

Improving Shock Treatment: Vasopressin in Refractory Traumatic Hemorrhagic Shock (VITRIS) Study

Study Protocol of a Multicenter, Randomized, Controlled Trial Assessing Arginine Vasopressin vs. Saline Placebo in Refractory Traumatic Hemorrhagic Shock Patients (VITRISstudy)

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Short Title: VITRIS Study

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ISSN 1867-1918

Summary

Physicians and EMS professionals have to deal with critical situations like hemorrhagic shocks that are unresponsive to common intervention. When volume replacement and common catecholamine treatment are ineffective, the hemorrhagic shock enters into an irreversible and for the patient often life-threatening phase. Aggressive volume replacement by crystalloid and hypo-osmolar solutions has not shown a better outcome. However arginine vasopressin is most likely to improve this situation, especially when administered prior to the regular volume replacement and catecholamine treatment. Arginine vasopressin is expected to stabilize the arterial blood pressure and shift blood supradiaphragmatically to ensure a better perfusion of heart and brain. Therefore it avoids a counterproductive aggressive volume replacement and consequently increases the survival rate of patients with hemorrhagic shocks significantly.

To prove these effects the study team, led by Prof. Volker Wenzel from the University of Innsbruck (Austria), designed a multicentre, randomized, controlled trial assessment study. The study is registered as EudraCT-study and has already passed authorization of Austria's ethic commission. However the explored results from former studies are promising. In Germany the study is still in the approval procedure of the general ethic authority in Berlin which has not given green light, yet, to start with the investigations and tests in Germany.

Four big European HEMS operators, ADAC Air Rescue, DRF (both Germany), ÖAMTC Austrian Air Rescue, and the Swiss REGA are directly involved in this important and potentially ground-breaking research project.

Stefan Becker

The following Study Design as available on website www.vitris.at

Introduction

Without research, trauma is the most common killer of children and working-aged adults will remain the „hidden epidemic of modern society“, and even seemingly simple questions about prehospital shock treatment are likely to remain unanswered.¹ Worldwide, there are more than 5 million injury-related deaths every year, as well as a tremendous burden of disability and economic loss;^{2,3} about one third of these probably suffers from trauma-associated hemorrhagic shock.⁴ Since many seriously injured patients die before arriving at hospital,⁵ the search for a simple and effective intervention to treat hemorrhagic shock is overdue; this is especially important when considering that 60% of non-central nervous system trauma deaths were judged to be preventable had bleeding.⁶

Although at the time of the first world war one expert stated that fluid resuscitation may be deleterious before hemorrhage is controlled,⁷ the subsequent management of uncontrolled hemorrhagic shock was to infuse large amounts of intravenous fluids in order to maintain cardiocirculatory homeostasis.⁸ While fluid replacement is established in controlled hemorrhagic shock, its use in uncontrolled hemorrhagic shock is still controversial,^{9,10} because it may worsen bleeding due to dilution of coagulation factors, and increase arterial blood pressure-mediated impairment of formation of new blood clots, and dislodgement of existing ones.¹¹⁻¹⁶ In agreement with these reports, a survival benefit was found in patients with penetrating torso injuries and subsequent uncontrolled hemorrhagic shock, when aggressive fluid resuscitation was deliberately delayed until surgical control of the bleeding site had been achieved.¹⁷

When arterial blood pressure during uncontrolled hemorrhagic shock is barely detectable, pharmacological support such as epinephrine is needed,¹⁸ but this strategy has been questioned.¹⁹ Since 1970, ornithine-8-vasopressin, an analogue of human endogenous arginine vasopressin,²⁰ and since 1988, arginine vasopressin²¹ have been used successfully in hemorrhagic shock patients unresponsive to fluid resuscitation. Similar results were reported in 1971 in a canine model of hemorrhagic hypotension using lysine vasopressin, another vasopressin analogue.^{22,23} In agreement with these studies, arginine vasopressin has recently been shown to be an effective vasopressor during the irreversible phase of hemorrhagic shock that is unresponsive to volume replacement and catecholamine vasopressors.²⁴

During cardiopulmonary resuscitation, arginine vasopressin shifts blood from the gut, muscle and skin towards the heart and brain, thus improving vital organ blood flow and survival in both normovolemic and hypovolemic animals.²⁵⁻²⁷ In a porcine model of uncontrolled hemorrhagic shock due to a liver laceration, all fluid resuscitation and all placebo pigs died within ~15 min of therapeutic intervention, whereas all arginine vasopressin-treated animals survived.^{28,29} fluid resuscitation was associated with increased blood loss, and saline placebo animals died of refractory cardiocirculatory shock.³⁰ In a porcine model of severe thoracic trauma followed by hemorrhagic shock, arginine vasopressin stabilized arterial blood pressure, cut the amount of fluid resuscitation volume in half, improved pulmonary function, and decreased mortality.³¹ This may indicate three beneficial effects of arginine vasopressin in this situation; increasing arterial blood pressure in fluid- and catecholamine-refractory shock,³² shifting blood away from a subdiaphragmatic bleeding site towards the heart and brain (Figure 1),³³⁻³⁵ and decreasing

fluid resuscitation requirements.³⁶ These mechanisms might have been beneficial in 14/34 (41%) of traumatized cardiac arrest patients who had liver and/or spleen ruptures.³⁷



Figure 1. Arginine vasopressin given during uncontrolled hemorrhagic shock shifts blood from the periphery towards the heart, lungs and brain (white arrows); which may increase vital organ perfusion pressure, and decrease bleeding.

Hypothesis

The purpose of this trial is to assess the effects of arginine vasopressin vs. saline placebo on hospital admission rate (primary study end point), as well as on hemodynamic variables, fluid resuscitation requirements and hospital discharge rate (secondary study end points) in prehospital, presumed traumatic hemorrhagic shock patients with a systolic arterial blood pressure below 90 mm Hg after more than 10 min but less than 30 min of standard shock treatment by the EMS physician. Accordingly, the study reflects an add-on design to standard traumatic shock therapy. The hypothesis is that both arginine vasopressin and saline placebo have comparable effects on hemodynamic variables, fluid resuscitation requirements, and hospital admission and discharge rate; the alternative hypothesis is that arginine vasopressin has more beneficial effects than saline placebo.

Study design

The study will be designed as a multicenter, randomized, placebo-controlled clinical trial with blinded assessment of the outcome in a study network with helicopter EMS units in Austria, Germany, Italy, and Switzerland. The protocol, information and consent procedure will be approved by the institutional review board of each center. Since this is a study randomizing unconscious patients who are unable to give informed consent at the time of randomization, the requirement of informed consent is planned to be waived in accordance with the ethical standards of national legislation of the above countries, and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal products. Depending on the patient's outcome, either the surviving patient, or the patient's family in case of death or survival with a mental handicap will be informed about the trial; the protocol specifies that if there are any objections, the patient will be withdrawn from the study. Treatment assignments of blinded study drugs will be randomly generated by computer in blocks of two, with stratification according to center. Before the start of the trial, staff at participating centers will be informed about the rationale of the protocol and the study; participating centers will be subsequently contacted and visited to ensure proper enrollment.

Inclusion criteria will be adult patients with shock (systolic arterial blood pressure <90 mm Hg) that is presumably caused by traumatic hemorrhage which does not respond during the first 10 min, but not longer than 30 min of standard shock treatment [endotracheal intubation, crystalloid-, colloid-, and hypertonic saline (up to 4 ml/kg) fluid resuscitation, and catecholamine (ephedrine, phenylephrine, norepinephrine, epinephrine) vasopressors] after arrival of the EMS physician. Since injuries in multiple trauma patients are usually complex, and local protocols, experience and settings may differ, there is no anticipated

benefit of a mandatory standardized shock treatment protocol, since this could result in a Hawthorne effect³⁸ and therefore a significant confounding variable. Instead, this project is aimed to determine whether pharmacological management of arterial blood pressure in patients with severe traumatic hemorrhagic shock is beneficial in current shock treatment protocols.

Exclusion criteria are terminal illness, no intravenous access, age less than 18 years, injury more than 60 min before randomization, cardiac arrest before randomization, presence of a do-not-resuscitate order, untreated tension pneumothorax, untreated cardiac tamponade, known pregnancy, or participation in another clinical study. Although other trauma studies have randomized patients immediately after initial on-scene assessment when systolic arterial blood pressure was below 90 mm Hg or when cardiac arrest had occurred,¹⁷ this does not take into account that standard shock treatment may be able to stabilize cardiocirculatory function, which would render additional experimental treatment futile. Moreover, since trauma patients with cardiac arrest on the scene or at hospital admission rarely survive,³⁹⁻⁴¹ randomizing these patients would dilute the chance of detecting a treatment effect.

If all inclusion criteria are met, and no exclusion criteria exist, patients can be randomized (Figure 2). The experimental intervention (10 IU arginine vasopressin vs. an equivalent amount of normal saline) will be administered intravenously during ongoing standard shock treatment. Study drug preparation will be in ready-to-inject syringes by a company specialized in supplying logistical support for clinical trials.

If an acceptable systolic arterial blood pressure (>90 mm Hg) is subsequently not achieved, up to two further consecutive injections of the study drugs will be given. This means that patients in the arginine vasopressin group may receive up to

three doses of 10 IU arginine vasopressin, while patients in the placebo arm may receive up to three times a comparable amount of normal saline. Exact duration between study drug injections will be decided by the EMS physician at the scene in order to allow the possibility of titrating arterial blood pressure individually; however, recommended injection intervals are every ~5 min if systolic arterial blood pressure is below 90 mm Hg. Both randomization and subsequent injections of the study drug are allowed at the scene and during transport to the hospital as well if the 30 min interval from the first contact with the randomizing EMS physician is not exceeded. If the patient's blood pressure remains unstable after three injections of the study drug, injection of open-label arginine vasopressin is not allowed. Investigators and physicians will be blinded to the study drug codes unless decoding becomes a clinical necessity for clinical management; in which case the Data Safety/Monitoring Board has to be informed.

The resuscitation attempt until initiation of surgery, or admission to an intensive care unit will be documented according to the Utstein-style,⁴² and the trauma registry⁴³ of the German Society of Trauma Surgery, and subsequently mailed to the central coordinating office in Innsbruck, Austria. The data will be scanned and automatically entered into a database of a previously validated data storage system (www.datapec.de); however, independent crosschecks by blinded investigators will be performed. Original data will be made available to the Data Safety/Monitoring Committee for independent scrutiny. An adjudication committee, unaware of treatment allocation, will assess patients who are randomized but do not meet the inclusion criteria, or have exclusion criteria. Patients judged to be ineligible are not included in the final analysis; but will be compared with those included in the analysis.

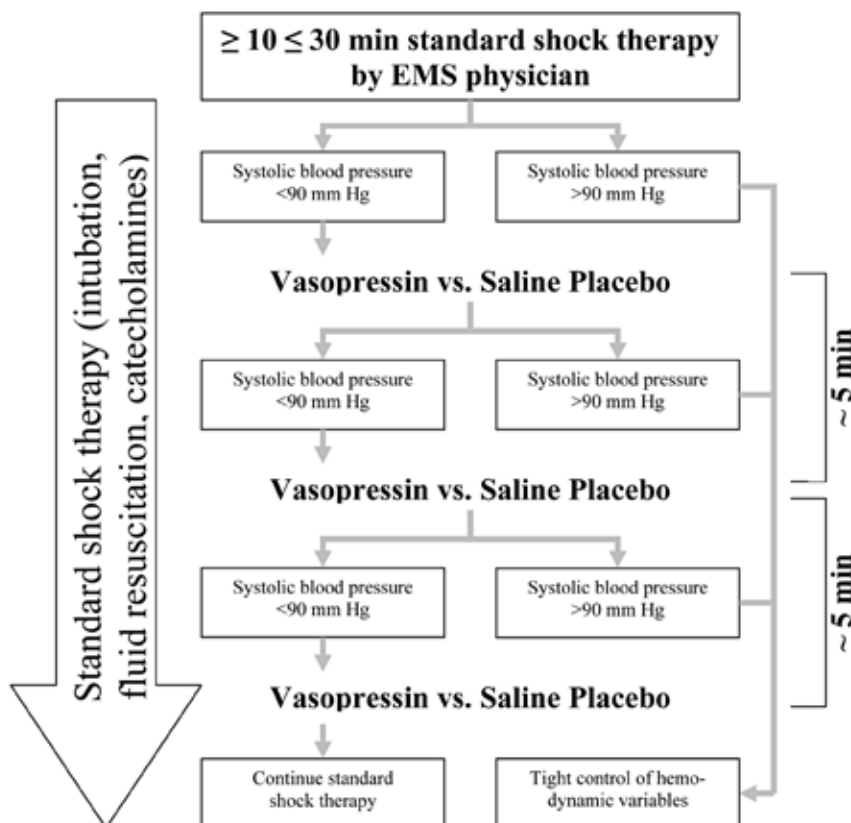


Figure 2. Study Algorithm

Randomization time point

Unfortunately, the exact timing of interventions and randomization is lacking completely in previous prospective trauma studies,^{17,44} with exact data stemming exclusively from CPR trials.⁴⁵ Out of 96,403 scene calls of the Austrian Automobile Association helicopter EMS (January 1st, 1998 to December 31st, 2005), 78,561 primary scene calls were identified. Out of 45,511 scene calls for trauma patients, NACA-5 cases were chosen due to an assumed severe trauma (almost 60% were intubated); CPR cases were excluded which would dilute intervention times due to different treatment strategies. The comparison of NACA-5 cases with vs. without intubation by the helicopter EMS crew [(treatment time 34 ± 27 min ($n=2,079$) vs. 24 ± 16 min ($n=1,486$))] reveals that endotracheal intubation is performed about 10 min after arrival of the emergency physician at the scene. Since induction of anesthesia with subsequent endotracheal intubation often results in additional hypotension in trauma patients, it may be wise to open the window for randomization 10 min

after arrival of the EMS physician, and close it 30 min after arrival of the EMS physician. In this way, the study has a chance of preventing cardiocirculatory collapse in trauma patients with life-threatening injuries, and preventing randomization of hopeless cases with prolonged ischemia which renders subsequent survival extremely unlikely. Furthermore, a randomization time window of 20 min enables the helicopter EMS crew to consider the decision to randomize carefully, and is unlikely to force them into a situation which renders problems that are not anticipated in the study protocol.

Estimated number of required patients

An estimation of the required number of patients for this trial is difficult because trauma patients with life-threatening hemorrhagic shock usually have very complex injuries. Also, early deaths due to non-survivable injuries, or skewed distribution of overall survival rates (for example, 93% survival rate)⁴⁶ may decrease the likelihood of determining a significant result.⁴⁷ These problems may have contributed to reporting non-significant results in trials for the use of selective decontamination of the digestive tract,⁴⁸ interferon on infection-related deaths,⁴⁹ hypertonic saline/dextrane infusion for hypotension,⁵⁰ tilirizad mesylate in head injury,⁵¹ and Diaspirin cross-linked hemoglobin for hemorrhage.⁵² Even when patients with a low chance of survival are studied (for example, when half of the patients only have a 10% chance of survival) and there is therefore a good chance that a given study intervention would be able to demonstrate its efficacy, >1,000 patients are needed. For example, if 15% of a given trauma patient cohort survive, and a drug improves survival by a conservative estimate of 30% to 19.5% ($\alpha = 0.05$; $\beta = 0.20$), 1,417 patients would be required for the entire trial in two groups. Unfortunately, it is very difficult to randomize such a large number of patients.

The most important beneficial effects of arginine vasopressin are stabilization of hemodynamic variables in catecholamine-refractory shock states.^{33,45,53} Accordingly, assessing effects of arginine vasopressin in trauma patients with life-threatening hemorrhagic shock that is refractory to standard shock treatment [including catecholamines (ephedrine, phenylephrine, norepinephrine, epinephrine) at the discretion of the treating physician] may have a discernable effect. In our trauma patients receiving arginine vasopressin for failing standard shock treatment,^{54,55} all patients had an increase in arterial blood pressure, which is similar to other investigators in Japan,³² Germany,^{34,56} and India.³⁵ Assuming that trauma patients with life-threatening hemorrhagic shock that is refractory to standard shock treatment will in 90% of cases continue to have an unstable arterial blood pressure and probably die, as compared to only 60% of arginine vasopressin-treated patients (conservatively estimating a 50% response rate instead of the 100% in our experience), 38 patients ($\alpha 0.05$; $\beta 0.20$) to 49 patients ($\alpha 0.05$; $\beta 0.10$) are needed per group. When incorporating a safety margin of 100% to compensate for the extremely difficult setting, about 100 patients would be randomized in each group, totaling 200 for the entire trial.

Only helicopter EMS units will be invited to participate in this study, because potentially eligible patients are not usually managed by ground EMS units in the required sample size. Conservative estimates are that about 10% of multiple trauma patients treated by a given helicopter EMS unit would fit our randomization criteria, which is about 5 patients per year per

helicopter EMS. Thus, if 200 patients need to be randomized and the study should not take longer than two years, at least 20 helicopter EMS units need to participate in the study to complete the trial within 2 years. When anticipating that some patients may not be randomized due to fewer trauma patients, personnel changes resulting in information deficits, logistic problems, and other miscellaneous shortcomings, about 40 helicopter EMS units should be recruited for the study. This strategy should meet the target randomization number of 200 over 1–2 years.

Statistical analysis

After cross-checking data for accuracy and validity, a Kolmogorov-Smirnov-Test will be performed to assess data distribution of numeric values (infusion requirements, arterial blood pressure). One factor analysis of variance, or Student's t-test will be then used to assess statistical differences if infusion requirement and arterial blood pressure data is normally distributed; if this data is not normally distributed, the Mann-Whitney-U test will be used. Hospital admission and hospital discharge rate will be analyzed with the chi-square, or Fisher's exact test. Analysis will be performed according to intention to treat. A logistic regression analysis will be used to control for possible confounding effects (for example, participating helicopter EMS unit or accident time) of variables related to the different endpoints. A subgroup analysis of the role of blunt vs. penetrating injuries will be performed as well. The Bonferroni correction for multiple comparisons will be applied wherever necessary.

Patient safety

Patients with high mortality rates being treated with novel interventions may have an additional risk. Examples demonstrating greater mortality with an experimental intervention over placebo include human growth hormone in critical care patients [mortality in two groups 39% vs. 20% (RR 1.9), and 44% vs. 18% (RR 2.4), respectively],⁵⁷ Diaspirin cross-linked hemoglobin in acute hemorrhagic shock (28-day mortality 46% vs. 17%; $P < 0.003$),⁵² and nitric oxide synthase inhibitors in septic shock (28-day mortality 59% vs. 49%; $P < 0.001$).⁵⁸ Because of a significant harmful effect of the study drug, some investigators argued that by reducing the size of the human growth hormone trial⁵⁷ eight deaths would have been prevented by randomizing 68 fewer patients, and as many as 44 deaths would have been prevented by randomizing 382 fewer patients.⁵⁹ Accordingly, an interim analysis in our study is planned to ensure safety. A further safety strategy is that the study drugs will be prepared in a sterile manner by a company specialized in manufacturing study drugs for clinical trials according to standards for good medicinal production. All standards will be strictly observed, and the study drugs will be randomly assessed by high-pressure liquid chromatography. Another safety aspect is to employ the study drug arginine vasopressin in this study in a similar setting²⁸⁻³⁰ and similar patients with post-traumatic hemorrhagic shock as in Japan,³² Germany,³⁴ India,³⁵ and Austria.^{54,55}

Data Safety/Monitoring Board

The Data Safety/Monitoring Board consists of three experts with different clinical/scientific backgrounds; namely Trauma Surgery, Biostatistics, and Anesthesiology and Critical Care Medicine. These specialists have an extensive background in clinical studies, data analysis and vasopressin physiology and

will evaluate the patient's records after 50% of patients (n=50 in each group) have been randomized, which will be done as close as possible in real time. Assessment will be carried out on whether randomization works properly, if concealment of study drug allocation is effective, and if the investigation has a chance of achieving a significant result. They will also continue monitoring the study after the interim analysis. The Data Safety/Monitoring Board will work according to guidelines of the European Agency for the Evaluation of Medicinal products (<http://www.emea.eu.int/pdfs/human/ewp/587203en.pdf>).

Discussion

The dilemma in trauma studies is a complex underlying pathophysiology,¹⁸ and lack of randomized controlled trials;⁶⁰ some authors even question the efficacy of on-scene advanced trauma life support.⁶¹⁻⁶³ According to traumatic shock management guidelines, for example, a patient with uncontrolled hemorrhagic shock due to a single laceration of the femoral artery may receive identical shock treatment as a patient with uncontrolled hemorrhagic shock due to multiple fractures and head trauma. Also, any trauma study attempting to include or exclude a given mechanism or pattern of injury may result in multiple broken protocols, because on-scene treatment has to be initiated before exact details of the injury are known.

Arginine vasopressin may be a simple, effective management for refractory traumatic shock, which maintains arterial blood pressure at a level which ensures vital organ perfusion.^{33-35,54,55} While the discussion about the type of fluid resuscitation,^{46,50,64} the target arterial blood pressure,⁴⁶ or the timing of fluid resuscitation¹⁷ ("permissive hypotension") remains inconclusive,⁶⁵ it is easily forgotten that head trauma patients require a certain minimal cerebral perfusion pressure in order to prevent harm. For example, the ability to maintain a cerebral perfusion pressure >50 mm Hg was the single most important survival predictor in children with traumatic brain injury.⁶⁶ Further, head trauma patients with hypotension at the accident site had a significantly higher morbidity and mortality than normotensive patients;⁶⁷ with an up to 150% increase in mortality when systolic arterial blood pressure at the accident site was below 90 mm Hg despite shock treatment.⁶⁸

In laboratory models of traumatic brain injury and severe hemorrhagic shock (mean arterial blood pressure below 30 mm Hg), arginine vasopressin given in combination with fluids vs. fluids alone had superior effects on intracranial pressure and cerebrovascular compliance, and prevented circulatory collapse in comparison with standard treatment.^{69,70} Regardless of the pattern of injury, hypotensive episodes of as little as 1 to 10 min as reflected by a systolic arterial blood pressure of below 50 mm Hg in the field, or below 70 mm Hg in the intensive care unit, resulted in 88% and 60% mortality, respectively.^{36,71} In agreement with these observations, hypotension (systolic arterial blood pressure below 90 mm Hg) in the field, but normotension in the emergency department resulted in 20% mortality, while normotension in both the field and emergency department only had a 2% mortality.⁷² This indicates that it is ethical and timely to assess the potentially beneficial effects of a drug which is able to increase arterial blood pressure in hypotensive trauma patients unresponsive to shock treatment, especially those with concomitant head trauma.⁷³

Despite studies reporting potentially beneficial effects, some researchers are concerned about problems associated

with arginine vasopressin such as negative cardiac inotropy and myocardial ischemia,^{74,75} and others have questioned the clinical value of results obtained with vasopressin in shock studies.⁷⁶⁻⁷⁸ However, extrapolating side effects of vasopressin observed during normal cardiocirculatory function with an intact baroreflex into the shock setting with autonomic insufficiency⁷⁹ may not be correct. In addition, when discussing possible complications of arginine vasopressin, it is easily forgotten that the dose used makes a great difference; for example, patients in vasodilatory shock (with autonomic insufficiency) can be successfully treated with arginine vasopressin infusion of 2 to 4 IU/h,^{80,81} whereas patients presenting with upper intestinal bleeding but not fluid-resuscitation refractory shock were given 10 to 20 IU bolus dosages.⁸²

In the 1990s, we reported that arginine vasopressin may be of benefit during cardiopulmonary resuscitation.²⁶ After proving in several laboratory studies^{27,83-87} that this agent deserves to be assessed in large clinical trials, we have now shown that arginine vasopressin improved the chances of survival of at least some cardiac arrest victims, indicating that taking an orphan drug from bench to bedside in purely academic research is both possible and realistic.⁴⁵ In addition, our work has generated planning groundwork for further large, prospective randomized cardiopulmonary resuscitation trials investigating thrombolysis (TROICA-study in Europe),⁸⁸ and a combination of arginine vasopressin and epinephrine (PY Gueugniaud, Lyon, France, personal communication, 2006). Research on arginine vasopressin has contributed to the successful treatment of critical care patients with vasodilatory shock using a continuous arginine vasopressin infusion⁸² thus enabling potentially life-saving options for shock patients. This project is aimed at generating timely, simple, inexpensive, and immediately clinically relevant knowledge in order to provide trauma patients in life-threatening hemorrhagic shock with a better chance of survival than at present. Results of the study will be published in peer-reviewed professional journals and made available to the international media to inform the lay public, as done in the past.⁸⁹⁻⁹² Every effort will be made to collaborate with industrial partners to further develop arginine vasopressin, and to market intellectual property rights, although this is restricted due to the expired patent of arginine vasopressin.

Parts of our previous projects have been funded by a grant from the Austrian Science Foundation, which expired in early 2004. Although departmental funds are being employed, they are clearly not sufficient to support a project of this size. No investigator has any personal conflict of interest regarding drugs investigated in our studies. The principal investigators are employed by the Innsbruck Medical University in Innsbruck, Austria; therefore, no personnel cost is budgeted. Further, no personal compensation of any investigator can be paid. In summer 2005, the Science Foundation of the Austrian National Bank provided 86,000 Euro for this project (grant 11448), finally enabling us to initiate this academic study.

In conclusion, the VITRIS study is designed to assess the effects of up to three injections of intravenous arginine vasopressin vs. saline placebo in patients with traumatic hemorrhagic shock which is not responsive to standard shock treatment with aggressive fluid resuscitation, airway management, and catecholamines.

Acknowledgments

We are indebted to Michael Loedl, Thomas Danninger, and Mag. Christian Gritsch for their dedicated technical assistance.

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