2$, $pCO_2$, pH and Hct in blood from the vein and artery.

C) Blood sampling following the administration of an enema
solution of 0.2 per cent H₂O₂ (10 ml/Kg of body weight) plus human whole blood (1.0 ml/Kg of body weight)-serial administration at 30 minute intervals.

Table 2. pO₂, pCO₂, pH and Hct. in blood of brachial vein and artery in a case of Tetralogy of Fallot

<table>
<thead>
<tr>
<th>pH</th>
<th>pO₂*</th>
<th>pCO₂*</th>
<th>Hct. (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.20</td>
<td>49.9</td>
<td>50.0</td>
<td>53.4</td>
<td>Venous blood, at 2:20 P.M.</td>
</tr>
<tr>
<td>7.25</td>
<td>46.1</td>
<td>47.1</td>
<td>54.0</td>
<td>Venous blood, at 3:35 P.M.</td>
</tr>
<tr>
<td>7.24</td>
<td>62.8</td>
<td>43.5</td>
<td>53.8</td>
<td>Arterial blood, at 2:20 P.M.</td>
</tr>
<tr>
<td>7.23</td>
<td>59.2</td>
<td>41.1</td>
<td>53.5</td>
<td>Arterial blood, at 3:35 P.M.</td>
</tr>
</tbody>
</table>

* expressed in mm Hg

Table 3. pO₂, pCO₂, pH and Hct. in venous blood following an enema of 0.2 per cent H₂O₂ solution

<table>
<thead>
<tr>
<th>pH</th>
<th>pO₂ (mm Hg)</th>
<th>pCO₂ (mm Hg)</th>
<th>Hct. (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.15</td>
<td>48.5</td>
<td>53.5</td>
<td>53.5</td>
<td>6:37 P.M. before H₂O₂ enema</td>
</tr>
<tr>
<td></td>
<td>6:40 P.M., 0.2 per cent H₂O₂ solution* 160 ml in.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.16</td>
<td>68.1</td>
<td>51.7</td>
<td>52.2</td>
<td>6:55 P.M. blood sampling</td>
</tr>
<tr>
<td></td>
<td>7:10 P.M. exchange the intest. contents with 16ml of whole blood and 0.2 per cent H₂O₂ sol. 160 ml enema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.17</td>
<td>64.3</td>
<td>50.0</td>
<td>52.5</td>
<td>7:25 P.M. blood sampling</td>
</tr>
<tr>
<td></td>
<td>7:40 P.M. exchange the intest. contents with 16 ml of whole blood and 0.2 per cent H₂O₂ solution 160ml enema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.21</td>
<td>60.0</td>
<td>45.7</td>
<td>53.4</td>
<td>7:55 P.M. blood sampling</td>
</tr>
</tbody>
</table>

* pH of H₂O₂ solution used was 6.6

The next day he was brought to the operating room of the cardiopulmonary laboratory where the following procedure and blood sampling were done. Under deep sedation with the above described method, the right brachial artery and vein were exposed and a catheter was introduced into the inferior vena cava through the right brachial vein and a needle inserted into the right brachial artery. Blood sampling was done from the IVC, right brachial artery and left brachial vein before giving the H₂O₂ enema as a control. pO₂, pCO₂, pH and Hct. were measured in each sample. Immediately
after the above blood sampling; 0.2 per cent $H_2O_2$ solution, 160 ml. was given by enema; 15 minutes later a second sampling was done; 13 minutes after this the intestinal contents were aspirated; 2 minutes later 16 ml of human whole blood was given by enema followed by a second enema of 0.2 per cent $H_2O_2$ 160ml. Fifteen minutes later, a third sampling was done and the procedure repeated once more. The results are as follows:

a) $pO_2$, $pCO_2$, pH and Hct. in the venous blood is shown in Table 3 and Fig. 10.

$pO_2$ level was markedly increased and $pCO_2$ decreased. After the first administration of $H_2O_2$ the cyanosis of the patient’s fingers and toes completely disappeared. His soles and palms became flushed.

b) $pO_2$, $pCO_2$, pH and Hct. in blood samples from the IVC is shown in Table 4 and Fig. 11, which reveal the $pO_2$ level was markedly increased 15 minutes after treatment, $pCO_2$ decreased, and the pH and Hct. values appear unchanged.

c) $pO_2$, $pCO_2$, pH and Hct. in arterial blood are shown in Table 5 and Fig. 12, which reveal the $pO_2$ was elevated, as compared with the control

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**Table 4.** $pO_2$, $pCO_2$, pH and Hct. in blood samples from the inferior vena cava

<table>
<thead>
<tr>
<th>pH</th>
<th>$pO_2$ (mm Hg)</th>
<th>$pCO_2$ (mm Hg)</th>
<th>Hct (°)</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| 7.17| 52.1           | 53.0            | 53.0    | 6:37 P.M. blood sampling before $H_2O_2$ enema.  
|     |                |                 |         | 6:40 P.M. 16ml whole blood plus 0.2 per cent $H_2O_2$ solution 160ml enema |
| 7.20| 65.1           | 51.7            | 52.2    | 6:56 P.M. blood sampling |
|     |                |                 |         | 7:10 P.M. exchange the intestinal contents with 16ml of whole blood and 0.2 per cent $H_2O_2$ sol. 160ml in. |
| 7.18| 59.0           | 49.9            | 52.8    | 7:25 P.M. blood sampling |
|     |                |                 |         | 7:40 P.M. exchange the intestinal contents with 16ml of whole blood and 0.2 percent $H_2O_2$ sol. 160ml enema |
| 7.19| 57.2           | 47.2            | 53.8    | 7:55 P.M. blood sampling |
Table 5.  \( \text{pO}_2, \text{pCO}_2, \text{pH} \) and Hct. in arterial blood

<table>
<thead>
<tr>
<th>pH</th>
<th>( \text{pO}_2 ) (mm Hg)</th>
<th>( \text{pCO}_2 ) (mm Hg)</th>
<th>Hct. (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.28</td>
<td>68.9</td>
<td>46.5</td>
<td>54.0</td>
<td>6:37 P.M. blood sampling before ( \text{H}_2\text{O}_2 ) enema</td>
</tr>
<tr>
<td>7.18</td>
<td>74.2</td>
<td>42.1</td>
<td>53.5</td>
<td>6:55 P.M. blood sampling</td>
</tr>
<tr>
<td>7.19</td>
<td>70.1</td>
<td>44.3</td>
<td>53.5</td>
<td>7:10 P.M. exchange the intestinal contents with 16 ml of whole blood and 0.2 per cent ( \text{H}_2\text{O}_2 ) sol. enema</td>
</tr>
<tr>
<td>7.19</td>
<td>69.3</td>
<td>45.0</td>
<td>53.8</td>
<td>7:25 P.M. blood sampling.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7:40 P.M. exchange the intestinal contents with 16 ml of blood and 0.22% ( \text{H}_2\text{O}_2 ) sol. 160 ml. enema</td>
</tr>
</tbody>
</table>

data, 15 minutes after the first administration of \( \text{H}_2\text{O}_2 \) solution by enema. Although it subsequently decreased, the values had not returned to the control level by one hour after the first administration of \( \text{H}_2\text{O}_2 \) solution.

**DISCUSSION**

Hydrogen peroxide is a good source of oxygen and has been used parenterally by some investigators as a means of extrapulmonary oxygenation for humans and in animals, 1920, 1948, 1966 (Feldman, et al.), 1966 (Urschel, et al.), 1967 (Stern et al.), 1967 (Faison, et al.), 1968 (Morgan, et al.) However, because of the formation of gas emboli and of methaemoglobinemia when given by the intra-arterial or by the intra-venous route the hazards of such treatment have been strongly emphasized 1948, 1966 (Feldman, et al.), 1967 (Faisan, et al.), 1997 (Stern, et al.). Shaw, et al. (1967) observed intestinal gangrene in a newborn due to gas emboli followed an enema with a 0.75 per cent \( \text{H}_2\text{O}_2 \) solution for the treatment of meconium ileus. Morgan, et al. (1968) have also reported the dangers of intraperitoneal infusion of \( \text{H}_2\text{O}_2 \) solution. Clinical application of this method neonatal resuscitation by causing a rapid oxygenation of small amounts of blood injected into the umbilical artery has been described. The blood transfused contains oxygenated blood to try to avoid gas emboli formation (1962, 1966 (White, et al.). However, there are practical difficulties for us to use blood transfusions to give oxygen by this method. However, it is still our desire to find a means which is effective, safe and simple procedure for extrapulmonary oxygenation. Such could alter the prognosis in asphyxia neonatorum, respiratory distress syndrome, cyanotic attacks in congenital heart diseases with right to left shunt, postoperative cardiac patient and in those having pulmonary insufficiency for any reason.

It is obvious that hydrogen peroxide could be used for the treatment of above conditions after we have found the means to prevent gas emboli and methaemoglobinemia while giving a high enough concentration of oxygen. The author adopted the method of intra-intestinal infusion of \( \text{H}_2\text{O}_2 \) solution because it was easy and safe when compared with all other methods if the means of avoiding the gas emboli and methaemoglobin could be found.

The dose of \( \text{H}_2\text{O}_2 \) solution used in this experiment, 10 ml/Kg of body weight, was well tolerated by animals and human beings. In the experiment of the single dose group, less than 0.4 per cent \( \text{H}_2\text{O}_2 \) solution would not produce even microbubbles in the portal vein, but 0.5 per cent \( \text{H}_2\text{O}_2 \) solution would produce moderate amount of microbubbles in the portal vein even when \( \text{pO}_2 \) in the portal vein had dropped below than the control. It was also found the dogs which did not pass a stool following the glycerin enema had a tendency to have prolongation of a higher \( \text{pO}_2 \) in both the portal vein and inferior vena cava when compared with the dogs had a good stool after the preoper-
ative glycerin enema. Although the lower the concentrations of H$_2$O$_2$ solution, the shorter the
duration of maintenance of the higher level in pO$_2$
in both the portal vein and the inferior vena cava
when compared with the control.

The experiment of serial enema administration
of the H$_2$O$_2$ was conducted to maintain a constantly
higher level of pO$_2$ in both the portal vein and
inferior vena cava over a long period. The exper-
iment with a single dose showed the pO$_2$ in both
the portal vein and inferior vena cava eventually
decreased when given in concentration which did
not produce oxygen bubbles in the portal vein. It
was found in this experiment that concentrations
lower than 0.2 per cent H$_2$O$_2$ would not produce
gas bubbles in the portal vein. Concentrations higher
than 0.25 per cent H$_2$O$_2$ produced microbubbles
after several exchanges done, also the pO$_2$ in the
portal vein dropped lower than that of the control
level. However, the pO$_2$ in the femoral arterial
blood steadily increased regardless of whether the
pO$_2$ in the portal vein and inferior vena cava
increased or decreased. It was also found in this
experiment that the pO$_2$ in both the portal vein
and inferior vena cava invariably fell after several
exchanges whenever the intestinal contents became
clear. This means that the presence of stool is
important for the H$_2$O$_2$ in the intestine to be
decomposed into oxygen and water. There were a few
exceptional experiments which maintained a higher
pO$_2$ in both the portal vein and inferior vena cava
even after the intestinal contents became clear. It
was not clear whether or not the stool of the dogs
contain catalase or bacterial flora. Stools containing
catalase rapidly decompose H$_2$O$_2$ into water and
oxygen. It was strongly felt that the presence of
the factors decomposing H$_2$O$_2$ into water and oxy-
gen was necessary to maintain the higher pO$_2$ even
a the serial administration experiment. This is the
reason why a serial administration of 0.2 per cent
H$_2$O$_2$ solution plus human whole blood was done.
Erythrocytes of human blood are said to contain
a large amount of catalase (1966 Paniker, et al.,
1966 White, et al.). With the addition of blood
to the enema, it was observed that the pO$_2$ level
in the portal vein, inferior vena cava and femoral
arterial blood were constantly higher than in the
controls. Paik (1969) studied histologic changes in
the liver tissue after the administration of hydrogen
peroxide at various concentrations, in single and
multiple dose. He observed that higher dose than
0.5 per cent H$_2$O$_2$ solution in single administration
causd degeneration of liver cells around the bran-
ches of the portal vein. These changes were com-
pletely healed three weeks after the enema of H$_2$O$_2$
solution. There was no histological changes in both
the control group and enema administration group
given 0.2 per cent H$_2$O$_2$ solution plus human whole
blood by enema. This means that the last method
of enema of H$_2$O$_2$ solution is safe and would not
damage any liver cells from gas emboli of ultra-
microbubbles of oxygen. In addition to this, met-
hamoglobin levels in the blood of the inferior vena
cava in two dogs given 0.2 per cent H$_2$O$_2$ solution
plus human whole blood by enema were decreased
as the pO$_2$ level increased.

This experiment indicated that there was no
demonstrable methaemoglobin formation at the dose
given. However, in a dog given 0.4 per cent H$_2$O$_2$
solution, by a single enema and in a dog given
0.2 per cent H$_2$O$_2$ solution, in serial administration
without addition of human whole blood, there was
a lower level of pO$_2$ than in the control. Here the
methaemoglobin level in the blood of the inferior
vena cava increased with time from 745 mgm/dl
to 2100 mg/dl. These results indicate that the
addition of human whole blood in H$_2$O$_2$ solution
by enema could prevent the formation of methaemo-
globin.

The experiment of giving oxygen by enema was
conducted to know if the intestine would be able
to absorb the oxygen gas directly. This experiment
demonstrated the oxygen could be absorbed from
the intestinal mucosa and could be delivered to the
systemic blood flow even though peaking in pO$_2$
in the portal vein and inferior vena cava was slo-
war. Of course, it would be impossible to give a large amount of oxygen into the intestine because of the fear of lung collapse secondary to extensive abdominal distension. It is important that oxygen gas given by enema would not cause gas bubbles in the portal vein. If \( \text{H}_2\text{O}_2 \) given by enema breaks down in the intestine into oxygen and water completely, there should be no reason for gas bubble formation in the portal vein, nor for the formation of methaemoglobinemia. If \( \text{H}_2\text{O}_2 \) is absorbed directly from the intestinal mucosa, it will not only form methaemoglobin in the blood, but also to form gas bubbles unless the erythrocytes of experimental animal have enough catalase or peroxidase completely to break down the hydrogen peroxide into oxygen and water.

The experiment on death by suffocation was performed to determine if oxygen absorbed from the intestinal mucosa by \( \text{H}_2\text{O}_2 \) could affect survival time. It was found that while the duration of audible heart sound was almost the same between two groups, the duration until death by E.K.G. was greatly different. In the group given \( \text{H}_2\text{O}_2 \) it was 21 minutes 35 seconds \pm 4 minutes 42 seconds, whereas in the control group it was 10 minutes 11 seconds \pm 1 minute 4 seconds. T. test revealed the value was 7.47, d.f. (degree of freedom) was 18, therefore the difference between two groups was statistically significant. The reason why the E.K.G. tracings of life in hydrogen peroxide group was longer than the control group in spite of not hearing heart sounds by the stethoscope was not clear. It was obvious this could be due to extrapulmonary oxygenation from the hydrogen peroxide given by enema.

On the basis of the experiments described above, a study was carried out on a case of Tetralogy of Fallot who was in a moderate hypoxic condition in order to see the effect of elevating \( \text{pO}_2 \) in the systemic blood without fear of forming gas emboli or methaemoglobinemia by using 0.2 per cent \( \text{H}_2\text{O}_2 \) solution plus human whole blood by enema, exchanging the intestinal contents every 30 minutes. This study showed a marked increase of \( \text{pO}_2 \) in the blood samples of both vein and inferior vena cava. It is not known why \( \text{pO}_2 \) in venous blood is so high in spite of the fact that \( \text{pO}_2 \) in arterial blood is not so high as would be expected.

From the results obtained by the study described above, it would seem that 0.2 per cent hydrogen peroxide solution plus a small amount of human whole blood could be used to relieve cyanotic attacks in patients of right to left shunt by providing extrapulmonary oxygenation. It may also prove useful in raising oxygen tension in other problems of respiratory insufficiency.

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