A retrospective analysis of terlipressin in bolus for the management of refractory vasoplegic hypotension after cardiac surgery

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Abstract

Cardiac surgery performed with cardiopulmonary bypass (CPB) may be complicated by hypotension due to low systemic vascular resistance (SVR). Often in those cases, hypotension is resistant to pressor catecholamines. We report six cases of norepinephrine-resistant postcardiectomy hypotension, treated by terlipressin (TP), a potent vasopressor agent. Between May 2007 and May 2008, we treated six patients with TP administration (1 mg bolus) for post CPB refractory vasodilatory hypotension. Analyzed parameters were: mean arterial pressure (m-AP), SVR, cardiac output index (CI), mean pulmonary pressure (m-PP), and lactate, at baseline (before TP bolus) and 3 h after injection. Before TP bolus, the average m-AP was 53.32 ± 8.86 mmHg, the CI was 3.45 ± 0.24 l/min/m², the SVR was 650 ± 62.03 dyne*s/cm² and the arterial lactate level was 4.6 ± 0.95 mmol/l. Three hours after the TP bolus, the m-AP increased to 81.83 ± 9.71 mmHg (P = 0.002), the CI decreased to 2.88 ± 0.14 l/min/m² (P = 0.002), the SVR increased to 1154 ± 116 dyne*s/cm² (P = 0.002), and arterial lactates decreased to 3.13 ± 0.78 mmol/l (P = 0.015), without significant modification of m-PP and CVP. We treated postoperative refractory low SVR hypotension by TP administration in bolus. Exogenous administration of TP normalized SVR and increased the systemic arterial pressure with a minimum effect on pulmonary pressure. Subsequently, the effect on systemic blood pressure enhanced urine output. No major collateral effects were observed. The administration of TP in bolus may result as a useful alternative for treating refractory low SVR hypotension post CPB.

Keywords: Shock (circulatory); Vascular tone and reactivity; CPB; Inflammatory response complications; Postoperative care; Surgery complications

1. Introduction

Cardiac surgery performed with cardiopulmonary bypass (CPB), may be complicated by hypotension due to low systemic vascular resistance (SVR).

This condition is reported in 5–22% of post-cardiac surgery patients [1]. Different causes have been attributed for it, like the hypothermia and duration of CPB, the total cardiopletic volume infused, the reduced left ventricular function, a preoperative treatment with angiotensin-converting enzyme (ACE) inhibitors, and the systemic inflammatory response syndrome (SIRS) [1], or the inappropriate low arginine vasopressin (AVP) secretion.

In this clinical scenario, the pressor catecholamines may have a reduced effect, due to cellular acidosis, opening of ATP sensitive channels, efflux of K+ and hyperpolarization of the myocytes, which prevents Ca++ channels from opening.

AVP is well known in treating norepinephrine-resistance vasodilatation and has been used for quite some years now in cardiac surgery. However, AVP treatment has been associated to rebound hypotension after the drug discontinuation. Terlipressin (TP) is a synthetic analogue of AVP. In fact, it is a prodrug rapidly converted by endopeptidases into lysine vasopressin, which binds on specific receptors, the V1 receptors on the vascular smooth muscle. TP is characterized by greater selectivity for the V1 receptor than AVP, and therefore, has a stronger vasopressor effect. TP is used to treat acute episodes of esophageal bleeding in patients with cirrhosis. Its use is new in cardiac surgery. TP has a longer duration of action compared to AVP, with a half life of 6 h (half life of AVP is 24 min).

In this retrospective study we analyse our experience with TP in bolus in patients with norepinephrine-resistant postcardiomyotomy hypotension. The aim of this retrospective analysis is to evaluate the effectiveness of TP given in bolus in the treatment of severe vasoplegic shock in post CPB patients.

2. Patients and methods

This is a single-centre retrospective study. Between May 2007 and May 2008, we treated six patients with TP administration (1 mg bolus) for post CPB refractory vasodilatory hypotension.
All of the treated patients presented prolonged low resistance profile (SVR < 700 dyne·s/cm\(^2\)) despite a high dose of norepinephrine (>0.9 μg/kg/min) and despite adequate volume resuscitation (PAOP 12–15 mmHg and CVP 8–12 mmHg) in the aim to maintain mean arterial pressure (m-AP) at 70 mmHg.

We excluded from the analysis patients with septic shock or cardiogenic shock. All patients were sedated with propofol and fentanyl and mechanically ventilated on low peep level (3–5 cm H\(_2\)O).

Haemodynamic monitoring included a pulmonary artery catheter (PAC) and a continuous thermolodization device for cardiac output determination (Vigilance II\(^\text{®}\), Edwards Life-sciences, Irvine, CA, USA).

Analyzed parameters were: m-AP, SVR, cardiac output index (CI), mean pulmonary pressure (m-PP), and lactate, at baseline (before TP bolus) and 3 h after injection.

Demographic and clinical characteristics of study population are reported as the mean and S.D. Mann–Whitney analysis was used when appropriate. P < 0.05 was considered statistically significant. Consent was obtained from the next of kin for all patients during the acute phase after CPB. The study was approved by the Anaesthesia and Critical Care Ethical Committee of ‘Policlinico G. Martino’ Hospital at University of Messina.

3. Results

Table 1 reports the demographics and clinical characteristics of patients. The study group consisted of six patients, four men and two women, with a mean age of 69.6 ± 7.84. All patients underwent coronary artery bypass graft (CABG) surgery on CPB. Four of these patients were treated preoperatively with ACE inhibitor. Total extracorporeal circulation time was 123.5 ± 31.7 min\(^{-1}\) and aortic cross-clamp was 50.8 ± 9.74 min\(^{-1}\). The lowest core temperature during CPB was 34.3 ± 0.51 °C. At intensive care unit admission, after adequate volume resuscitation and norepinephrine titration, the average m-AP was 53.32 ± 8.86 mmHg, the CI was 3.45 ± 0.24 l/min/m\(^2\), the SVR was 650 ± 62.03 dyne·s/cm\(^2\) and the arterial lactate level was 4.6 ± 0.95 mmol/l.

Following TP bolus, systemic vasoconstrictive effect was observed within 15 min. This was followed by haemodynamic improvements. However, in two patients, to increase the vasopressor effects, a second bolus of 1 mg of TP was used 1 h after the first dose.

Three hours after the TP administration, the m-AP increased to 81.83 ± 9.71 mmHg (P = 0.002), the CI decreased to 2.88 ± 0.14 l/min/m\(^2\) (P = 0.002), the SVR increased to 1154 ± 116 dyne·s/cm\(^2\) (P = 0.002), and arterial lactates decreased to 3.13 ± 0.78 mmol/l (P = 0.015), without significant modification of m-PP and CVP (Fig. 1).

Norepinephrine dosage was reduced after TP administration in all patients.

No other vasopressor drugs were administered together with norepinephrine and TP. There was no need to resume norepinephrine higher dosage after the effect of the TP dose wore-off. TP administration did not cause hypertension requiring treatment in any of the patients. And, there were no adverse effects related to TP. Recovery from postoperative vasodilatory shock was complete in all patients within 6 h.

Haemodynamic improvement reflected also on urine output. During vasoplegic status, the mean urine output was 13.83 ± 4.66 ml/h. This increased to 85.83 ± 14.28 (P = 0.004) after TP treatment.

We observed reduction of heart rate to normal values, as well. Patients were discharged at home after a mean of 10 ± 3 days.

4. Discussion

Cardiac surgery, particularly following CPB, may be complicated by vasodilatory hypotension unresponsive to norepinephrine [2]. This may be the expression of a more generalized SIRS. CPB contributes to such an inflammatory response through several mechanisms most notably the generation of shear forces from roller pumps driving blood through the bypass circuit, with exposure to the artificial surfaces. Along with systemic hypothermia of circulating blood, CPB activates numerous cascades, including kallikrein and coagulation, as well as the complement systems leading to the generation and release of endogenous inflammatory mediators. To treat unresponsive vasodilatation, AVP has been used [3]. AVP is a non-apeptide hormone synthesized in the nuclei paraventriculares and supraoptici of the hypothalamus and stored in the posterior pituitary gland. AVP is involved in the regulation of osmotic, volemic and cardiovascular homeostasis. Endogenous AVP secretion is triggered by an increase in blood osmolality, by arterial hypotension and hypovolemia. AVP has an important vasoconstrictor capacity by activating vascular V\(_1\) receptors. This vasoconstrictive effect has been used during cardiopulmonary resuscitation and vasodilatory shock [4]. AVP is

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>EF%</th>
<th>EuroSCORE</th>
<th>CPB time (min)</th>
<th>Aortic clamp (min)</th>
<th>CPB T(_\text{°}) (°C)</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>75</td>
<td>M</td>
<td>45</td>
<td>10</td>
<td>164</td>
<td>54</td>
<td>34</td>
<td>CABG (Redo)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>64</td>
<td>M</td>
<td>43</td>
<td>6</td>
<td>145</td>
<td>65</td>
<td>34</td>
<td>CABG + AF ablation</td>
</tr>
<tr>
<td>Patient 3</td>
<td>81</td>
<td>M</td>
<td>25</td>
<td>13</td>
<td>77</td>
<td>39</td>
<td>35</td>
<td>CABG</td>
</tr>
<tr>
<td>Patient 4</td>
<td>71</td>
<td>F</td>
<td>55</td>
<td>13</td>
<td>123</td>
<td>48</td>
<td>34</td>
<td>CABG</td>
</tr>
<tr>
<td>Patient 5</td>
<td>68</td>
<td>M</td>
<td>53</td>
<td>8</td>
<td>134</td>
<td>57</td>
<td>35</td>
<td>CABG</td>
</tr>
<tr>
<td>Patient 6</td>
<td>59</td>
<td>M</td>
<td>65</td>
<td>4</td>
<td>98</td>
<td>42</td>
<td>34</td>
<td>CABG</td>
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also known as an antidiuretic hormone for its regulatory effects on water excretion by the kidney (V₂ receptors-mediated effect). TP is a synthetic analogue of AVP characterized by greater selectivity for the V₂ receptor than AVP [5].

AVP and TP have been used in arterial hypotension conditions. Adverse effects have been reported for both: splanchnic malperfusion, or coronary vasoconstriction. The spasmogen role for AVP in human internal mammary artery (IMA) during CABG has recently been investigated [6].

However, rebound hypotension has not been reported after discontinuation of TP [7–9] as instead observed with AVP [10].

Both AVP and TP are effective in the treatment of sepsis related arterial hypotension and show reduced catecholamine requirements [8–11].

In post cardiac surgery patients, after CPB, low SVR hypotension may represent an important problem. The effectiveness of pressor catecholamine is impaired due mainly to cellular acidosis provoking reduced Ca²⁺ influx into the cell and smooth muscle contraction is halted [1–10].

The AVP plays a role in the regulation of water balance, and in the vascular regulation of blood pressure. Especially during the shock status, AVP plays an important role in the maintenance of normal blood pressure, and the response to exogenous administration of AVP is increased [12].

Patients after CPB have usually elevated levels of AVP, however, low levels of AVP have been seen after left ventricular device implantation [12]. It seems that long-term congestive heart failure may lead to exhaustion of AVP secretion and a relative deficiency in AVP may correlate with episodes of vasodilatory shock [12]. Exogenous administration of AVP or its synthetics analogue TP may result in

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Fig. 1. Mean arterial pressure, cardiac index, systemic vascular resistance, central venous pressure, arterial lactate, mean pulmonary pressure values before and after (3 h) TP bolus.
an improved and stable haemodynamic state. The increased blood pressure will reflect on glomerular filtration volume and increase in urinary output.

In the series of patients analysed, we report after use of TP in bolus, a statistically significant increase in SVR, increase in MAP, a reduction of lactate level associated to reduction of CI.

After TP treatment all of the patients underwent reduction of norepinephrine dosage. All of this reflected in an improved haemodynamic status, showing that administration of TP bolus is effective to restore normal blood pressure. In none of the patients, we observed clinical manifestations of an excessive systemic or visceral vasoconstriction. Nevertheless, in none of the treated patients, we experienced rebound effect that instead has been reported with AVP use. This may represent an advantage in the literature on the use of TP in bolus after cardiac surgery, and this probably is due to the reported risk of excessive vasoconstriction. However, this report, even if on only a small sample of patients, shows that TP given with accuracy may be of help in particular clinical settings.

5. Conclusion

We treated postoperative refractory low SVR hypotension by TP administration as a bolus. Exogenous administration of TP normalized SVR and increased the systemic arterial pressure with a minimum effect on pulmonary pressure. Subsequently, the effect on systemic blood pressure enhanced urine output. No major collateral effects were observed. The administration of TP in bolus may result as a useful alternative for treating refractory low SVR hypotension post CPB. Further studies, with a higher number of patients and possibly randomised trials comparing TP to other vasoconstrictor agents, including as well a group with methylene blue treatment, would be of help in defining the real advantage or not of its use in this clinical setting.

References


[10] Luckner G, Dunser MW, Jo frustrated that in our series of patients, 4 out of 6 had a preoperative treatment with ACE inhibitors not stopped in advance. The presence of ACE inhibitors therapy in those patients is important to be considered, because many of the cardiac patients undergoing CPB are often on this treatment. Chronic ACE inhibitors therapy has shown to play a role in intra-operative refractory hypotension [13], and TP has already been assessed in patients treated with ACE inhibitors [14] undergoing non-CPB surgery.

A recent study [15] reports on the use of TP in post CPB patients, with improvement in SVR and MAP. In that study, differently than in our series, the authors used TP as a continuous infusion. However, the authors comment that the choice of continuous infusion was taken in the ‘attempt to avert the potentially harmful effects of the drug on systemic, coronary and gastrointestinal circulation’. However, the authors continue affirming that the avoidance of a bolus dose could have been the critical point in their non-surviving patients, being ‘continuous infusion insufficient to restore vascular reactivity’. In fact, patients in post CPB vasopleagogenic shock may be in such a phase of vasoparalysis unresponsive to continuous infusion of TP. Instead, with the use of bolus, the rationale we followed is to give to the patient an isolated stronger dosage of medication in a limited length of time. This approach will give a stronger help, allowing for rapid increase of SVR and m-AP, improving rapidly the haemodynamic status. Nevertheless, in consideration of the longer half-life of TP the administration can be repeated, as we did in two patients to reach a better vasopressor result. It is also to be considered that in our series of patients, 4 out of 6 had a preoperative treatment with ACE inhibitors not stopped in advance.

4.1. Study limitation

The stronger limitation of this analysis is the presence in the study of only six patients. This is a retrospective analysis, and there is not a comparative group using other medication, or the same drug TP given in infusion. However, to the best of our knowledge, there are no other reports in the literature on the use of TP in bolus after cardiac surgery, and this probably is due to the reported risk of excessive vasoconstriction. However, this report, even if on only a small sample of patients, shows that TP given with accuracy may be of help in particular clinical settings.
