Title: Intravenously Infused Vasopressors in Traumatic Haemorrhagic Shock – A Critically Appraised Topic

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Scenario

Paramedics are dispatched to a 28-year-old female patient at the scene of an MVA. The patient was unrestrained and ejected from the vehicle. On assessment the patient is unconscious with a haematoma to the occiput, contusions and distension in the right hypochondriac region and instability on palpation of the pelvis. You suspect a TBI with catastrophic internal haemorrhagic. The patient presents in a shocked state with absent peripheral pulses, hypotension at 70/45mmHg and tachycardia at 140bpm. You apply a pelvic binder and administer 1000mL of fluid with no remarkable effect. A CCP arrives on scene who decides to intravenously infuse adrenaline to increase perfusion pressure.

PICO (Population – Intervention – Comparison – Outcome) Question

In patients suffering from traumatic haemorrhagic shock, does an intravenously infused vasopressor improve acute and long-term clinical outcomes, when compared to standard fluid therapy?

Clinical Rationale

Whilst fluid resuscitation remains the cornerstone of prehospital haemorrhagic shock management, a growing body of evidence suggests that early fluid administration, prior to definite haemostasis can lead to; dilutional coagulopathy and accelerated blood loss. This evidence has led to renewed interest in fluid-sparing adjuncts, such as vasopressors, which can maintain perfusion pressure without excessive fluid administration. Thus, the objective of this study was to evaluate current literature on the clinical impact of vasopressors in patients with haemorrhagic shock.

Search Strategy

A search of the literature was undertaken using the medical electronic databases; Medline (Ovid) and EMBASE from 2010 to August 2020. The following MeSH keywords were used: prehospital; pre-hospital; out-of-hospital; EMS; IV; inject; intravenous; vasopressor; adrenaline; noradrenaline; epinephrine; AVP; vasopressin; hypovolemia; hypovolemic shock; haemorrhage; haemorrhagic shock; bleeding and trauma. Studies were included if they were; completed in the pre-hospital setting, emergency department, hospital or ICU; conducted by paramedics or physicians; and if they studied vasopressor administration in isolation; in conjunction with fluid therapy; or in patients with refractory shock. Articles were excluded if they were: not written in English; conducted on paediatric patients;

featured animals in the study; or were letters to the editor, editorials, literature reviews or meta-analysis. See Appendix for PRISMA flow diagram.

Table One: Summary of Included Articles

Author, Date	Title	Population: Sample Characteristics	Design / (Level of Evidence)	Results	Main Limitations	Main Strengths
Uchinda et al., 2020	The impact of early administration of vasopressor agents for the resuscitation of severe haemorrhagic shock following blunt trauma	40 patients >16years admitted to the Trauma and Critical Care Center of Osaka City University Hospital with haemorrhagic shock following blunt trauma to the torso	Single-center retrospective study (2b)	Patients administered a vasopressor within one hour of hospital admission had a significantly higher mortality rate ($p = 0.0001$)	Non-controlled study: greater volume of blood transfused in surviving patients Small sample size ($n = 40$) – lacks internal validity Results excluded short term mortality – death with 24h of admission Generalisability is limited as conducted by physicians Retrospective design has increased risk of inaccurate data inclusion	Longitudinal study with data collected over 4-years – enables evaluation of long-term health outcomes Published in a high-quality journal; BMC, with an impact factor of 6.782
Aoki at al., 2018	Use of Vasopressor Increases the Risk of Mortality in Traumatic Haemorrhagic Shock: A Nationwide Cohort Study in Japan	3,551 adult patients with systolic hypotension (< 90mmHg) and a concurrent blood transfusion, at 260 emergency hospitals in Japan between 2004 and 2015	Retrospective cohort study (2b)	Noradrenaline was associated with increased in-hospital mortality – 35% vs. 22% Noradrenaline led to a higher blood transfusion requirement Noradrenaline caused end-organ hypoperfusion and ischemia	Limited control of extraneous variables and contained selection bias Generalisability is limited as conducted by physicians Retrospective design has increased risk of inaccurate data inclusion	Large sample size ($n = 3551$) and multi-centre trial – good internal and external validity Published in a high-quality journal; CCM, with an impact factor of 7.442
Sims et al., 2019	Effect of Low-Dose Supplementation of Arginine Vasopressin on Need for Blood Product Transfusions in Patients with Trauma and Haemorrhagic Shock	Trauma patients (aged 18-65 years) who received at least 6U of any blood product within 12 hours of injury were eligible – received 0.4U/mL of AVP	Single-center, randomised, double-blind clinical trial (1b)	Administration of AVP concurrently with fluid decreased blood product transfusion without increasing mortality AVP stimulated V_1 receptors on vascular smooth muscle – improving vascular tone AVP enhanced renal perfusion by causing efferent arteriolar vasodilation and	Non-controlled study; patients received varying volumes of PRBCs and the AVP dose was inconsistent Generalisability is limited as conducted physicians Single institution trial – limiting the scope and depth of results Small sample size ($n = 100$) – lacks internal validity	Placebo control group facilitated effective comparison of clinical outcomes Robust control of confounding variables Published in a high-quality journal; JAMA surgery, with an impact factor of 13.625

				promoted haemostasis by inducing VWF exocytosis	AVP administered after 6U of blood, limiting transferability to the pre-hospital setting where blood transfusion is a specialised skill – HARU	
Gauss et al., 2018	Effect of early use of noradrenaline on in-hospital mortality in haemorrhagic shock after major trauma: a propensity-score analysis	Adult trauma patients triaged to one of six regional, designated trauma centres in Paris, in which 1000 – 1500mL of crystalloid fluid had failed to restore the target arterial BP	Pre-hospital prospective multicentre trauma trial (1b)	SBP remained below 85mmHg in 40% of patients after noradrenaline administration After adjustment for confounding variables, early noradrenaline administration was not associated with a higher in-hospital mortality rate – higher mortality was caused by the cumulative effect of; more severe injuries, circulatory insufficiency and aggressive ECR	Clinical management was at the discretion of a physician, therefore, does not reflect paramedics ability to clinically identify haemorrhagic shock	Robust control of confounding variables using propensity score matching Results incorporated pre-hospital noradrenaline infusion Large sample size (n = 518) and multi-centre trial – good internal and external validity
Cohn et al., 2011	Impact of Low-dose Vasopressin on Trauma Outcome: Prospective Randomized Study	Adult (>18years) patients who exhibited clinical evidence of an acute traumatic injury with a systolic blood pressure <90 mmHg, were either administered fluid alone or fluid plus vasopressin	Prospective double-blind Randomised Trial (1b)	Patients receiving AVP required less total fluid than the control group (AVP = 3.8L & ECR = 5.4L) Mortality rate after 24hours and at 5days was lower in the AVP group compared to the ECR group; 13% vs. 23%	Small sample size (n = 78) – lacks internal validity Trial was terminated early due to accrual problems – proposed longitudinal study was incomplete Generalisability is limited as conducted by physicians	Randomised design ensured extraneous variables were evenly distributed Placebo control group facilitated effective comparison of clinical outcomes
Plurad et al., 2011	Early Vasopressor Use in Critical Injury Is Associated with Mortality Independent from Volume Status	Intensive care unit (ICU) database was queried for all adult (age >15 years) trauma patients who either received a vasopressor or standard fluid resuscitation therapy	Single-center retrospective review (2b)	Vasopressor administration was independently associated with mortality regardless of fluid status Patients receiving vasopressors required a greater volume of resuscitative fluids and PRBCs Vasopressor agents caused vasoconstriction-induced end organ hypoxia – evidenced by elevated CPK and creatinine levels	Study used CVP as the indicator of volume status – assumed patients didn't have pre-existing cardiovascular disease Generalisability is limited as conducted by physicians Single institution – limited scope and depth of results Limited control of extraneous variables and contained selection bias Retrospective design has increased risk of inaccurate data inclusion	Large sample size (n = 518) – good internal validity Placebo control group facilitated effective comparison of clinical outcomes

Abbreviations: ED; Emergency Department, THS; Traumatic Haemorrhagic Shock, AVP; Arginine Vasopressin, VWF; Von Willebrand Factor, HARU; High Acuity Response Unit, ECR; Early Crystalloid Resuscitation, CVP; Central Venous Pressure, PRBC; Packed Red Blood Cells, CPK; Creatine Phosphokinase, CCM; Critical Care Medicine, BMC; BioMedical Central

Comments

- Early noradrenaline administration is independently associated with increased blood transfusion requirements and long-term mortality. Studies show that noradrenaline, when administered to patients in haemorrhagic shock, causes vasoconstriction-induced end-organ hypoxia and increases the likelihood of acute organ failure and mortality.
- The available literature suggests that low-dose AVP administered concurrently with crystalloid fluid reduces PRBC requirements without increasing mortality. Studies suggest that AVP counteracts hypotension, enhances renal perfusion and promotes haemostasis, thereby improving acute and long-term patient outcomes.
- AVP is considered a potential vasoactive agent in patients with refractory haemorrhagic shock, but its use alone cannot replace fluid therapy.

Considerations for Clinical Practice

Based on the literature reviewed, noradrenaline is not indicated in the resuscitation phase of haemorrhagic shock as it increases mortality. Low-dose AVP presents some clinical benefit in patients with shock unresponsive to fluid therapy, however, this pharmacological agent is currently confined to the in-hospital environment and there is a significant deficit in high-quality research pertaining to its use in the prehospital setting. A large, randomised control trial evaluating the impact of AVP when incorporated into the pre-hospital treatment regime is required before conclusive results can be drawn.

Clinical bottom line

Rapid identification and control of catastrophic haemorrhagic with conservative fluid resuscitation to achieve adequate tissue perfusion (permissive hypotension, SBP >90mmHg), remains the optimal treatment regime for patients with haemorrhagic shock in the pre-hospital setting. Intravenously infused AVP may physiologically benefit patients with refractory shock, especially those in geographically isolated regions where high acuity response units and PRBCs are unavailable and transport time is prolonged. With this said, the introduction of AVP into the pre-hospital setting and expansion of the paramedic scope of practice is non-recommended until comprehensive studies, evaluating the benefits and potential complications of prehospitally infused AVP, are conducted.

References

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Referencing Manager: EndNote

Appendix

Chart One: PRISMA Flow Diagram Representing Search Results and Selection