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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 204485 / SN_0000

Drug Name: Pitressin® (arginine vasopressin injection, AVP)

Indication(s): Treatment of vasodilatory shock, including post-cardiotomy shock and septic shock

Applicant: JHP Pharmaceuticals, LLC

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The clinical studies identified from the published literature seem to suggest that Pitressin® may have an effect to increase blood pressure, measured by SBP, DBP, MAP, to treat or prevent hypotension in the acute peri-operative setting, and septic shock. Although a large body of published literature is available, these studies do not rise to the level to be able to provide evidence for concluding the effectiveness of Pitressin® in prevention and management of vasodilatory shock, or septic shock after cardiac surgery.

1.2 Brief Overview of Clinical Study

This NDA is a 505(b) (2) application that relies on published literature to support the nonclinical profile, clinical pharmacology, safety, and efficacy of Pitressin® in prevention and management of vasodilatory shock or septic shock. The proposed indication is the parenteral use via intravenous injection to increase blood pressure in acute hypotensive states, such as shock and in the post cardiac surgery setting.

The sponsor conducted extensive literature search covered the time period from 1932 to 2012. A total of 52 studies were identified, including prospective/retrospective, randomize/non-randomized, placebo/active controlled and blind/open label trials in both adults and pediatrics. Nineteen (19) studies were summarized in the Module 2.5 of Clinical Overview submitted by the sponsor. The sponsor concluded that AVP significantly decreased norepinephrine dosages needed for maintenance of blood pressure, decreased pulmonary vascular resistance, and increased urine output. It also reduced the amount of catecholamines needed to maintain blood pressure.

1.3 Statistical Issues and Findings

The clinical efficacy data in this NDA come from published literatures. Therefore the data inherit biases such as publication bias, time lag bias, multiple publication bias, location bias, citation bias, language bias and outcome reporting bias.

In the clinical studies identified to support efficacy, none of them meets the standards of “adequate and well controlled study” for conducting a confirmatory trial. Statistical issues are found in all the studies, such as no pre-defined primary endpoint, multiple endpoints yet without multiplicity adjustment, un-approved comparator as controls, selectively reporting study result, etc.

Therefore, the evidence for concluding the efficacy of Pitressin® in the prevention and management of vasodilatory shock or septic shock does not appear to be solid, because of the potential biases from published literature and the unresolved issues that hinder proper

interpretation of the results of the studies. In this reviewer's opinion, the results from the identified studies and analyses are only exploratory. They do not provide confirmative evidence to support the effectiveness of Pitressin® in prevention and management of vasodilatory shock, or septic shock after cardiac surgery.

2. INTRODUCTION

2.1 Overview

Vasodilatory shock is characterized by low arterial blood pressure and decreased tissue perfusion, resulting from decreased systemic vascular resistance. Vasodilatory shock often occurs after surgery requiring cardiopulmonary bypass. Vasopressor catecholamines are used to treat this syndrome, but catecholamine resistance is common and significant toxicity occurs at high doses.

Vasopressin (AVP) is an intriguing hormone in that it has little vasoconstrictor effect in hemodynamically normal subjects, but is an important pressor in states where arterial pressure is threatened. It has been used in prevention and management of vasodilatory shock, as an alternative of catecholamine pressors.

Pitressin® has been used for over 75 years. The first publications on the clinical use of phenylephrine date back to 1932 and the publications have continued over decades. Several contemporary studies were published in 2012.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of <\\cdsesub1\EVSPROD\NDA204485\204485.enx> of the Center's electronic document room.

3. STATISTICAL EVALUATION OF EFFICACY

3.1 The sponsor's Evaluation

3.1.1 Literature Search Strategy and Data Source

The sponsor conducted a comprehensive literature search using PubMed, FDA.gov, and ClinicalTrials.gov databases, along with the review of the use of vasopressors for hypotensive shock conducted by the Cochrane Collaboration (Havel 2011). The search criteria employed for the Cochrane Report included a MEDLINE search (from 1966 to March 2010), EMBASE (from 1989 to March 2010), PASCAL BioMed (from 1996 to March 2010), and BIOSIS (1990 to March 2010). Additional relevant literature citations

contained in the references obtained through these electronic searches were also examined and included in their review.

3.1.2 Clinical Efficacy Studies

The primary published literature consists of peer-reviewed journal articles of 52 clinical studies. The efficacy of Pitressin® in prevention and management of vasodilatory shock was supported by the studies conducted in both adult and pediatric populations. Eighteen studies were reviewed by the sponsor. These studies were separated into two categories: the first was for post-cardiotomy vasoplegic shock and the second was for septic shock, septic and post-cardiotomy shock. These studies will be reviewed separately in the following.

The first part of the clinical summary considers the 10 studies for post-cardiotomy vasoplegic shock, which are summarized in the following table.

Table 1 Clinical Studies of AVP for Post-Cardiotomy Vasoplegic Shock

Author/Date	N	Study Design	AVP Dose	AVP Diluent	Placebo Control
Post-Cardiotomy Vasoplegic Shock					
Alten 2012	37 (19 AVP, 18 no AVP)	Pediatric (neonates): retrospective	0.0003 U/kg/min	Not stated	N/A
Argenziano 1998	40 AVP	Adults: retrospective	0.1 U/min	Not stated	N/A
Argenziano 1999	20	Adults: retrospective	0.1 U/min	Not stated	N/A
Argenziano 1997	10	Adults: randomized, placebo-controlled	0.1 U/min	Saline (personal communication, Dr Landry)	Saline
Dunser 2002	41	Adults: retrospective	0.06–0.1 U/min	Not stated	N/A
Hasija 2010	47	Adults: randomized, double-blind	0.03 U/min	Saline	
Lechner 2007	17	Pediatric (neonates): retrospective	0.00005–0.0002 U/kg/min	Not stated	N/A
Morales 2003	27 (13 AVP, 14 saline placebo)	Adults: randomized, double-blind	0.03 U/min	Saline (confirmed by personal communication Dr Landry)	Saline
Papadopoulos 2010	50	Adults: randomized, double-blind	0.03 U/min	Not stated	Saline
Rosenzweig 1999	11	Pediatric: retrospective	0.0003–0.002 U/kg/min	Not stated	N/A

(Source: 2.5 Clinical Overview)

3.1.2.1 Clinical Efficacy in Clinical Studies: Post-Cardiotomy Vasodilatory Shock in Adults

Among the 18 studies reviewed by the sponsor, 10 of them were conducted on post-cardiotomy vasodilatory shock, 7 in adults and 3 in children. The sample sizes for adult studies were from 10 to 50. Among them, 4 studies were randomized prospective studies. Of these 4 studies, 3 were placebo-controlled. The outcome variables were the hemodynamic variables such as MAP, SVR, pulmonary vascular resistance (PVR), central venous pressure (CVP), the decrease in requirement of NE and urine output. One

study also considered incubation time and the time of ICU stay as the outcome variables. One study was designed for prophylactic use of AVP. No type I error rate was controlled for the outcome variables in these studies. The last randomized prospective study was designed to assess the effect of discontinuing ACE inhibitor on hemodynamic stability using AVP on the patients using ACE inhibitors who undergoing coronary artery bypass graft (CABG) surgery. Three of the 7 adult studies were retrospective studies on the change of hemodynamic variables such as MAP and SVR, required use of NE, cardiac function such as heart rate change.

Summary and conclusions:

- These studies seem to support the use of AVP in the management of vasodilatory shock. Their results suggest that AVP administration produced significant increases in hemodynamic variables such as MAP and SVR.
- The increase in hemodynamic variables was often accompanied by significant reduction of NE requirement as well as improved cardiac function and reduction in intubation time and length of ICU stay.
- One study suggests the response of hemodynamic variables was not affected by the severity of shock, irrespective of the starting value of MAP.
- The study of prophylactic use of AVP suggests that the AVP treated patients had lower required NE use, a shorter intubation time and a shorter length of stay in ICU.

3.1.2.2 Clinical Efficacy in Clinical Studies: Post-Cardiotomy Vasodilatory Shock in Pediatric Patients

At the same time, 3 studies were conducted on pediatric patients. They were all retrospective studies with sample size went from 11 to 37. One study with a sample size of 37 children was for neonates and had a comparison group matched for demographic characteristics, surgical procedure and ICU therapy. The other two studies did not have comparison groups. The outcome to be compared were systolic arterial pressure (SAP), MAP, CVP, HR, vasopressor score, urine output, mean fluid intake, duration of ICU, etc. In the two groups without comparison group, the outcomes before and after the administration of AVP were compared. No type I error rate was controlled.

Summary and conclusions:

- In the two studies without comparison groups, mean SBP, MAP and SRP were significantly increased post AVP administration. The average fluid requirement was significantly reduced after the administration of AVP.

- In the study with a matched comparison group, no significant difference was found between the groups in HR, MAP, CVP, maximum lactate, urine output, etc. However, the AVP group had a significant lower intake of inotrope score, and significant lower mean fluid intake.
- The difference in the durations of mechanical ventilation, stay in ICU and time to chest closure were not statistically significant.

The second part of the clinical summary considers the 8 studies for septic shock, which are summarized in the following table.

Table 2 Clinical Studies of AVP for Septic Shock

Author/Date	N	Study Design	AVP dose	AVP diluent	Placebo Control
Septic Shock, Septic and Post-cardiotomy shock continued					
Lauzier 2006	23 (13 AVP; 10 NE)	Adults: randomized, controlled, open-label	0.04–0.2 U/min	Not stated	NE (diluent not stated)
Malay 1999	10 (5 AVP; 5 Placebo)	Adults; double-blind	0.04 U/min	Not stated	Saline
Patel 2002	24 (13 AVP; 11 NE)	Adults; randomized, double-blind, controlled	0.06 U/Min (0.05, 0.06 U/min)	Not stated	NE (diluent not stated)
Russell 2008	778	Adults; randomized, double-blind, controlled	0.01–0.03 U/min	D5W	Not stated
Torgersen 2010	50 (25 0.033 U/min, 26 0.067 U/min AVP)	Adults: randomized, controlled, open-label	0.033, 0.067 U/min	Saline (personal communication, Dr Dunser)	N/A
Choong 2009	69 (33 AVP; 32 Placebo)	Pediatric, multicenter, randomized, controlled	0.003–0.002 U/kg/min	Not Stated	Saline
Dunser 2003	48 (24 AVP; 24 NE)	Adults: randomized, controlled	0.067 U/min	Saline (personal communication, Dr Dunser)	NE
Holmes 2001b	50	Adults: retrospective	0.01–0.06 U/min	Not stated	N/A

(Source: 2.5 Clinical Overview)

3.1.2.3 Clinical Efficacy in Clinical Studies: Septic Vasodilatory Shock in Adults

Among the 8 studies reviewed by the sponsor for septic shock, septic and post-cardiotomy shock, 7 of them were conducted in adults. One study (VASST, Russell 2008) had a sample size of 778. The other had sample sizes from 10 to 50. Among them, 6 studies were prospectively conducted which were randomized, controlled either by placebo or NE, either open labeled or double blinded. One study compared two doses of AVP.

VASST (Russell 2008) was a large multicenter, randomized, NE controlled, stratified study. The sample size was 778 (396 in AVP and 382 in NE) and the primary endpoint was 28-day mortality rate and the secondary endpoints included 90-day mortality, days alive and free of organ dysfunction during the first 28 days, days alive and free of vasopressor use, mechanical ventilation or renal replacement therapy, etc.

The outcome variables for other prospective studies were the hemodynamic variables MAP, SVR, PVR, CVP, the decrease of required of NE, organ dysfunction and adverse events. No type I error rate was controlled.

Among these 7 studies conducted in adults, one was a case-control study for severe septic shock patients on the change of hemodynamic variables MAP and SVR, required use of NE, and adverse events.

Summary and conclusions:

- These studies seem to support the use of AVP in the management of septic shock. They suggest that AVP administration produced significant increase in hemodynamic outcomes such as MAP, SVR, systolic ABP, and urine output, improved mean cardiac index and reduced required NE intake compared to placebo or active control of NE.
- The primary endpoint of 28 day mortality rate in study VASST was not statistically different between the treatment groups (35.4% in AVP vs. 39.3 in NE, with $p=0.26$), neither was the secondary endpoint of 90 day mortality rate. However, post-hoc study suggested that the heart rate was significantly lower in AVP group over the first 4 days, so was the NE infusion rate during the same period. Post-hoc subgroup analysis suggested that AVP might have had improved mortality in subgroup with low lactate level. These were all exploratory.
- The case-control study (Holmes 2001b) showed that the lower AVP infusion (below 0.04 U/min) increased MAP and urine output, and decreased pressor requirements in patients with severe septic shock.

3.1.2.4 Clinical Efficacy in Clinical Studies: Septic Vasodilatory Shock in Pediatric Patients

There was one multicenter, randomized, placebo controlled study on pediatric patients with vasodilatory shock (Choong 2009). The sample size was 69 (35 in VAP vs. 34 in placebo). The primary endpoint was time to vasoactive-free hemodynamic stability. The secondary endpoints included mortality, organ-failure free days, length of ICU stay, and adverse events.

Summary and conclusions:

- There was no statistically significant difference between the two groups in the primary outcome. No significant differences were found in secondary endpoints of mortality, organ-failure free days, length of ICU stay, and adverse events.

3.2 Statistical Reviewer's Evaluation

3.2.1 Review Strategy

The NDA included a large body of published literature on AVP use in various populations. The statistical reviewer decides to focus on prospective, randomized, double-blinded, placebo/active controlled studies that demonstrated efficacy of AVP. No formal statistical analysis was conducted, studies were critiqued and results were summarized and integrated.

3.2.2 Review of Clinical Studies

3.2.2.1 Placebo Controlled Studies

The sponsor identified four prospective, randomized, double-blinded/ open-label, placebo controlled studies that demonstrated superior efficacy of AVP. The studies are discussed individually as follows (Tables 3-5):

Table 3 Papadopoulos et al study (*J. of Cardiothoracic Surgery* 2010, 5:17)

Study Design	A randomized, double-blinded, single-center clinical study of perioperative infusion of low- dose of AVP
Sample Size	50
Population	Patients undergoing CABG who were on ACE inhibitor for ≥ 4 weeks and who had impaired left ventricular ejection fraction
Treatment Group and Dose	Group A (n=25), patients received AVP infusion (0.03 IU/min); Group B (n =25), patients received normal saline intraoperatively
Administration Route	Infusion (0.03 U/min) for 4 postoperative hours
Primary Endpoint (s)	Not clearly specified. Major interests are: <ul style="list-style-type: none"> • Hemodynamic status including: MAP, CVP, SVP, ejection fraction (EF), HR, MPAP, cardiac index (CI), PVR. • Incidence of vasodilatory shock • Requirement of catecholamine support • Blood-loss and urine output, etc.
Secondary Endpoint (s)	Unspecified.
Statistical Method	<ul style="list-style-type: none"> • Comparison of continuous variables between groups was conducted by the two-sample t-test. • Categorical data were analyzed using the chi-square test or Fisher's exact test. • Type I error rate was $p= 0.05$
Results	<p>No significant differences were found regarding HR, MPAP, CI, and PVR. Values of MAP, CVP, SVR, and EF following extracorporeal circulation showed significantly higher values in group A.</p> <p>In Group A, norepinephrine was necessary in fewer patients ($p=0.002$) and with a lower mean dose ($p=0.0001$), additive infusion of epinephrine was needed in fewer patients ($p = 0.001$). Group A was associated with a higher postoperative urine output during the first 24 hours ($p = 0.0001$), and lower postoperative blood loss for the first 24 hours ($p = 0.0001$).</p>
Comments	Although it is double blinded, this is a single-center study and thus the apparent drug effects have potentially limited external validity. The primary endpoints of interest were not clearly specified. In fact, no study objective statement was given in the paper. At least 19

	comparisons were performed as listed in Table 3 without multiplicity adjustment for the comparison of the outcomes between groups. Although the low p-value seems to suggest a positive signal of the effectiveness of AVP in prevention and management of vasodilatory vasoplegic syndrome in patients undergoing CABG, such conclusions are post hoc.
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Table 4 Hasija et al study (*J. Cardiothoracic and Vascular Anesthesia* 2010; 24 II: 230-238)

Study Design	A randomized, double-blinded, single-center clinical study
Sample Size	47
Population	Patients on the ACE inhibitor ramipril for 6 weeks before undergoing elective primary CABG surgery on cardiopulmonary bypass (CPB)
Treatment Group and Dose	Patients were randomized into three groups: Group A (n=16), patients discontinued ACE inhibitor ramipril 24 hours before surgery; Group B (n =16), patients continued ramipril until the morning of surgery; and Group C (n=15), patients continued ramipril until the morning of surgery and received VAP infusion (0.03 U/min).
Administration Route	vasopressin infusion (0.03 U/min)
Primary Endpoint (s)	Unspecified. However, multiple hemodynamic parameters (HR, MAP, CVP, MPAP, pulmonary capillary wedge pressure (PCWP), CI, and SVR) seem to be of the main interest.
Secondary Endpoint (s)	Unspecified.
Statistical Method	To detect a 20% decrease in MAP, the sample size of 47 (16, 16, and 15, respectively in the 3 groups) carried 75% statistical power and 0.05 level of significance. Qualitative data were analyzed by a chi-square test. Quantitative data were analyzed by analysis of variance or the Mann-Whitney U test.
Results	No specific p-values were given, but the comparisons with p-value below 0.05 were considered as statistically significant. Specifically, compared to Group B, AVP group (Group C) significantly reduced HR at arrival of ICU and postoperative Day 2, significantly increased MAP at post-CPB, and significantly increased SVR at post-CPB and before shifting.
Comments	Although it is double blinded, this is a single-center study. The primary endpoints of interest were not clearly specified. No multiplicity was controlled for the comparison of the outcomes between groups. The conclusions are post-hoc.

Table 5 Morales et al study (*Ann Thorac Surg* 2003; 75: 926–30)

Study Design	A randomized, double-blinded, placebo controlled, single-center clinical study
Sample Size	33 (17 in AVP vs. 16 in normal saline)
Population	Patients undergoing CABG or valvular surgery on pre-op ACE inhibitors for > 2 weeks.

Treatment Group and Dose	AVP (0.03 U/min) vs. equal volume of normal saline starting 20 minutes before CPB.
Administration Route	vasopressin infusion (0.03 U/min)
Primary Endpoint (s)	Unspecified. However, multiple hemodynamic parameters, cardiac output, episodes of hypotension, peak NE, the duration of catecholamine vasopressor use and complications seemed to be of the main interest. ICU lengths of stay and intubation time were also recorded.
Secondary Endpoint (s)	Unspecified.
Statistical Method	<ul style="list-style-type: none"> • All interval data were analyzed by the two-sample t-test. • Nominal data were analyzed using the Fisher exact test. • Count (frequency) data were compared using Poisson regression techniques. • Type I error rate was $p=0.05$.
Results	<ul style="list-style-type: none"> • Peak NE dose and duration of catecholamine use were significantly reduced by AVP ($p<0.05$). • The number of hypotensive episodes was lower in AVP group ($p<0.01$). • Intubation time and ICU stay time were significantly shortened ($p<0.05$) by AVP.
Comments	This is a single-center study. The primary endpoints of interest were not clearly specified. No multiplicity was controlled for the comparison of the outcomes between groups. The conclusions are post-hoc.

Summary:

- These studies were conducted in patients undergoing CABG who were on ACE inhibitor; vasopressin infusion was the common route. The studies seem to suggest that Pitressin® improve hemodynamic profiles (measured by increased MAP, SVR, CVP, reduced HR, and hypotensive episodes), reduce the requirement of NE infusion and duration of catecholamine use, reduced the number of hypotensive episodes, reduced intubation and ICU stay time, and increase urine output, etc.
- There were a number of statistical issues. These studies were all single center studies and hence the interpretability of the study results is very difficult, due to possibly unique clinical environment and interventions, possibly unique baseline risks, etc. In general, the results of such single center studies should be exploratory in nature for further research, rather than being considered as the conclusive evidence for the effect of the treatment. In addition, the primary endpoints in these studies were not pre-specified. There were often multiple endpoints of major interest, without controlling multiplicity. The apparent statistically significant results were more likely to be reported. The conclusions are post-hoc and need to be replicated in at least one multi-center trial.

3.2.2.2 Active Controlled Studies

Three active controlled studies that were claimed to have demonstrated superior efficacy over the control arm by the sponsor were identified. The studies were summarized as follows:

Table 6 Lauzier et al study (*Intensive Care Med* (2006) 32:1782–1789)

Study Design	A randomized, active controlled, open-label, multicenter clinical study comparing AVP and NE
Sample Size	23 (13 in AVP group vs. 10 in NE group)
Population	Patients with early hyperdynamic septic shock
Treatment Group and Dose	AVP at 0.04-0.2 U/min vs. NE at 0.1 - 2.8 µg/kg/min
Administration Route	Infusion
Primary Endpoint (s)	Unspecified. However, outcomes of major interest include multiple hemodynamic variables (MAP, HR, SVRI, PVRI, MPAP, CVP, PAOP), organ dysfunction variables, and adverse events.
Secondary Endpoint (s)	Unspecified.
Statistical Method	Differences within groups were analyzed by one-way analysis of variance for parametric variables. The Kruskal-Wallis test was used for comparison within groups and the Mann-Whitney U test with Bonferroni's adjustment for comparisons between pairs. Differences between groups were analyzed by linear mixed-effects models to consider death-related dropouts. All comparisons with a p value less than 0.05 were considered as statistically significant.
Results	The major hemodynamic variables were not significantly different between the two groups (Table 2). AVP group had a lower modified Sequential Organ Failure Assessment (SOFA) score at the end of the experiment than NE group (p = 0.04).
Comments	Primary endpoint was not specified. The major hemodynamic variables of major interest were not significantly different between the two groups. The conclusions are post-hoc. There is no way to know whether p = 0.04 is a chance finding or not.

Table 7 Dunser et al study (*Circulation*. 2003; 107: 2313-2319)

Study Design	A randomized, active controlled, open-label, single center clinical study comparing AVP and NE
Sample Size	48 (24 in AVP + NE group vs. 24 in NE alone group)
Population	Patients with advance vasodilatory shock, with a MAP 70 mm Hg
Treatment Group and Dose	AVP at 4U/h vs. NE was adjusted to maintain MAP ≥ 70 mm Hg.
Administration Route	Infusion
Primary Endpoint (s)	Hemodynamics during the 48-hour observation period. This includes: HR, MAP, mean PAP, pulmonary capillary wedge pressure, and cardiac and stroke volume indices, SVR, left ventricular stroke work index (LVSWI), systemic oxygen transport, and consumption index.
Secondary Endpoint (s)	Changes in other single-organ functions, including tonometrically derived gastric parameters during the study period.
Statistical Method	Differences in hemodynamic and single-organ variables between groups and within repeated measurements were analyzed by using

	linear mixed-effects models to account for death-related dropouts. Main comparisons with a $p < 0.05$ were considered as statistically significant.
Results	<ul style="list-style-type: none"> • HR decrease in AVP group was significantly lower ($p=0.003$). • MAP increase in AVP group was significantly higher ($p<0.001$). • LVSWI increase in AVP group was significantly higher ($p<0.001$). • NE requirement in AVP group was significantly lower ($p<0.001$). • Total bilirubin concentrations in AVP group was significantly higher ($p=0.037$).
Comments	This is a single-center study. Multiple primary and secondary endpoints were designed. Multiple comparisons between treatment groups were made. No multiplicity was adjusted. The patients receiving AVP in this study seemed to have a better myocardial performance, as assessed by cardiac index, stroke volume index, and LVSWI, than NE patients.

Table 8 Torgensen et al study (*Intensive Care Med* (2010) 36:57–65)

Study Design	A randomized, open-label, single-center clinical study comparing two doses of AVP
Sample Size	50 (25 in 0.033 IU/min AVP group vs. 0.067 IU/min AVP group)
Population	Critically ill patients with vasodilatory shock subsequent to sepsis, SIRS, or cardiac surgery requiring norepinephrine > 0.6 $\mu\text{g}/\text{kg}/\text{min}$
Treatment Group and Dose	Two doses of AVP at 0.033 IU/min and 0.067 IU/min.
Administration Route	Infusion
Primary Endpoint (s)	Hemodynamic responses include: HR, MAP, PAP, SVR, etc.
Secondary Endpoint (s)	Differences in organ function and laboratory variables, AVP and prolactin plasma levels as well as the rate of adverse events.
Statistical Method	<ul style="list-style-type: none"> • ITT population was analyzed. • Student-t (continuous) or Fisher's exact test (categorical) was used to compare clinical parameters and the rates of adverse events between groups. • To compare the hemodynamic response, changes in laboratory variables as well as plasma hormone levels over time between groups, a linear mixed effects model was applied to account for dropouts during the observation period. • Type I error rate is $p = 0.05$ for statistical significance.
Results	<ul style="list-style-type: none"> • No significant difference in hemodynamic variables was found between the two AVP groups. • AVP plasma levels increased in both groups but were higher in the high AVP dose group ($P < 0.001$). • There was no difference in the course of prolactin plasma levels between the two AVP groups. • High dose AVP group required less NE than the low dose group ($p=0.006$).
Comments	This is a single-center study. Multiple primary and secondary endpoints were designed. Multiple comparisons between treatment groups were made. No multiplicity was adjusted. The patients receiving high AVP dose level in this study did not seem to have a larger improvement on hemodynamic variables, as assessed by HR, MAP, PAP, SVR, etc. The higher AVP dose level seemed to improve plasma level and reduce NE requirement.

Summary:

- Three studies were conducted on Pitressin®, two were actively controlled and one included a high dose and a low dose. These studies gave mixed messages. Only one study suggested that Pitressin® improve hemodynamic profiles (measured by increased MAP, LVSWI, reduced HR. etc.), reduce the requirement of NE infusion. The other two did not show benefit on the hemodynamic profiles although they seemed to show other benefits for the use of AVP, e.g., the high dose increased the AVP plasma level.
- Among the three studies, only Dunser et al. (2003) seemed to suggest that the patients receiving AVP have a better myocardial performance, as assessed by cardiac index, stroke volume index, and LVSWI, than NE patients; however, this is a single center study and needs a multi-center study to confirm the results. Other two active controlled studies did not provide support for the similar benefit of AVP.

3.3 Conclusion

The identified randomized, double-blinded, placebo/active controlled studies seem to suggest that Pitressin® may have an effect on improving hemodynamic profiles in various populations. Pitressin® seems to have other benefits such as reducing the NE requirement, increasing urine output, reducing intubation and ICU stay time, increasing bilirubin concentrations, etc. As these studies shed some light on the possible signals on the benefits, based on the aforementioned reasons, they do not provide conclusive evidence for the effectiveness of Pitressin® in prevention and management of vasodilatory shock, or septic shock after cardiac surgery.

4. CONCLUSIONS AND RECOMMENDATIONS

The clinical studies identified from the published literature seem to suggest that Pitressin® may have an effect to increase blood pressure, measured by SBP, DBP, MAP, to treat or prevent hypotension in the acute peri-operative setting, and septic shock. Although a large body of published literature is available, these studies do not rise to the level to be able to provide evidence for concluding the effectiveness of Pitressin® in prevention and management of vasodilatory shock, or septic shock after cardiac surgery.

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