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Possible significance of hemodynamic and immunomodulatory effects of early stress-dose steroids in cardiac arrest

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See related research by Donnino et al., http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1257-x

In an interesting randomized clinical trial (RCT), Donnino et al. [1] studied a mixed out-of-hospital cardiac arrest and in-hospital cardiac arrest (IHCA) population and found no hydrocortisone versus placebo hemodynamic or in-hospital outcome benefit. In the hydrocortisone group, the median time to study intervention was 9.9 h after return of spontaneous circulation (ROSC) [1]. This time lag probably exceeds the therapeutic window for the prevention of detrimental episodes of early post-resuscitation hypotension [2] through a mean arterial pressure (MAP)-stabilizing effect of steroids [3, 4].

Analyses of pooled post-resuscitation shock data from our IHCA vasopressin-steroids-epinephrine (VSE) RCTs [3, 4] also showed no between-group differences in the time to, or proportions of, discontinuation of vasopressors, and post-ROSC day 1 hemodynamic support (Table 1). However, VSE patients had higher, early post-ROSC systolic arterial pressure (SAP) and MAP during post-resuscitation follow-up [3, 4]. This reflected an improved hemodynamic response to similar vasopressor support titrated to a "wide" MAP range of 70–100 mmHg [4].

Recordings of "early post-ROSC SAP >90 mmHg" (i.e., "absence of early post-resuscitation hypotension" [2]) and "≥1 recorded/analyzed, day 1 MAP value of >80 mmHg [2]" were significantly more frequent in VSE patients than controls. Importantly, such SAP/MAP levels corresponded to more frequent survival to hospital discharge with favorable neurological outcome [4] (Table 1).

Early post-resuscitation hemodynamics of VSE patients could be partly attributable to the steroids-vasopressin combination during cardiopulmonary resuscitation (CPR) [3, 4]. However, a previously postulated major CPR-VSE effect, i.e., shorter advanced life support duration [4], possibly leading to attenuated post-resuscitation cardiovascular dysfunction was not clear in the current subgroup analysis (Table 1). Hence, according to the short (i.e., 24 min) half-life of vasopressin, we propose that the more frequent day 1 MAP >80 mmHg was largely due to a post-ROSC steroid-induced augmentation of vascular responsiveness to vasopressors [3, 4]. A mediation analysis of VSE outcome benefit through day 1 MAP is warranted. Analysis of day 1 MAP data from the study by Donnino et al. might causally link between-RCT differences in corticosteroid timing with differences in survival/neurological outcome results [1, 3, 4].

Post-resuscitation disease is a "sepsis-like" syndrome. In sepsis, acute kidney injury severity is associated with mortality and elevated interleukin (IL)-6. Furthermore, high post-ROSC IL-6 is associated with organ dysfunction and poor long-term outcomes [5]. Notably, post-resuscitation hydrocortisone has been associated with reduced IL-6 levels [1, 3], and VSE patients versus controls had more renal failure-free days [3, 4].

Conclusively, available evidence prompts toward further evaluation of early, stress-dose steroids in cardiac arrest.

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Table 1 Pooled results (from [3] and [4]) on early post-enrollment hemodynamics in survivors for ≥4 h with post-resuscitation shock

Survivors for ≥4 h with post-resuscitation shock[a]	VSE group ($n = 103$)	Control group ($n = 88$)	*P* value
Time to discontinuation of vasopressors (days), median (IQR)[b]	4 (2–8)	3 (2–6)	0.86
Discontinuation of vasopressors during follow-up, *n* (%)	43 (41.7)	34 (38.6)	0.77
Estimated cumulative vasopressor dose (μg/kg) over the first 24 h post-ROSC, median (IQR)[c,d,e]	552 (216–1225)	629 (321–1236) ($n = 87$)	0.15
Cumulative 24-h post-ROSC fluid balance (mL), mean ± SD	2168 ± 2398 ($n = 78$)	2034 ± 2198 ($n = 60$)	0.74
SAP >90 mmHg within 15–20 min post-ROSC, *n* (%)	76 (80.9) ($n = 94$)	40 (55.6) ($n = 72$)	0.001
At least 1 recorded/analyzed MAP value >80 mmHg over day 1, *n* (%)	82 (80.4) ($n = 102$)	35 (42.2) ($n = 83$)	<0.001
ALS duration (min), median (IQR)	10 (6–16)	12 (6–20)	0.11
	SAP >90 mmHg ($n = 116$)	SAP ≤90 mmHg ($n = 50$)	*P* value
Survival to hospital discharge with CPC score of 1 or 2, *n* (%)	23 (19.8)	3 (6.0)	0.02
	MAP >80 mmHg ($n = 117$)	MAP ≤80 mmHg ($n = 68$)	*P* value
Survival to hospital discharge with CPC score of 1 or 2, *n* (%)	25 (21.4)	4 (5.9)	0.006

Data reported as *n* (%) were analyzed with the Fisher's exact test; data reported as median (IQR) were analyzed with the Mann-Whitney exact *U* test; and data reported as mean ± SD were analyzed with the independent samples *t* test

[a]Defined as sustained (>4 h), new post-arrest circulatory failure or post-arrest need for ≥50 % increase in any pre-arrest vasopressor/inotropic support targeted to MAP >70 mmHg [3, 4]

[b]Defined as number of days from study enrollment until the first circulatory failure-free day; the latter corresponds to a sequential organ failure assessment (SOFA) circulatory subscore <3; in both studies [3, 4], the SOFA score was determined daily through follow-up days 1–60 post-randomization

[c]With respect to [3]: average daily infusion rates (IRs) of vasopressors were already available as they were calculated by the investigators who conducted the follow-up; corresponding results were reported in the supplement of the originally published article. Consequently, Day 1 dose of a vasopressor (VD) (μg/kg) = average daily IR (μg/kg/min) × 1440 (min)

[d]With respect to [4]: for patients with IR data (μg/kg/min) available at 20 min post-ROSC (IR20M), 4 h post-ROSC (IR4H), and 24 h post-ROSC (IR24H) ($n = 108$), VD (μg/kg) was estimated as follows: VD = average (IR20M; IR4H) × 240 (min) + average (IR4H; IR24H) × 1200 (min). For patients with available IR20M and IR4H ($n = 39$), VD (μg/kg) was estimated as follows: VD = average (IR20M; IR4H) × 240 (min) + IR4H × (number of min until death after the completion of 4-h survival). For patients with available IR20M only ($n = 1$), VD (μg/kg) was estimated as follows: VD = IR20M × (number of min until death)

[e]For both [3] and [4], total day 1 VD (μg/kg) was calculated as follows [1]: VD = norepinephrine (μg/kg) + dopamine/2 (μg/kg) + epinephrine (μg/kg)

ALS advanced life support, *CPC* cerebral performance category, *IQR* interquartile range, *MAP* mean arterial pressure, *ROSC* return of spontaneous circulation, *SAP* systolic arterial pressure, *SD* standard deviation, *VSE* vasopressin-steroids-epinephrine

Abbreviations

CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; IL, interleukin; MAP, mean arterial pressure; RCT, randomized clinical trial; ROSC, return of spontaneous circulation; SAP, systolic arterial pressure; VSE, vasopressin-steroids-epinephrine

Availability of data and materials

For the purpose of the above-mentioned re-analysis protocol (Clinicaltrials.gov identifier, NCT02408939), we extracted individual peri-arrest and follow-up data from survivors for ≥4 h with post-resuscitation shock ($n = 191$) from an electronic masterfile containing de-identified data from references [3] and [4]. Extracted, de-identified data was saved in a Microsoft Excel datafile. Data will not be shared because we plan to use it in a future mediation analysis mentioned in the fourth paragraph of the current main text.

Authors' contributions

SDM is responsible for the conception and drafting of the manuscript, conduct and accuracy of the data analyses, and interpretation of the results. NM, TX, and SGZ contributed to the interpretation of the results, and to critically important revisions of the original draft. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The pooled data analyses reported herein were performed as post hoc subanalyses of a re-analysis protocol of synthesized and de-identified data from references [3] and [4]. The aforementioned re-analysis protocol has received the following Institutional Review Board (IRB) approvals: Evaggelismos General Hospital approval No. 14/9/1/2015; 401 Greek Army Hospital approval No. 3/2015/5/2/2015; and Larissa University Hospital approval No. 58905/2014/14/1/2015. Modifications of the aforementioned re-analysis protocol have been approved by the Evaggelismos IRB (respective approval Nos. 29/25/2/2016 and 30/25/2/2016), and these approvals were ratified by the IRBs of the other two participating centers (401 Greek Army Hospital, IRB Decision No.: 4-2016/6/4/2016; Larissa University Hospital, IRB Decision No.: 5/19-5-2016/Θ.18). All the aforementioned, de-identified data analyses were conducted under a waiver of informed consent, because they were not associated with any clinical intervention.

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