BIOLOGIA (LAHORE)
December, 2019, 65 (II), 301-307

PKISSN 0006 – 3096 (Print)
ISSN 2313 – 206X (On-Line)

Comparative efficacy of whole blood and hypertonic colloid solution on some blood parameters in resuscitation of acute hemorrhagic shock in Dogs

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ARTICLE INFORMAION

Received: 24-05-2019
Received in revised form: 12-10-2019
Accepted: 31-10-2019

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Original Research Article

ABSTRACT

The present study was conducted to compare the efficacy of fluid resuscitation using whole blood and hypertonic colloid fluid in dogs suffering from experimental hypovolemia. Acute hemorrhagic shock was developed in dogs to a touchstone blood pressure of 50 mm Hg, maintained up to 30 minutes. Resuscitation therapy was carried out using autogenous whole blood in dogs of group A (n=6) and hypertonic colloid fluid equal to the volume of lost blood in dogs of group B (n=6). Post-treatment recoveries in conscious state and hematological components to original limits were evaluated, while another group of 6 dogs (group C) served as untreated control. The clinical reclamation to normal state of consciousness, respiration and heart rates were comparable among both treatment groups. No adverse reaction was observed following transfusion of blood or Haes-steril™ in any experimental dog. Hematological parameters like total leukocytic count (TLC), red blood cells (RBC), hemoglobin (Hb) and total proteins were also studied. Blood parameters such as RBC, Hb and total proteins were significantly different among dogs of both treatment groups. The changes in TLC values were insignificant amongst both treatment groups. Hypertonic colloid fluid can effectively be used as resuscitation fluid in medical emergencies.

Keywords: Dog, Hemorrhagic shock, Hypertonic colloid solution, Resuscitation

INTRODUCTION

In recent years, veterinary emergency services have expanded manifolds and increased the economic status of the owners. The veterinary emergencies are applicable to any acute disorders of pulmonary, cardiovascular, neurologic, renal, endocrine, hematologic, or gastrointestinal systems. Sudden respiratory distress, hypovolemia, shock, hemorrhage and cessation of urine are amongst some of the life-threatening conditions requiring emergency attention (Geeraedts *et al.*, 2015). Survival from hypovolemic shock relies on the restoration of transport of oxygen, blood volume and its flow through vessels. Rapid compensation of lost blood volume is the effective and standard method of resuscitation of hypovolemic shock and evading death. It is the only requirement in case of hemorrhagic shock that can be supplied by the donor animal (Knotzer *et al.*, 2006; Kuldeep *et al*., 2019)

For blood transfusion, there are many considerations for the selection of donor animals. The donor should be in good physical condition, free from communicable diseases and pre-vaccinated against common infectious diseases (Moore *et al*., 2004). Therefore, the selection of the donor animals, without knowing the previous history of vaccination

Author's Contribution: M.A.A., **S.M.R.D.**, **M.I.A. & M.A.S.**, Performed experimental hypovolemic shock and resuscitation in dogs; **M.A.K.,** Designed and conceived study plan. **W.A. & M.R.H.,** Wrote manuscript; **M.M.A.**, **F.H. & H.A.,** Performed statistical analysis;

or treatment, is somewhat risky in emergency cases.

Immunological hazards also exist with the heterogeneous transfusion of whole blood or its components. Among these, intravascular hemolytic catastrophes and allergic type reactions are common. Some of the adverse reactions are preventable and others are not (Donohoe, 2012). Albumin is used in human patients as a source of colloid fluid for the maintenance of lost blood volume, but species-specific albumin is not available for animal use. Keeping in mind these critical situations, the loss and benefits must be weighed where transfusion of either whole blood or its constituents are considered.

The efficacy of hypertonic crystalloids or plasma substitutes (Dextran, Hetastarch solutions) for resuscitation of hypovolemic shock and maintenance of blood pressure has been demonstrated both in human and veterinary medicine (Kalla & Herring, 2013). The colloids are considered more effective blood volume expanders than the crystalloid fluids. The hemodynamic benefits in using hypertonic colloids include improved cardiac output, stroke volume and decreased capillary resistance (Zhao *et al*., 2009) In addition, they are non-antigenic, inexpensive and proved to be as good as albumin (Buckley & Kishen, 2013).

Disruption of hemostasis may be one of the important predicaments for the routine clinical use of hypertonic colloids. The hemostatic abnormalities associated with colloids were only observed when used in larger doses as plasma expander. However, small volume (20 ml/kg) has minor alterations in clotting time (Donohoe, 2012).The use of these solutions for initial resuscitation appeared attractive because of non-availability of customary donors in both small and large animal practice. The purpose of this study was to evaluate the effects of hypertonic colloids in comparison with whole blood in resuscitation of hemorrhagic shock in dog model.

MATERIALS AND METHODS

Experimental Animals and Clinical Examination

A total of 18 adult, healthy mongrel dogs were utilized for the comparative evaluation of resuscitation fluids, i.e. dextran (hyperosmotic colloid fluid) and autogenous whole blood, through intravenous infusion in experimentally induced hemorrhagic shock. During the acclimatization period of one week, all the animals were subjected to clinical and laboratory examinations, including complete blood count, faecal and urine tests to ascertain the health status of the animals. All the institutional and animal welfare guidelines were adopted to carry out required experimental procedures. In this regard, the procedure to perform experimental shocks in dogs was adopted from G Crile 1906. The procedure meant to induce minimum pain, and discomfort to the dog. The written procedure was first went into review process in the ethical and research committee of the said university of the principal author and the study was performed after the approval had been granted. The dogs were kept in separate indoor kennels, and maintained under uniform managemental and feeding regimens throughout the study period.

These dogs were randomly divided into 3 groups, i.e. A, B, and C, comprising 6 animals each. Animals of groups A and B were infused with whole autogenous blood and hypertonic colloid intravenously through cephalic vein, in volume equal to the amount of blood withdrawn respectively. Dogs in group C were kept as un-treated control.

Induction of hemorrhagic (hypovolemic) shock

A measured amount (60%) of blood was withdrawn in animals of group A and B to develop experimental hemorrhagic (hypovolemic) shock. The blood was collected in IV collection bags, containing anticoagulant fluid. The blood pressure (BP) was monitored during bleeding of each animal using aneroid sphygmomanometer, from the femoral artery, for the assessment of hypovolemic shock. A systolic BP level of 50 mm Hg was considered cut-off point to stop blood withdrawal. This BP level was maintained for 30 minutes before the initiation of resuscitation (Wurlod *et al*., 2015).

Treatment protocol

For animals of group A and B, intravenous infusion lines were applied for the administration of resuscitation fluids. The autogenous blood (harvested previously in blood bags) and hypertonic fluid, i.e6% Haes-steril^{TM}, containing poly (O-2 hydroxyethyl) starch in 0.9% sodium chloride were then administered through the cannula to respective groups. After 30 minutes of experimentally induced hypovolemia, all animals of groups A and B were transfused with resuscitation fluids, at a rate of 11 ml/minute with gravity flow (Machado *et al*., 2005).

Clinical examination

After transfusion treatment, all animals were monitored for any alteration in vital signs of health, such as body temperature, heart rate, respiration, mucous membrane color, hydration, urine output, appetite and defecation, at morning and evening hours for a period of 4 weeks. Animals showing primary defects of hemostasis, i.e. epistaxis, hemoptysis, melena, hematuria, petechial, or ecchymotic hemorrhage, and hematoma formation were also recorded (Jagodich & Holowaychuk *et al*., 2016)

Hematological analysis

The blood was subjected to hematological analysis for comparative evaluation of the two treatment regimen. Eight milliliters blood sample was collected from each animal under investigation at different time periods for the investigation of different hematological parameters. The blood sampling was done and identified as followed; before production of shock (sample 1), half hour after the production of shock (sample 2), just after the transfusion (sample 3), 6, 12, 24, 48 and 96 hours after the transfusion (sample 4, 5, 6, 7 & 8 respectively).

Blood chemistry profile

Complete blood counts, including total leukocytes, platelets, red blood cells, hemoglobin were studied utilizing standard laboratory procedures (Rana *et al*., 2016). Total serum protein was measured from stored serum samples by using a commercial kit "Protei 2" (Winer Lab, Serio, Argentina).

Statistical analysis

The data of hematological values of all groups were analyzed statistically using randomized complete block design (RCBD) and Duncan's Multiple Range Test (DMR) (Seliskar *et al*., 2011).

RESULTS

Clinical examination

All the treated and control dogs remained clinically healthy before the experimentation and later throughout the study period using both treatment protocols. None of the dog under investigation died of any disease or hemorrhagic (hypovolemic) shock.

Hypovolemic shock

The state of hypovolemic shock was achieved by measuring the systolic blood pressure to 50 mm of Hg, using sphygmomanometer and constantly monitored and maintained for 30 minutes before the start of resuscitation. This shock state was reached by an average withdrawal of 36.20 and 38.90 ml/kg of blood in groups A and B dogs, respectively. A uniform rate of transfusion fluids (whole blood or colloid), i.e. ml/min, was maintained in all animals during the 2 treatment protocols. The total volume of transfusion in hypertonic colloid solution was kept equal to the amount of total blood withdrawn of the animal.

Effects of treatments on complete blood count

Total leukocytic count (TLC, thousand/cmm)

Time dependent changes in the means TLC values of each group A, B, and C dogs are presented in Table I.

Table I: TLC (thousands/cmm) of dogs (n=6) treated with whole blood and hypertonic

Sample No.	Group A	Group B	Group C
1	8.133 ± 0.635	9.708 ± 1.373	12.325 ± 3.022
2	9.604 ± 0.912	8.425 ± 0.812	11.645 ± 2.934
3	8.133 ± 0.634	6.658 ± 0.804	14.050 ± 2.569
4	8.137 ± 1.683	9.875 ± 1.723	9.875 ± 1.723
5	8.087 ± 0.637	10.021 ± 1.731	14.041 ± 2.533
6	9.650 ± 0.907	10.758 ± 1.585	11.795 ± 2.942
7	8.087 ± 0.641	14.653 ± 1.948	12.758 ± 1.600
8	9.650 ± 0.910	12.200 ± 1.295	12.566 ± 3.039

The overall mean TLC values in thousands/cmm were 8.685 ± 0.322, 10.287 ± 0.577, and 12.600 ± 0.901 of blood in group A, B, and C animals, respectively. The mean baseline TLC values were 8.133 ± 0.635, 9.708 ± 1.373, and 12.325 ± 3.022 in groups A, B and C dogs, respectively. Soon after the initiation of treatments, the mean TLC values were 8.133 ± 0.634, 6.658 ± 0.804, and 14.05± of groups A, B, and C, respectively. At 12^{th} hour, the mean TLC values were 8.087 ± 0.637 and 10.02 ± 1.731 in treatment groups A and B, respectively. After a period of 48 hours, the mean TLC values were 8.087 ± 0.641 and 14.653 ± 1.948 in both treatment groups A and B, respectively and in control group C, it was 12.758 ±1.600. Similarly, the mean TLC values at 96^{th} hour were 9.650 ± 0.910 and 12.200 ± 1.295 of treatment groups A and B, respectively. Statistically, the TLC values in group A and B showed highly significant difference ($P<0.01$) compared to the group C (control). However, among the two groups (A & B) the trend was similar and non-significant.

Red blood cells (RBC, millions/cmm)

The RBC count of all animals in groups A, B and C are presented in Table-II. The overall mean of RBC values (million/cmm) were 3.83 ± 0.05, 5.57 ± 0.25, and 3.44 ± 0.07 in animals of groups A, B and C, respectively. Following the development of hypovolemic shock, the mean baseline values of RBC were 3.83 ± 0.10, 7.04 ± and 3.37 ± 0.24 in groups A, B, and C, respectively. Just after treatment in animals of A and B groups, the mean RBC values were 3.85 ± 0.11 and 5.22 ± 0.77, respectively.

At 12th hour, the mean RBC values were 3.82 ± 0.09 and 5.42 ± 0.56 in treatment groups A and B, respectively and 3.62 ± 0.28 in control group C. After 48 hours of study period, the mean RBC values were 3.85 ± 0.08 and 4.67 ± 0.34 of group A and B animals, respectively and 3.55 ± 0.19 in control C. Similarly, after 96 hours post infusion, the mean RBC values were 3.87 ± 0.20 and 5.43 ± 0.53 in treatment groups A and B, respectively. Statistically, the RBC values in group B (hypertonic colloid) showed highly significant (P<0.01) difference compared to group A (whole blood) and control C (Table II).

Table II: RBC (million/cmm) of dogs (n=6) treated with whole blood and hypertonic colloid

Sample No.	Group A	Group B	Group C
1	3.83 ± 0.10	7.04 ± 0.85	3.37 ± 0.24
2	3.80 ± 0.21	6.12 ± 0.90	3.47 ± 0.10
3	3.85 ± 0.11	5.22 ± 0.77	3.57 ± 0.26
4	3.82 ± 0.20	5.61 ± 0.69	3.380 ± 0.17
5	3.82 ± 0.09	5.42 ± 0.56	3.62 ± 0.28
6	3.82 ± 0.18	5.06 ± 0.68	3.32 ± 0.19
7	3.85 ± 0.08	4.67 ± 0.34	3.55 ± 0.19
8	3.87 ± 0.20	5.43 ± 0.53	3.28 ± 0.12

Hemoglobin (% Hb)

The Hb values of animals in groups A, B, and C are presented in Table-III. The overall mean Hb values were 69.85 ± 1.12, 62.02 ± 2.35, and 60.92 ± 1.28% in animals of groups A, B, and C, respectively. The mean baseline values of Hb were 70.0 ± 1.37, 53.0 ± 6.67, and 62.0 ± 4.23 of blood in group A, B, and C respectively. Just after treatment in group A and B, the mean Hb values were 70.33 ± 1.38 and 64.83 ± 8.98, respectively. At 12 hour, the mean Hb values were 69.67 ± 0.71 and 66.17 ± 9.38 of groups A and B, respectively and 65.50 ± 4.77 in control group C. After 48 hours, the mean Hb values were 70.50 ± 0.56 and 56.33 ± 7.03 in treated groups A and B, respectively and 64.33 ± 3.30 in group C animals. Similarly, after 96th hour, the mean Hb values were 70.33 ± 4.67and 60.33 ± 4.94 in treated groups A and B animals, respectively and 56.17 ± 2.47 in group C animals. On statistical analysis using ANOVA, the Hb value in group A were highly significant (P<0.01),compared to groups B and C (Table III).

Table III: Haemoglobin (%) of dogs (n=6) treated with whole blood and hyper tonic colloid

Sample No.	Group A	Group B	Group C
1	70.0 ± 1.37	53.0 ± 6.67	62.0 ± 4.23
2	69.0 ± 4.99	65.67 ± 5.48	61.67 ± 2.12
3	70.33 ± 1.38	64.83 ± 8.98	61.33 ± 4.73
4	69.50 ± 4.81	68.67 ± 5.48	58.67 ± 3.31
5	69.67 ± 0.71	66.17 ± 9.38	65.50 ± 4.77
6	69.50 ± 4.47	61.17 ± 5.17	57.67 ± 3.55
7	70.50 ± 0.56	56.33 ± 7.03	64.33 ± 3.30
8	70.33 ± 4.67	60.33 ± 4.49	56.17 ± 2.47

Serum Protein (gm/dl)

The total serum protein values in animals of groups A, B and control group C are presented in Table-IV. The overall mean of total serum protein values were 7.83 ± 0.20, 9.62 ± 0.21, and 7.72 ± 0.21 in animals of groups A, B, and C, respectively. The mean baseline values of total serum protein were 7.61 ± 0.53, 11.47 ± 0.49, and 6.78 ± 0.23 of groups A, B, and C, respectively. Just after the treatment in groups A and B, the mean total protein values were 7.52 ± 0.52 and 7.93 ± 0.51 of groups A and B, respectively, and in group C, it was 6.67 ± 0.27.

After 12 hours, mean total serum protein values were 7.60 ± 0.54, 9.50 ± 0.26, and 6.63 ± 0.31 in groups A, B, and C, respectively. At 48th hour, the mean total serum protein values were 7.65 ± 0.54 and 10.17 ± 0.45 in treatment groups A and B, respectively. Similarly, after 96 hours of treatment, the mean total serum protein values were 8.07 ± 0.66, 9.57 ± 0.27, and 8.95 ± 0.56 in groups A, B and C, respectively. On statistical analysis, using DMR, total serum protein values of groups B (hypertonic colloid) were highly significant (P<0.01) compared to group A (whole blood) and control group C. Among these three groups, any means sharing the same superscript letters were not significantly different according to Duncan's Multiple Range Test (P<0.05). Significant difference was also observed among groups and within groups at different time intervals (Table IV).

Table IV: Serum protein (grm/dl) of dogs (n=6) treated with whole blood and hypertonic colloid

Sample No.	Group A	Group B	Group C
1	7.61 ± 0.53 [a]	11.47 ± 0.49 [a]	9.78 ± 0.23 [b]
2	7.98 ± 0.67 [a]	9.33 ± 0.67 [bc]	8.43 ± 0.50 [a]
3	7.52 ± 0.52 [a]	7.93 ± 0.51 [c]	6.67 ± 0.27 [b]
4	8.05 ± 0.70 [a]	9.07 ± 0.78 [bc]	8.88 ± 0.56 [a]
5	7.60 ± 0.54 [a]	9.50 ± 0.26 [b]	6.63 ± 0.31 [b]
6	8.15 ± 0.73 [a]	9.93 ± 0.40 [b]	8.85 ± 0.63 [a]
7	7.65 ± 0.54 [a]	10.17 ± 0.45 [ab]	6.58 ± 0.21 [b]
8	8.07 ± 0.66 [a]	9.57 ± 0.27 [b]	8.95 ± 0.56 [a]

DISCUSSION

Transfusion therapy is now considered one of the essential components of life saving medicaments. The benefits and adverse effects associated with blood transfusion have been well demonstrated in the literature (Godinho-Cunha *et al*., 2011). In blood transfusion medicine, blood group incompatibility is one of the most important hazards. The adverse effects are uncountable, involving immediately as anaphylactic shock to reactions occurring in year's span (Ekerbicer *et al*., 2006; Seliskar *et al*, 2011). It has already been stated that state of hypovolemic shock can be achieved by withdrawing animal blood, at a rate of 40 ml/kg, in dogs and cats (Mathews, 2006). In the present study, the state of hemorrhagic (hypovolemic) shock was also achieved by withdrawing blood from jugular vein, with an average withdrawal of 36.20 and 38.90 ml/kg of blood, in groups A and B dogs respectively. This was nearly equivalent to the previous reports.

Transfusion reactions were commonly observed like hemolysis, hemoglobinuria, hemoglobinemia, hypotension, acute hypersensitivity, platelet sensitivity, acute heart failure, citrate toxicity, disseminated intravascular coagulopathies, air embolism, hypothermia, or septicemia (Plunkett & Mcmichael, 2008; Donohoe, 2012). Similarly, clinically apparent hemostatic defects may also be observed with the use of hypertonic or hyperosmotic fluids. These may include epistaxis, anaphylaxis, hypotension, petechiation, and hematoma formation (Wardrop, 2004). In the present study post blood transfusion or hypertonic fluid treatment, no immediate or delayed type adverse reactions were noted throughout the experiment phase in any dog under investigations. It could be due to the use of autogenous blood in the experimental animals, stored in sterile containers containing dextrose. However, alterations in response to resuscitation therapy in different hemodynamic parameters were observed during the study period.

Intravenous infusion line was established beforehand, by introducing a Brannula in cephalic vein, in each dog under treatment investigations, before the development of shock. As the collapsed vein, in shocked animals could cause difficulties in installation of infusion lines. Heparin solution was used for flushing the Brannula line before the initiation of resuscitation fluids. This has helped in prevention of needle blockage by blood clots.

The hemodynamic alterations evaluated following the use of resuscitation fluids [whole blood and Hydroxy ethyl starch, (Haes-steril^{TM})] were considerably analogous in dogs of groups A and B. Both groups responded to the two treatment regimens within the first 2 hours, as observed in regaining normal conscious state, parallel to untreated healthy dogs. A minor alteration in TLC was noted within each experimental group of dogs following the use of both treatment protocols. With the use of whole blood, the alterations in TLC were minimal as compared to the baseline values. However, in dogs of group B, where hydroxy ethyl starch was used, the TLC values returned near to the base line values slowly (Table-1). An alarming change in TLC values was expected following the withdrawal of a sufficient quantity of blood in the experimental dogs. However, the time dependent minor alterations in TLC count were observed. It appeared that the compensatory mechanisms, i.e. evacuation of blood from store houses and the TLC response to handling or other stress factors reported earlier (Godinho-Cunha *et al*., 2011; Volz *et al*., 2019) could have modified the TLC counts in experimental dogs. The mean TLC values in groups A and B dogs however, were significantly different compared to the dogs of control group.

In group B, the RBC values never regained its base line values throughout the experimental period. A slight increase in RBC values was noted in group A at 96 hours post-treatment. In this group, this minor increase in RBC could also be associated with the role of compensatory mechanism and restitution

of total lost blood volume. In addition, the number of RBC/cmm of blood might have remained within normal limits for a while due to compensation following the lost blood (Klein & Anstee, 2008).

In hypertonic fluid resuscitation group, the RBC change was significant which remained significant throughout the study period. Research studies showed that plasma volume expanders, using hypertonic and hyperosmotic fluids, cause hemodilution and increase in central venous pressure (Molter *et al.*, 2003, Palmaers *et al*., 2019). It was also reported that with the use of volume expanders there is sudden increase in cardiac output and oxygen delivery system, which is however required in hypovolemic animals. Similar observations were also reported earlier (Wardrop, 2004; Plunkett & Mcmichael, 2008).

In shock associated with severe anemia and dehydration, the hemoglobin concentration is an indicator of blood or fluid resuscitation. In this study, pre and post treatment hemoglobin values were within their respective group base line values in the dogs of treatment and control groups. Minor alterations were noted in all experimental dogs at different time intervals (Table-3), but statistically, the Hb values in group A were highly significantly different ($P<0.01$) compared to dogs in groups B and C.

Though serum protein values were significantly different in group B, but these values were within their normal limits of the species in all dogs under investigation (Table-4). Hence, the use of hypertonic fluid may be used in cases of hypo-proteinemia, as also reported (Duchesne *et al*., 2015; Seliskar *et al*., 2011).

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