Hemodynamic Characteristics of Vasopressin in Dogs with Severe Hemorrhagic Shock

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(Received 1 November 2005/Accepted 22 May 2006)

ABSTRACT. The effect of vasopressin was compared with that of the established vasopressor epinephrine in experimentally induced hemorrhagic shock. After rapid crystalloid resuscitation in a ratio of three volumes of 0.9% saline to one volume of blood (3:1 crystalloid resuscitation), six dogs were given 0.4 IU/kg vasopressin and another six dogs were given 0.1 mg/kg epinephrine. Five dogs in the control group were given fluid resuscitation in the same manner as above without administration of any drugs. Administration of vasopressin increased diastolic arterial pressure (DAP) from 45.0 ± 4.9 to 91.2 ± 9.6 mmHg within 5 min, compared with epinephrine from 46 ± 4.0 to 51.8 ± 7.7, and control from 47.3 ± 7.5 to 46.3 ± 7.3. Systolic arterial pressure (SAP) did not increase significantly following vasopressin compared with epinephrine and control group. Results of DAP and systemic vascular resistance index (SVRI) suggested that vasopressin administration was vasoconstrictive after fluid resuscitation in decompensatory hemorrhagic shock in dogs, whereas epinephrine did not compared with control. In addition, epinephrine did not affect the cardiac index (CI) and SVRI, while a significant decrease in CI and increase in SVRI were observed in vasopressin group. The pressor effect of epinephrine in the vascular system was abrupt and only lasted a short period of time (within 5 min), while that of vasopressin was steady and lasted for more than 1 hr, especially regarding to DAP. When compared with epinephrine, vasopressin can be a more effective and safer choice in patients with severe hemorrhagic shock.

KEY WORDS: canine, epinephrine, hemodynamics, hemorrhagic shock, vasopressin.

In the late phase of hemorrhagic shock, the compensation mechanism fails to recover blood flow and global tissue perfusion is severely compromised. Cardiovascular support drugs are indicated for the cases where aggressive intravascular volume resuscitation has not been sufficient to increase cardiac output (CO), blood pressure, and oxygen use [17]. Positive inotropic drugs, such as dobutamine, dopamine [16], and epinephrine [14] increase stroke volume and cardiac output. Dopamine and epinephrine also possess vasopressor action. However, the use of catecholamine has some disadvantages, including increasing myocardial oxygen demand more than delivery, predisposing the myocardium to arrhythmias, and producing lactic acidosis [20].

Vasopressin has been identified as a treatment that effectively restores circulation in the late phase of hemorrhagic shock in cases unresponsive to blood replacement and catecholamines in dogs [15]. Moreover, vasopressin enabled short- and long-term survival in a porcine model of uncontrolled hemorrhagic shock after penetrating liver trauma [23, 24] and has been successfully used in a small number of patients with intra-abdominal bleeding and subsequent shock that was unresponsive to volume replacement [23]. Despite reports of successful resuscitation with vasopressin, vasopressin has not yet been applied to clinical canine patients with hypovolemic shock. The purpose of this investigation was to determine the hemodynamic characteristics of vasopressin in hypovolemic shock in dogs to provide essential data for application of vasopressin to veterinary critical cases. Accordingly, the present study was designed as follows. Hemorrhagic shock was induced in dogs and the effect of vasopressin on arterial pressure, CO, and oxygen delivery function was evaluated and compared with those of the more conventional vasopressor in veterinary medicine, epinephrine [2].

MATERIALS AND METHODS

Seventeen healthy mixed-breed dogs of both sexes weighing between 8.1 and 9.8 kg were divided into a vasopressin (n=6), epinephrine (n=6) and control groups (n=5). All dogs were preconditioned to the laboratory environment at least 2 days before the experiments. The dogs were cared for in the facility using procedures that follow the standards established by the Seoul National University for Accreditation of Laboratory Animal Care. Food was withheld from the dogs for 12 hr prior to experimentation.

Cephalic veins were used for administration of supplemental anesthesia and fluids. Anaesthesia was induced with ketamine HCl (KEIRAN Inj., Korea United Pharm, Korea) 10 mg/kg IV via an endotracheal tube and maintained by using isoflurane (Rhodia Isoflurane Liq., Hana Pharm, Korea). A femoral artery was percutaneously cannulated with over-the-needle polyethylene catheters (18G, 1.25 inch) for measurement of arterial pressure and blood sampling. Arterial blood was collected at a spontaneous bleeding rate. Blood pressure was maintained at 60 mmHg for 30 min by withdrawing blood as necessary. The blood was collected into 50 mL sterile plastic syringes containing CDPA.
anticoagulant. Hemorrhaged blood was kept at room temperature and rein infused into the dogs via a venous catheter after the experiment.

To evaluate the hemodynamic states, SAP, DAP, central venous pressure (CVP), CO, pulmonary capillary wedge pressure (PCWP), and heart rate (HR) were measured. Measurement of hemodynamic parameters followed the procedure of Jeong [8]. Cardiac index (CI) was expressed as the cardiac output divided by the dog’s body weight at the time of the control study. Body surface area (BSA) was calculated with K=10.1 as described previously (Boothe, 2001). Mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) were calculated as followed [3, 12]:

\[
\text{MAP} = \frac{\text{DAP} + (\text{SAP} - \text{DAP})}{3} \text{(mmHg)}, \\
\text{SVRI} = \frac{\text{MAP} - \text{CVP}}{\text{CO} \times \text{BSA}} \times 79.9 \text{(dynes}\cdot\text{s}/\text{cm}^5).
\]

For sampling of the blood gases arterial blood was collected into heparinized syringes through a catheter in the femoral artery, and mixed venous blood was collected through Swan-Ganz catheter. \(\text{PaCO}_2\), \(\text{PaO}_2\), \(\text{PvCO}_2\), \(\text{PvO}_2\), \(\text{SvO}_2\), \(\text{SaO}_2\), and \(\text{Hb}\) were measured immediately using a blood gas analyzer (OPTI Critical Care Analyzer with Roche OPTI Cassettes E-Ca, OPT3, AVL Scientific Corp, Roswell, U.S.A.). From the above data, arterial oxygen content (\(\text{CaO}_2\)), mixed venous oxygen content (\(\text{CVO}_2\)), oxygen delivery index (DO\(_2\)I), and oxygen consumption index (VO\(_2\)I) were calculated as described previously [3, 12].

Baselines of hemodynamic parameters were measured before initiation of controlled hemorrhage. Total blood volume was measured for each dog. At completion of induced shock, dogs received 3 ml of 0.9% normal saline for every 1 ml of bled (3:1 resuscitation) via intravenous catheter as rapidly as possible [4].

After finishing crystalloid resuscitation, bolus administration of either vasopressin at a dose of 0.4 IU/kg in the vasopressin group or epinephrine [Epinephrine HCl (1:1,000), Dai Han Pharm. Co. Ltd., Korea] at a dose of 0.1 mg/kg in the epinephrine group was given to each animal intravenously, respectively. In the control group, no drugs were given after crystalloid. Evaluation of bolus injection of epinephrine during shock has only been conducted in one report [13]. This experiment used the bolus method and estimated the safety and effectiveness of the method for hemorrhagic shock in dogs.

Before inducing shock, baseline hemodynamic parameters were measured. At the completion of crystalloid resuscitation, oxygen delivery parameters were recorded as a baseline. The systolic and diastolic pressures were measured after induction of shock, at completion of crystalloid resuscitation, and at 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 min after drug infusion or crystalloid resuscitation in the control group. CO and PCWP were determined after induction of shock, at completion of crystalloid resuscitation, and at 15, 20, 45, and 60 min after drug infusion or crystalloid resuscitation in the control group. Oxygen delivery parameters were recorded at 30 and 60 min after drug infusion or crystalloid resuscitation in the control group.

Analysis was performed using statistical software (SPSS v. 12.0K). Statistical analysis included analysis of variance (ANOVA) with repeated measures followed by Duncan’s multiple range test and Student’s paired t-test. Data are presented as means ± SD. A p<0.05 was considered significant and used for significance in all statistical tests. One-way ANOVA was used to compare all pairs of means between groups, and data at the same time points were compared between groups. Comparison of blood pressures at 1, 2, 3, 4, and 5 min after drug infusion in vasopressin and epinephrine groups was evaluated by Student’s t-test.

RESULTS

As shown Fig. 1, SAP increased (294 ± 13 mmHg) abruptly after administration of epinephrine and declined rapidly at 3, 4, and 5 min to 123 ± 23 mmHg, the same level as the vasopressin-treated group (p<0.05). Administration of vasopressin induced a moderate rise in arterial pressure that remained steady for 5 min.

Figure 2 shows the change in DAP before and after induction of shock, at completion of crystalloid resuscitation, and after vasopressin or epinephrine administration. There were no especially significant differences between the epinephrine and control groups after 5 min during the course of experiment. However, the DAP was significantly (p<0.05) higher following administration of vasopressin compared with the epinephrine and control groups, and this tendency was maintained for 55 min, with DAP maintained above 60 mmHg.

Administration of vasopressin or epinephrine did not cause any significant changes in PCWP (Table 1). Administration of epinephrine did not exert different effect on the CI and SVRI compared with the control group. However, in the vasopressin group, the cardiac index decreased and the systemic vascular resistance index increased significantly compared with the control group (p<0.05). The HR decreased after administration of vasopressin compared with the control group (Table 1).

There was no difference in baseline DO\(_2\)I and VO\(_2\)I among the groups (Fig. 3). DO\(_2\)I was significantly decreased in the vasopressin group versus the control group at 30 min (p<0.05). VO\(_2\)I decreased after vasopressin administration at both 30 min and 60 min. Epinephrine showed a tendency to decrease DO\(_2\)I and VO\(_2\)I, but was only statistically significant for VO\(_2\)I at 60 min (p<0.05).

DISCUSSION

This study focused on comparison of the use of vasopressin and epinephrine during uncompensatory hemorrhagic shock. Vasopressin had a longer half-life compared with epinephrine and consequently it may have a detrimental effect on uncompensatory hemorrhagic shock. We evaluated the effects of epinephrine and vasopressin on
cardiovascular function between 1 min and 1 hr after drug administration. The results demonstrated that diastolic arterial pressure was increased during the hour after vasopressin administration when compared with epinephrine administration, while the CI and oxygen delivery/consumption indexes were significantly reduced in the vasopressin group. DAP is suggested to be the best hemodynamic predictor of return of spontaneous circulation and is especially important because it directly influences coronary perfusion pressure [11].

A decrease in CO was also identified in other reports [1]. The use of vasopressin infusion caused a decrease in CI when vasopressin was given in doses >0.04 IU/min [7]. Pregel et al. [18] suggested that the resultant increased afterload after vasopressin administration might contribute to the reduction in CI after restoration of spontaneous circulation in comparison with epinephrine. In comparison with the control group, the oxygen delivery/consumption index was

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Fig. 1. Systolic arterial pressure before and after the induction of shock, at completion crystalloid resuscitation, and after drug administration. B†: Before the induction of shock (Baseline). S‡: Induction of shock. C¶: Completion of crystalloid resuscitation. *Significant (p<0.05) differences were noted between the vasopressin and epinephrine groups.

Fig. 2. Diastolic arterial pressure before and after the induction of shock, at completion crystalloid resuscitation, and after drug administration. a,b Significant (p<0.05) differences were noted among the different dose groups. Values with different superscript letters are significantly different. See Fig. 1 for more information.
Fig. 3. Oxygen delivery index and oxygen consumption index at completion of crystalloid resuscitation and after drug administration. In the control group, the oxygen delivery parameters were measured after crystalloid resuscitation without any drug administration. NS Completion of crystalloid resuscitation. a, b: Significant (p<0.05) differences were noted among the different dose groups. Values with different superscript letters are significantly different.

Table 1. Hemodynamic variables before and after the resuscitation phase in the dogs (mean ± SD)

<table>
<thead>
<tr>
<th>Variable (Unit)</th>
<th>Group</th>
<th>Baseline*</th>
<th>Shock†</th>
<th>NS‡</th>
<th>Time after drug administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>Vasopressin</td>
<td>5.0±1.4</td>
<td>2.8±0.8</td>
<td>9.3±0.8</td>
<td>7.3±1.6</td>
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<tr>
<td></td>
<td>Epinephrine</td>
<td>5.7±1.4</td>
<td>2.8±0.2</td>
<td>9.0±2.4</td>
<td>6.0±3.0</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5.5±1.0</td>
<td>3.5±1.0</td>
<td>10.5±1.0</td>
<td>7.8±0.9</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
<td>5.49±0.54</td>
<td>2.13±0.42</td>
<td>8.11±1.33</td>
<td>5.14±0.56</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>5.77±0.58</td>
<td>2.12±0.13</td>
<td>8.68±1.17</td>
<td>6.18±1.03</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>5.38±0.58</td>
<td>2.15±0.22</td>
<td>8.77±0.74</td>
<td>6.84±0.16</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
<td>1483±174</td>
<td>2613±488</td>
<td>603±67</td>
<td>1245±91</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>1397±121</td>
<td>2574±172</td>
<td>590±84</td>
<td>830±151</td>
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<tr>
<td></td>
<td>Control</td>
<td>1502±228</td>
<td>2577±311</td>
<td>485±79</td>
<td>822±105</td>
</tr>
<tr>
<td></td>
<td>Vasopressin</td>
<td>135±20</td>
<td>137±17</td>
<td>146±20</td>
<td>124±16</td>
</tr>
<tr>
<td></td>
<td>Epinephrine</td>
<td>140±21</td>
<td>137±4</td>
<td>165±47</td>
<td>147±20</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>143±19</td>
<td>129±12</td>
<td>155±19</td>
<td>155±17</td>
</tr>
</tbody>
</table>

* Before the induction of shock. † Completion of shock. ‡ Completion of infusion of 0.9% NaCl (3 mL/m2 of bleeding). a, b: Significant (p<0.05) differences were noted among the different dose groups. Values with different superscript letters are significantly different.

decreased at 30 and 60 min with vasopressin administration. This may be caused by decreased cardiac function because CI is a constituent of both DO2I and VO2I.

To resuscitate clinically ill patients, especially during shock, treatment is directed toward goals based on oxygen delivery parameters, including clinical and metabolic markers and organ function indicators [12]. Shoemaker et al. [22] revealed that hemodynamic parameters using a pulmonary artery catheter, including CI, SVRI, and VO2, showed good specificity and sensitivity for predicting survival. However, there are some reports that CO and PCWP showed less prognostic values [6, 27]. The beneficial effect of vasopressin in shock patients is the increase systemic vascular resistance, which results in effective restoration of blood pressure. Another advantage of vasopressin is maintenance of blood flow to vital organs, such as the brain, lungs, and kidneys [10, 19, 25]. Cardiac output in all groups after vasopressor administration rose to baseline levels (Table 1). However, only the vasopressin group showed maintenance of blood pressure. Therefore, the decreased cardiac output in the vasopressin group does not seem to produce a worse prognostic value for patients with vasopressin administration within a few hours of administration. Blood pressure is a more beneficial hemodynamic parameter than cardiac output for evaluating vasopressin effects in dogs with hemorrhagic shock.

There was no significant difference in systemic vascular resistance between the epinephrine and control groups, which indicates that epinephrine did not work any more effectively on the vascular system than fluid resuscitation without vasopressor. Thus, vasopressin can be chosen as an effective vasopressor in decompensatory hypovolemic shock refractory to fluid resuscitation or other catecholamines, although some cardiac functions (esp. cardiac output) are decreased.

In the epinephrine group, SAP abruptly increased to 294 ± 13 mmHg at 2 min and vasopressin increased SAP to 146 ± 12 mmHg at 1 min after drug administration in this study. Hemorrhaging is commonly associated with trauma in clin-
ics, as is translocation of fluid, with both resulting in decreased circulatory volume [26]. Decompensatory shock in the dog can be complicated by closed-cavity hemorrhage or an abnormality in lungs or brain where interstitial fluid overload can severely affect organ function [21]. Head trauma patients with cerebral edema are probably capable of handling large volumes of crystalloid fluid because most of the crystalloid fluid extravasates to the interstitium within 1 hr of administration.

Epinephrine is commonly administered in veterinary practice by constant rate infusion (CRI) for shock patients due to its short half-life. Bolus injection of epinephrine is preferred in detrimental states requiring cardiopulmonary resuscitation. Mink et al. tried to use and evaluate the effectiveness of bolus injection of epinephrine in dogs with anaphylaxis shock [13, 14]. However, the results were not as favorable as those for CRI. This study also ascertained that a bolus injection of epinephrine can not sustain its vasoactive function and that it has a potential danger for complications with transient hypertension.

Administration of large volumes of crystalloids may potentially worsen the clinical signs associated with pulmonary contusion [5]. These kinds of internal bleeding and trauma patients can face the potential danger of acute severe hypertension for several minutes with epinephrine administration. Thus, vasopressin can be used more safely than epinephrine in patients suspected to have brain or lung injuries or unknown internal bleeding. However, it has been reported that vasopressin was not shown to be beneficial for direct replacement of norepinephrine in patients with septic shock due to a substantial reduction in cardiac output and an increased gastric PCO2 gap [9].

The hemodynamic data reported by Morales et al. [15] was produced by adding vasopressin with a constant rate infusion of norepinephrine. The present experiment was designed to compare the hemodynamic effects of vasopressin with epinephrine without interference between the drugs. Isoflurane might affect the cardiovascular effect of vasopressin. There are few reports concerning the influence of isoflurane on vasopressin and epinephrine when given to dogs in the state of shock, and therefore this requires further study.

REFERENCES


