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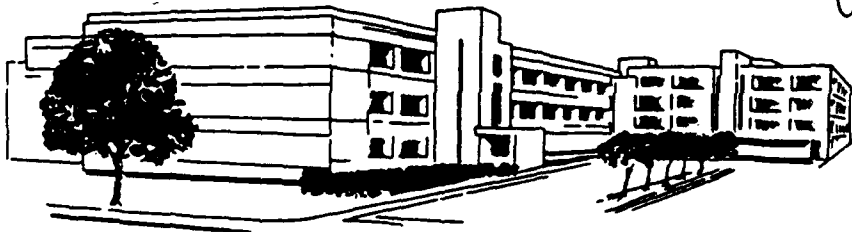
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Dose Effect of HSD on Survival Following Hemorrhage

DIVISION OF MILITARY TRAUMA RESEARCH

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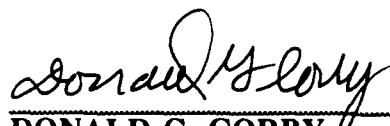
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<p>The comparative effectiveness of various dosages of hypertonic saline/dextran (HSD) for the treatment of severe hemorrhage was investigated in conscious swine bled 46 ml/kg over 15 min. Five minutes after the completion of hemorrhage, the animals were treated with 1, 2, 4 or 11.5 ml/kg HSD and were observed over the next 96 hours. The 11.5 ml dose was superior to all other doses, effecting 100% survival. Survival incidence with 4, 2 and 1 ml/kg was 83, 64 and 13%, respectively. In terms of survival time, the 11.5 and 4 ml doses were not significantly different. Therefore, optimum resuscitative effectiveness of HSD is achieved within the dose range of 4 to 11.5 ml/kg.</p>			
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### ABSTRACT

The comparative effectiveness of various dosages of hypertonic saline/dextran (HSD) for the treatment of severe hemorrhage was investigated in conscious swine bled 46 ml/kg over 15 min. Five minutes after the completion of hemorrhage, the animals were treated with 1, 2, 4 or 11.5 ml/kg HSD and were observed over the next 96 hours. The 11.5 ml dose was superior to all other doses, effecting 100% survival. Survival incidence with 4, 2 and 1 ml/kg was 83, 64 and 13%, respectively. In terms of survival time, the 11.5 and 4 ml doses were not significantly different. Therefore, optimum resuscitative effectiveness of HSD is achieved within the dose range of 4 to 11.5 ml/kg.

### PREFACE

The results and conclusions contained in this report were extracted from data recorded in official LAIR notebooks, No. 85-05-15 and No. 85-05-15.1, that were issued to Dr. Peter A. Maningas during his tenure of active duty at Letterman Army Institute of research. Other aspects of his work with HSD have been reported in the open literature (2,7).

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## Dose of HSD on Survival following Hemorrhage.

### INTRODUCTION

Hypertonic saline/dextran (HSD) is now recognized as a highly effective resuscitation solution for the treatment of life-threatening hemorrhagic hypotension. (1-4). Administration of HSD (7.5% NaCl in 6% Dextran 70) thus corrects many of the hemodynamic and metabolic sequela of hemorrhage, ultimately leading to an improvement in survival (2,3,5-7). Doses ranging from 2.5 to 11.5 ml/kg have been used (2,8), but few efforts have been made to determine the optimum dosage level. The present report addresses this question, presenting experimental data on the duration and incidence of survival following the administration of 1, 2, 4 or 11.5 ml/kg of HSD to conscious pigs that were subjected to a normally lethal hemorrhage insult.

### METHODS

Five days before experimental use, immature barrows and gilts, obtained from a commercial breeder (J.G. Boswell, Corcoran, CA) weighing 19 to 25 kg were premedicated with 0.09 mg/kg atropine sulfate, 2.2 mg/kg ketamine HCL and 2.2 mg/kg xylazine administered intramuscularly. Halothane anesthesia was then induced (0.05% halothane, 1.0% methoxyflurane, N<sub>2</sub>O and oxygen), and catheters were implanted in the left external jugular vein and descending aorta for blood withdrawal and functional measurements. The health and well being of the animals was periodically assessed during the recovery period.

On the day of study, following an overnight fast with water available, each pig was transported to the laboratory and placed in a holding cage that restricted its movements. The conscious animal was then subjected to a 46 ml/kg hemorrhage over a fifteen minute period, an insult that is fatal in 87% of untreated pigs (2). Five minutes after the completion of hemorrhage, the animal was randomly assigned to one of 4 groups and was resuscitated with either 1, 2, 4 or 11.5 ml/kg of HSD, administered by rapid intravenous (jugular catheter) infusion. The resuscitation solution, 7.5% NaCl in 6% Dextran 70, was obtained from Pharmacia, Inc., Sweden (Turbodex, Batch I-328510 exp. date 86-10-01). Following resuscitation, the animal was observed over the next 96 hours, and if death occurred, the duration of survival was recorded.

Between-group resuscitative effectiveness in terms of survival versus nonsurvival during the 96 hour observation period was evaluated with a Chi-square test followed by Marascuilo's method of multiple comparison. Between-group resuscitative effectiveness in terms of survival time before death (or 96 h if death did not occur) was evaluated with a generalized Wilcoxon test, after appropriate adjustments for multiple comparisons.

Differences between mean values were considered significant when  $P < 0.05$ . Values in the text are represented by Means  $\pm$  SEM.

### RESULTS

All pigs resuscitated with 11.5 ml/kg of HSD were alive at the end of the 96 hour observation period, and resuscitative effectiveness of this dose was significantly superior to all other doses, at least in terms of survival enhancement (Table 1, Fig 1). Resuscitation with 4 ml/kg HSD, and to a lesser extent the 2 ml/kg, also enhanced survival; respectively, 83 and 64% of the animals in these groups were alive at the end of the observation period. In contrast, a 1ml/kg dose was followed by only 13% survival, a value that was equal to that observed in this animal model when no resuscitative treatment is provided (2).

Between group comparisons of survival time following resuscitation also revealed significantly different dose effects (Table 2, Fig 2). As previously indicated, all animals treated with 11.5 ml/kg dose survived the 96 hour observation period. Resuscitation with 4 ml/kg of HSD resulted in a mean survival time of  $80 \pm 10$  hours, a value that was not significantly different than that observed following the 11.5 ml/kg dose. Survival time for the 2 ml/kg dose was  $67.5 \pm 13.8$  hours, significantly less than the 11.5 ml/kg dose, but not different than the time observed with the 4ml/kg dose. Pigs receiving the 1 ml/kg dose survived  $13.3 \pm 8.7$  hours, a value that was significantly less than observed with all other doses.

### CONCLUSION

On the basis of the data recorded here, it appears that severely hemorrhaged swine can be effectively resuscitated with HSD at dosage levels of 4 to 11.5 ml/kg. The lower value, while not 100% effective, did provide highly significant improvements in both the incidence and duration of survival. Wade et al. (4) have previously shown that 4 ml/kg of HSD in hemorrhaged swine produced a survival rate incidence of 66%, appreciably less than the 80% survival rate of the same dose in the present study. Velasco and coworkers (9) have reported a survival incidence of 92% in hemorrhaged anesthetized dogs that were administered 6 ml/kg of HSD. The present study suggests that the dose of 4 ml/kg is not fully effective for insuring survival, but does extend survival time following hemorrhage.

The clinical dose presently recommended for HSD is 250 ml administered intravenously (5,10). This dose was selected arbitrarily on the assumption that a greater dose would result in hypernatremia and neurological dysfunction (5,11). If the average soldier weighs 70 kg and is administered 250 ml of HSD, the dose should be 3.6 ml/kg. Although below the optimal dose demonstrated in the present study, a dose of 250 ml would be as effective in expanding blood volume as the present resuscitation fluid used by the field medic. The medic has 2000 ml of Ringers lactate available, of which only 40% (800 ml) will remain in the vascular space following administration (12). On the other hand, 250 ml of HSD expands vascular volume by 900 ml (4). The presently recommended dose of HSD, therefore, is within the effective range for improving survival of the combat casualty, but below the level which could assure a maximal advantage.

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**TABLE 1:** Outcome following resuscitation from hemorrhagic hypovolemia with varying doses of hypertonic saline/dextran (HSD).

Dose (ml/kg)	11.5	4.0	2.0	1.0
Live	14	15	9	2
Died	<u>0</u>	<u>3</u>	<u>5</u>	<u>13</u>
Total	14	18	14	15

TABLE 2: Survival time in hours

Time in hours

<u>Animal #</u>	<u>HSD DOSE</u>			
	<u>11 ml/kg</u>	<u>4 ml/kg</u>	<u>2 ml/kg</u>	<u>1ml/kg</u>
1	96	96	96	0.23
2	96	96	96	0.25
3	96	96	96	0.60
4	96	96	0.9	1.3
5	96	96	96	0.75
6	96	96	96	96
7	96	1.0	96	96
8	96	96	96	1.87
9	96	96	0.3	0.27
10	96	96	0.42	0.15
11	96	96	96	0.65
12	96	96	0.6	0.47
13	96	0.5	96	0.63
14	96	96	0.62	0.40
15		96		0.45
16		96		
17		1.0		
18		96		

8 -- HSD Dosage

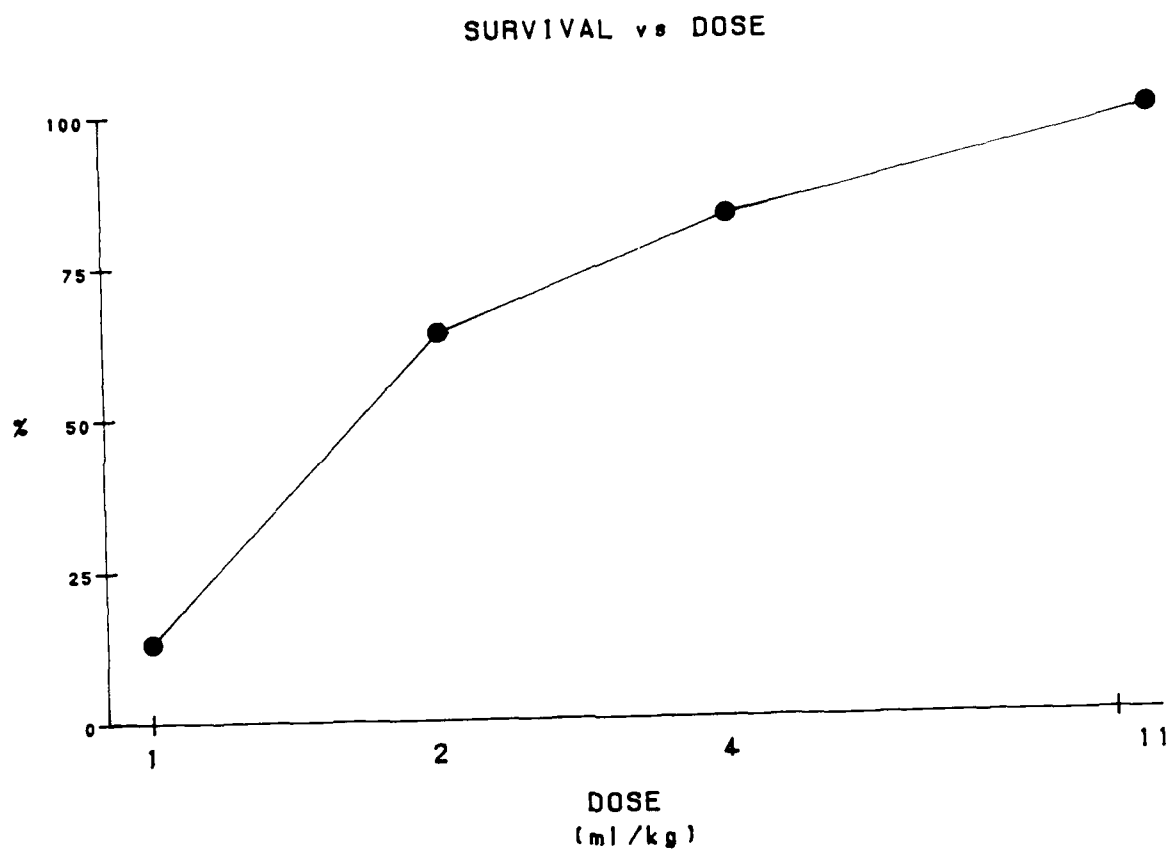


Figure Legend: Percent survival of hemorrhaged swine treated with varying doses of HSD.

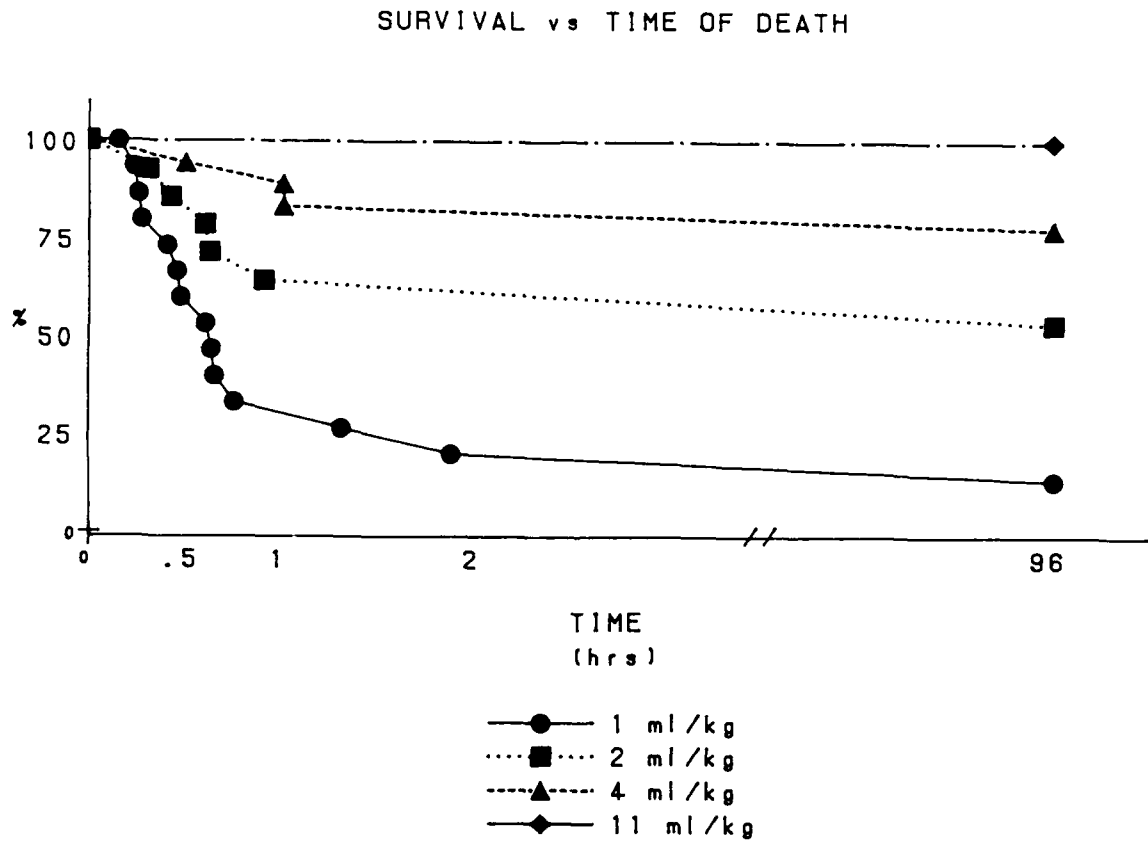


Figure Legend: Survival vs. Time of Death of hemorrhaged swine treated with varying doses of HSD.

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