

The Efficacy of Terlipressin *versus* Adrenaline in Swine Cardiopulmonary Resuscitation

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Summary: Ovalle CCIS, Moreira MM, Martins LC, Araujo S – The Efficacy of Terlipressin *versus* Adrenaline in Swine Cardiopulmonary Resuscitation.

Background and objectives: The objective of the present study was to evaluate the efficacy of terlipressin (TP) vs. adrenaline (ADR) in increasing coronary perfusion pressure (CPP) and return of spontaneous circulation (ROSC) in swine CPR.

Methods: Under anesthesia with ketamine/thiopental, ventricular fibrillation was induced in 44 female immature pigs, remaining unassisted for 10 minutes, followed by 2 minutes of manual CPR (100 compression/10 ventilations/min with air). Animals were, then, divided into four groups: 1) ADR (45 $\mu\text{g}\cdot\text{kg}^{-1}$); 2) saline-placebo (10 mL); 3) TP 20 $\mu\text{g}\cdot\text{kg}^{-1}$; and TP (20 $\mu\text{g}\cdot\text{kg}^{-1}$) + ADR (45 $\mu\text{g}\cdot\text{kg}^{-1}$). Defibrillation was performed after 2 minutes, observing surviving animals for a 30-minute period. Electrocardiogram, systemic BP, DBP, and PetCO₂ were monitored continuously.

Results: Terlipressin did not differ from placebo regarding the effects on CPP, with low rates of ROSC in both groups (1/11 vs. 2/11; $p = \text{NS}$). Adrenaline increased CPP from 13 ± 12 to 54 ± 15 mmHg ($p < 0.0001$), similar effect to TP + ADR (from 21 ± 10 to 45 ± 13 mmHg; $p < 0.0001$), with high rates of ROSC/survivors in both groups (10/11 vs. 9/11, respectively). Among survivors, greater MAP was observed in the TP + ADR group vs. ADR (105 ± 19 mmHg vs. 76 ± 21 mmHg; $p = 0.0157$) groups.

Conclusions: Adrenaline and TP + ADR were effective on maintaining CPP/ROSC in this experimental model, but isolated TP did not differ from placebo. However, in surviving animals in the TP + ADR group, greater hemodynamic stability was observed after ROSC, suggesting that TP can be a useful medication in the management of post-CPR hypotension.

Keywords: Ventricular Fibrillation; Cardiopulmonary Resuscitation; Epinephrine; Arginine Vasopressin.

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INTRODUCTION

Despite the lack of conclusive scientific evidences showing beneficial effects in humans, vasopressors such as adrenaline (ADR) and vasopressin (VP) are still recommended to increase cerebral and coronary perfusion pressures during CPR^{1,2}.

Terlipressin (TP), a pro-drug, is a VP synthetic analogue, with a long half-life than VP³. Recently, some potential beneficial effects of this drug have been reported in patients with septic shock⁴ and pediatric refractory cardiac arrest^{5,6}.

However, to date, only one experimental trial has evaluated the role of TP in an infant animal model of asphyxial cardiac arrest with disappointing results⁷. Thus, the main objective of this study was to evaluate the efficacy of TP *versus* ADR to increase coronary perfusion pressure (CPP) and restoration of spontaneous circulation (ROSC) in pigs undergoing ventricular fibrillation (VF). Our main hypothesis was that TP, due to its pharmacologically characteristics, should not be superior to ADR during CPR.

METHODS

This research was approved by our Institutional Review Board for Animal Experimentation (CEEA-IB-Unicamp-1276-1/2007) and conducted at the Laboratory for Experimental Medicine and Surgery of the Faculty of Medical Sciences-Universidade de Campinas (Unicamp), São Paulo, Brazil, between March and December 2009.

Forty-four Large White immature female pigs aged 6-8 weeks, weighing approximately 20 kg, divided into four equal groups, were studied. The sample size was estimated considering that a 20-30% of ROSC rates were expected in placebo group *versus* 80-100% in ADR group. Under ketamine (10 $\text{mg}\cdot\text{kg}^{-1}$ IM) and sodium thiopental (25 $\text{mg}\cdot\text{kg}^{-1}$ IV) anes-

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thetia, the animals were orotracheally intubated and ventilated with air, with a fixed respiratory rate ($10 \cdot \text{min}^{-1}$) and tidal volume varying from $15\text{-}20 \text{ mL} \cdot \text{kg}^{-1}$ (Ventilator DX-3010-Dixtal-Brazil) to keep PetCO_2 between 36-44 mmHg (CO_2SMO -Dixtal-Brazil). Surgical vascular catheterizations were done to measure thoracic aorta and right atrium (RA) pressures (DX-2020 - Dixtal-Brazil).

Through a bipolar pacing wire located into the right ventricular cavity VF was induced and remained unattended for 10 min. Then the animals kept in the supine position were reconnected to the mechanical ventilator and manual closed-chest CPR was initiated (100 chest compressions/10 ventilations/min, continuously).

Two minutes later the animals allocated into four equal groups received centrally IV: 1) ADR ($45 \mu\text{g} \cdot \text{kg}^{-1}$); 2) saline-placebo (10 mL); 3) TP* ($20 \mu\text{g} \cdot \text{kg}^{-1}$; *Glypressin®, Ferring Laboratories-Brazil-Ltd); and 4) TP ($20 \mu\text{g} \cdot \text{kg}^{-1}$) + ADR ($45 \mu\text{g} \cdot \text{kg}^{-1}$). All drugs were diluted with normal saline (10 mL), in identical syringes, remaining blind to the main rescuer.

Two minutes after drug injection, defibrillation was tried by delivering sequential 200 J DC-shocks (Biphasic Defibrillator-Cardiomax-Instamed-Brazil) until ROSC, the achievement of a non-fibrillatory rhythm or two-minute attempts. Successful ROSC was defined as the recovering of spontaneous heart beats, with a systolic AP ≥ 60 mmHg for a time ≥ 5 min. Animals were considered survivors when they remained alive, with a systolic AP ≥ 60 mmHg, until 30 min have elapsed since ROSC.

On completion of the experiment, all successfully resuscitated animals were sacrificed with thiopental overdose and potassium chloride injection.

Statistical analysis

Kruskal-Wallis test or analysis of variation (ANOVA) was used to compare baseline characteristics between groups. ANOVA for repeated measures was used to compare variables measured between groups and times, with rank transformation, followed by multiple comparisons using Tukey's test and contrast profile test. The χ^2 -test was used to verify the differences between proportions. Statistical tests were two-sided and the significance level adopted was 5% ($p < 0.05$).

RESULTS

Baseline characteristics of the animals are shown in Table I. No significant differences were found between groups.

CPP (mean \pm SD) at the 2nd min-CPR in ADR, saline-placebo, TP, and TP + ADR groups were 13.0 ± 1.6 ; 21.5 ± 13.3 ; 20.2 ± 15.5 ; and 21.3 ± 10.3 mmHg ($p = 0.2895$), respectively. At the end of the 4th min-CPR (after drug injection), CPP (mean \pm SD; mmHg) was significantly greater when comparing ADR (54.2 ± 14.9) and ADR+TP (44.5 ± 13.1) vs. saline-placebo (7.0 ± 10.5) and TP (7.0 ± 10.5) groups, respectively, ($p < 0.0001$). These data are shown in Figure 1.

ROSC rates obtained in each group were: 9/11 (82%) in ADR; 2/11 (18%) in saline-placebo; 1/11 (9%) in TP, and 9/11 (82%) in TP + ADR [placebo = TP (mean \pm SD) was significantly greater in TP + ADR vs. ADR group (105 ± 19 vs. 76 ± 21 mmHg, respectively; $p = 0.0157$)].

Table I – Baseline Characteristics of the Animals [Mean (\pm SD)] during the Control Period (Before Ventricular Fibrillation)

Groups	ADR	Placebo	TP	TP+ADR	*p-value
Variables					
Weight (kg)	20.6 (1.1)	19.9 (0.7)	20.7 (1.7)	20.7 (1.0)	0.2632
PetCO ₂ (mmHg)	39.4 (3.0)	42.0 (3.8)	40.8 (4.9)	41.2 (3.7)	0.4923
Hb (g.dL ⁻¹)	10.7 (0.9)	10.5 (0.8)	11.0 (0.9)	10.6 (1.3)	0.6489
SpO ₂ (%)	94.7 (3.3)	94.0 (2.9)	94.8 (3.1)	94.3 (3.7)	0.8864
T (°C)	39.0 (0.7)	39.0 (0.5)	39.3 (0.6)	39.6 (0.4)	0.2085
HR (bpm)	132.4 (22.1)	135.0 (19.6)	141.1 (28.2)	138.4 (16.4)	0.8788
SAP (mmHg)	114.9 (18.8)	114.3 (24.0)	108.6 (23.0)	109.6 (23.3)	0.9428
DAP (mmHg)	86.4 (18.2)	87.0 (18.3)	83.3 (20.0)	84.1 (19.3)	0.9925
MAP (mmHg)	99.6 (18.1)	99.4 (17.6)	93.6 (22.1)	97.2 (20.9)	0.9351
RAP (mmHg)	9.0 (1.9)	7.8 (2.3)	8.2 (2.0)	8.3 (2.0)	0.3963
CPP (mmHg)	90.8 (18.9)	91.5 (17.5)	85.5 (23.2)	88.9 (21.0)	0.9403

* (Kruskal-Wallis test). ADR: Adrenaline; CPP: Coronary perfusion pressure (calculated as MAP - RAP); DAP: Diastolic arterial pressure; Hb: Hemoglobin; HR: Heart rate (bpm: beats per minute); MAP: Mean arterial pressure; PetCO₂: End-tidal pressure of carbon dioxide; RAP: Right atrial pressure; SAP: Systolic arterial pressure; SpO₂: Peripheral oxygen saturation (lingual); T: Rectal temperature; TP: Terlipressin.

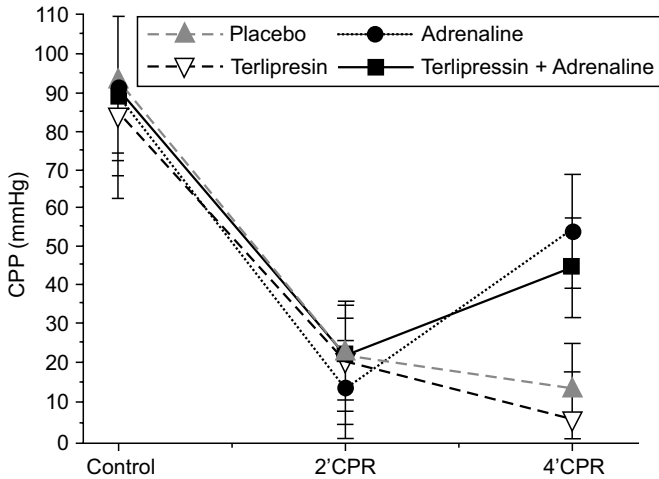


Figure 1 – Coronary Perfusion Pressure (CPP; Mean ± SD; mmHg) Recorded during the Control Period (Before Ventricular Fibrillation), at the End of the 2nd min of CPR (Before Drug Injection) and at the End of the 4th min of CPR (2 min after Drug Injection) in Each Group. (#) (Placebo = TP < ADR = TP+ADR; p < 0.0001).

DISCUSSION

This experimental model in which the unattended VF time was very long (10 min) has shown to be very useful to evaluate the effects of vasopressor drugs on CPR. In fact, at the end of the 4thmin-CPR (post-drug), the placebo group has shown a mean CPP of only 13.4 ± 11.4 mmHg, resulting in a very low ROSC rate (only 18%), similar to that obtained in TP group (9%; p = NS). To explain these poor results, we can not rule out the possibility of some cardiovascular depression induced by the combined ketamine/thiopental anesthesia, leading to an absolute need of potent vasopressors for increasing CPP and ROSC in these animals. However, ketamine was used only once (for anesthesia induction) and thiopental was used intermittently in small doses. Additionally, a recent experimental study has shown that for open-heart surgery and bypass in minipigs, ketamine-pentobarbital anesthesia was associated with stable cardiovascular conditions ⁸.

Despite the fact that during the last two decades vasopressin had been extensively investigated as a possible alternative to ADR for use in CPR, many controversies regarding its use in humans still remain, and no clear advantage of VP over ADR has yet been demonstrated ^{1,9}.

Terlipressin is considered a prodrug with vasopressor effects mediated by its metabolite, lysine-vasopressin, which is gradually released over several hours, with a long half-life (approximately 6 h) than that of VP (10-20 min) ³. Thus, TP effects last longer (2-10 h) than VP (30-60 min), but its maximal effects on arterial pressure are only seen 10-20 min after its intravenous injection ^{3,10}.

In the present study, TP was not different from placebo. In addition, the association TP + ADR was similar to ADR alone regarding CPP increasing and ROSC rates, suggesting

that TP does not add any early benefit to ADR during CPR. However, interestingly, in survival animals, greater MAP was noted in TP + ADR vs. ADR group (105 ± 19 vs. 76 ± 21 mmHg, respectively; p = 0.0157). This finding can be attributed to the peculiar pharmacological properties of each individual vasopressor, i.e., the fast and powerful ADR alpha-adrenergic effects are responsible for CPP increase ¹, and, otherwise, the delayed onset of action, long half-life, and long-lasting effects of TP ^{3,10} strongly suggest that it is, in fact, a prodrug. Thus, accordingly to the main hypothesis of this trial, our results indicate that TP alone is not useful during early CPR, and additionally, adds no beneficial effect to ADR for increasing CPP and ROSC in this animal model.

Few retrospective case series in children ^{5,6}, and only one recent experimental trial evaluating the role of TP in cardiac arrest⁷ have been published.

Matok et al. ⁵ reported seven cases of children who have suffered refractory cardiac arrest in ICU and received TP (15-20 µg.kg⁻¹) in bolus. ROSC was achieved in 6/8 episodes of cardiac arrest, and four patients survived to hospital discharge without neurological sequel. They concluded that the combination of ADR+TP could have synergistic benefit effects on pediatric victims of cardiac arrest ⁵.

Gil-Antón et al. ⁶ have also reported the effects of TP on five children with refractory cardiac arrest in ICU that received TP (10-20 µg.kg⁻¹) up to two doses IV in bolus. Sustained ROSC was achieved in four cases, and two of them survived with good neurological condition. They concluded that TP + ADR could contribute to ROSC during in-hospital CPR in children.

In a recent experimental investigation, López-Herce et al. ⁷, in an infant pig model of asphyxial cardiac arrest, have compared the efficacy of TP (20 µg.kg⁻¹) vs. ADR (0.01 mg.kg⁻¹ and 0.1 mg.kg⁻¹) and the combination of TP (20 µg.kg⁻¹) + ADR (0.01 mg.kg⁻¹). Their findings were quite disappointing, with only a non-significant trend towards a better outcome when TP + ADR was compared to ADR or TP alone (p = 0.099).

In the present investigation, using immature pigs, thus simulating a pediatric CPR scenario, the early effects of TP + ADR on CPP and ROSC rates were not different from those observed with ADR alone. Moreover, it has been noted that TP alone was not different from placebo, suggesting that this drug would not be useful as a first line vasopressor in CPR.

CONCLUSIONS

TP alone was not different from placebo, and adds no beneficial effect when combined to ADR for increasing CPP and ROSC. These results suggest that TP, due to its peculiar pharmacological characteristics, alone or combined with ADR, is not useful in early CPR management in this particular experimental model.

CONFLICT OF INTEREST STATEMENT

The authors disclose that there are no financial and/or personal relationships with other people or organizations that could inappropriately influence the conduction of this trial.

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