

TERLIPRESSIN IN BRAIN DEATH ORGAN DONORS MANAGEMENT REDUCES THE NEED FOR NORADRENALIN CONTINUOUS INFUSION

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Abstract

Management of potential brain death organ donors (BDOD) requires strategies to manage severe cardiovascular and metabolic impairment. Terlipressin is a synthetic analog of vasopressin characterized by greater selectivity for the V1 receptor than vasopressin itself. The aim of this case series is to demonstrate if terlipressin reduces the need for noradrenaline in potential BDOD with hemodynamic instability.

Terlipressin was utilized in 49 consecutive cases during a 24-month period. Reduction of amine dose was considered as the end point. Norepinephrine mean dose before terlipressin administration was 0.229 mcg/kg/min versus 0.055 mcg/kg/min after treatment ($p < 0.0001$).

Our results suggest a role for terlipressin in hormonal replacing therapy in instable BDOD, especially when vasopressin is lacking.

Keywords: *Terlipressin, brain death, organ donors managements, hormonal replacement therapy, grafts survival*

Introduction

Brain death (BD) causes dramatic systemic impairment involving mainly cardiovascular, respiratory, renal and endocrine systems. Hemodynamic instability can potentially lead to the loss of up to 20 per cent of potential organ donors^{1,2}. BD is often characterized by an early catecholamine storm phase, followed by a hypotensive phase managed with fluid replacement and vasoactive drugs. Moreover, levels of cortisol, T₃ and T₄, and antidiuretic hormones dramatically drop. Norepinephrine is commonly used to maintain blood pressure levels in BDOD but peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and possible ischemic injury are described.

Novitzky et al., in late '80s, evaluated the potential effects of hormonal therapy in Brain-Dead Potential Organ Donors³. They administered T₃, cortisol, insulin intravenously and observed a significant improvement of hemodynamic status with decreased requirement of inotropic drugs, and a reduction of serum lactate-pyruvate level. Nowadays, several evidences suggest that management of BD potential organ donors with standardized haemodynamic and hormonal replacement therapy (HRT) protocols improve the number of organs suitable for transplantation and survivor rates due to haemodynamic stabilization and even optimization anti-inflammatory imbalance^{3,4}. Generally, HRT treatment includes levothyroxine, methylprednisolone or hydrocortisone, vasopressin, insulin and desmopressin. Since vasopressin is hardly available in Italy, some centres adopt protocols with terlipressin, instead of vasopressin⁵. Terlipressin is a synthetic analogue of vasopressin characterized by selectivity for the V₁ receptor. It is mainly used in the treatment of acute variceal haemorrhage, in hepatorenal syndrome, and in septic shock^{6,8}.

To date, the efficacy of terlipressin as a vasopressor agent for potential brain death organ donors (BDOD) is not sufficiently tested. We report our experience with a case series of potential BDOD treated with terlipressin for their hemodynamic instability

Methods

The hypothesis we tested was if terlipressin could be useful to reduce the need for norepinephrine infusion in BDOD. At "Maurizio Bufalini" Hospital, from March 2014 to March 2016, cerebral death was diagnosed 65 times by an ad hoc commission. 35 potential BDOD were identified and 32 actual donors were selected eventually.

Data for this study were collected by retrospective evaluation of the medical records; patients who did not receive terlipressin were ruled out.

Our standard clinical practice in any potential BDOD is:

- Pressure control (MAP about 60–70 mmHg, urine output >1 ml/kg/h);
- Blood Transfusion (haemoglobin > 7.0 g/dl);
- Diabetes insipidus management (Desmopressin 0.1 mcg);
- Electrolytes control;
- Glycaemic control (with insulin therapy).

Moreover, HRT was started on every potential BDOD administrating Hydrocortisone (bolus of 50 mg e.v. plus continuous infusion of 150 mg/die) and Thyroxine (75 mcg/die, enteral). Terlipressin (bolus of 0.2-0.5 mg, every 6h and titrated according to hemodynamic response) was added to the HRT cocktail only for haemodynamically unstable patients requiring norepinephrine.

Results

The final population enrolled was 49 patients. We found that the mean terlipressin dose was 0.348 mg and median administration time was 2 (IQR 2). Norepinephrine mean dose was 0.229 mcg/Kg/min (std Dev ± 0.21 mcg/Kg/min) before terlipressin administration and it decreased to 0.055 mcg/kg/min (std Dev ±0.06 mcg/Kg/min) after terlipressin therapy (p<0.0001) (fig 1).

Following Italian law, authorization for organ donation was obtained in 30 cases out of 49 BDOD receiving terlipressin; 3 patients were discharged for incompatibility reasons or organ unsuitability, leaving 27 final donors. No organ was discarded for ischemic lesion. 7 Hearts, 23 livers, 19 kidneys, 3 lungs and 1 pancreas were successfully transplanted.

Discussion

Vasopressor agents are fundamental for BDOD due to peculiar and severe cardiovascular and metabolic impairment that take place during brain death. In fact, due to alteration of the function of the

hypothalamo-pituitary axis that occurs during brain death, pituitary and hypothalamic hormone secretion are altered⁹. To date, vasopressin is considered the first-line vasoactive drugs by the Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations for the treatments of hemodynamic instability and diabetes insipidus in BDOD¹. In fact, vasopressin plays an important role as vasopressor in cases of refractory shock.

Vasopressin or antidiuretic hormone (ADH) is a polypeptide synthesized in the hypothalamus, it is involved in the control of the body's osmotic balance and blood pressure regulation. Arterial baroreceptors in the aortic arch and the carotid sinus are stretch receptors that are stimulated by the variation of the arterial wall due to pressure variation. Hypotension is a main stimulus of vasopressin secretion through this mechanism. ADH exerts its effects by binding to the V receptor on the late distal tubule and collecting ducts of the kidney. This binding is responsible of G activation and of a subsequent increase in the second messenger cyclic AMP. The final result of the activation of this intracellular cascade is the expression of aquaporin-2 (AQP2) channel into the apical membrane¹⁰. Through this channel, water can move passively guided by osmotic gradient, thus reabsorbing water¹¹. Even more, ADH also has a second action on vascular smooth muscle. This mechanism is synergistic with water reabsorption in elevating blood pressure¹⁰. Taking into account that vasopressin is hardly accessible in Italy, an alternative to vasopressin has to be found.

Terlipressin is an analogue of vasopressin and acts as a vasoactive drug through the binding of V1 receptor. It is used mainly in the treatment of acute variceal haemorrhage, in hepatorenal syndrome, and in septic shock^{6,8,12}. In fact, the use of terlipressin leads to an increase of systemic vascular resistance (particularly due to its effects on the splanchnic area) and contemporarily to a reduction of pressure in esophageal varices and portal pressure¹³. Up to now, few data are available on the efficacy of terlipressin in BDOD⁵. Consequently, wishing that our work may represent a contribution to the management of BDOD, we decided to report our experience with the use of terlipressin in these peculiar patients. We

acknowledge the main limitation of this preliminary report: we did not investigate the long-term transplantation outcome. In fact, previous studies on Terlipressin in septic shock highlighted a potential problem of terlipressin therapy, the aforesaid mentioned effect of prolonged vasoconstriction on the splanchnic territories^{6,14}. Nevertheless, we have to emphasise the usefulness of terlipressin in reducing amine dosage. Furthermore, our preliminary data show that the use of terlipressin in BDOD was not associated with an increasing number of organs discarded for ischemic lesion.

Our pilot evaluation cannot be a definitive answer and further larger and well-designed studies are needed to assess the effectiveness of this alternative strategy, especially on long-term transplantation outcome. Our results suggest a role for terlipressin in hormonal replacing therapy in instable BDOD, to reduce norepinephrine infusion request.

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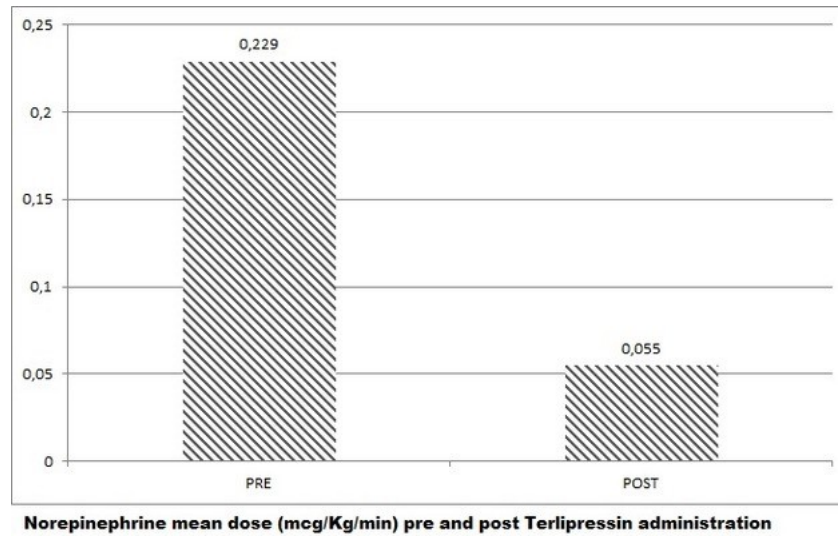


Figure 1. Terlipressin bolus of 0.2-0.5 mg, every 6 hours and titrated according to hemodynamic response was administered to haemodynamically unstable patients requiring norepinephrine