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Should we give steroids after out-of-hospital cardiac arrest?

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The pathophysiology of post-cardiac arrest syndrome features ischaemic/reperfusion injury and the release of high levels of inflammatory cytokines [1]. These inflammatory markers include interleukin-6 (IL-6), C-reactive protein (CRP), tumour necrosis factor, procalcitonin and pentraxin 3 [2]. Observational studies suggest that IL-6 levels appear to increase early after cardiac arrest, whereas most other markers peak at around 24–48 h [3]. The magnitude of the increase of these inflammatory markers appears to be associated with the severity of the circulatory shock, the development of organ failure and, in some studies, also neurological injury and functional outcome [4, 5]. Therefore, efforts to curb this inflammatory response are of particular interest to researchers. Other studies that have investigated the use of hydrocortisone during intensive care unit care after cardiac arrest have shown conflicting results, with no indications of decreased mortality but some hints of improved functional outcome in the survivors [6]. One problem with these previous studies is that the timing of the delivery of steroids was delayed. Nonetheless, there are also studies in which steroids were administered during cardiopulmonary resuscitation, which resulted in some changes in post-arrest haemodynamics [7]. If early reperfusion causes the release of inflammatory mediators, it would make sense to provide anti-inflammatory agents as soon as possible after the return of spontaneous circulation (ROSC) [8].

The STEROHCA trial was a randomised controlled prehospital trial of an intravenous bolus of 250 mg methylprednisolone administered to patients with ROSC following out-of-hospital cardiac arrest (OHCA) in Denmark (Fig. 1) [9]. The primary outcome was levels of IL-6 and neuron-specific enolase (NSE) at 48 h. The researchers of the STEROHCA study designed a study to allow the patient to receive the intervention in the fastest possible time by allocating the treatment in the prehospital setting. The enrolment criteria included cardiac arrest due to a presumed cardiac cause and the patient remaining unconscious after ROSC. The median time to randomisation was 20 min from ROSC. The results showed that methylprednisolone, as expected, appeared to reduce inflammation. The IL-6 levels were similar in both groups at baseline, but a significant reduction in IL-6 levels occurred in the intervention group, and this reduction was sustained through to 48 h. However, a reduction in inflammation did not appear to affect brain injury, such that NSE levels did not significantly change over time or between the groups. Similar findings were also seen for the more selective brain injury biomarker of neurofilament light chain. This phase II study was not powered for patient-centred outcomes, and whilst there were more survivors in the intervention group at 6 months (75% versus 64%, non-significant in unadjusted analysis, significant after multivariate analysis), there were higher absolute numbers of a cerebral performance category score = 1 in the placebo group (not significant).

Several factors should be considered when evaluating the STEROHCA trial. First, certain patients were excluded after randomisation as they were not transported to a study hospital. Second, the authors opted not to correct the alpha risk for secondary outcomes to maintain a more exploratory approach in uncovering potential associations. Although this strategy allows a broader examination of potential findings and generates hypotheses for further investigation, the results involving the secondary outcomes should be considered very exploratory. Third, the authors powered their trial towards evaluating an inflammatory biomarker (IL-6) associated with poor outcomes after OHCA and a biomarker (NSE) that aligns with established clinical guidelines for assessing brain injury. In hindsight, other surrogate markers for outcome, such as neurofilament light chain, which has demonstrated superior predictive performance compared to NSE in indicating poor outcomes following OHCA, could have been of interest for powering their trial [10,11]. Despite all these considerations, the safety data from this trial were reassuring.



Many intensivists have given pulse steroids to critically ill patients with conditions not quite understood to try to hold off the inevitable, without success [12]. As such, the STEROHCA study's results do not appear surprising. To the neuro-critical care researcher, they provide several promising developments to follow, even though the lack of difference in brain injury biomarkers is disappointing. It may be that alternative inflammatory mediator targets hold more promise. For example, in an 80-patient pilot randomised controlled trial, the use of the selective IL-6 inhibitor tocilizumab resulted in lower levels of CRP and leukocytes over the first 72 h [13]. In addition, levels of creatine kinase and troponin as markers of cardiac injury decreased, whereas brain injury NSE did not change, nor did survival or neurological outcomes. Even if anti-inflammatory targets are not the key to improving neurological outcomes, the STEROHCA investigators should be congratulated for conducting the first prehospital post-arrest trial that demonstrated the ability of early high-dose glucocorticoid treatment to mitigate the complex inflammatory response observed in the postcardiac arrest phase. Their partnership with prehospital clinicians was a sensible way of achieving this and should be considered for further post-cardiac arrest trials.

Author contributions

All authors contributed to the writing of this editorial.

Declarations

Conflicts of interest

The authors have no conflicts of interest to disclose.

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