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Review article

Cerebral oximetry and return of spontaneous circulation after cardiac arrest: A systematic review and meta-analysis☆

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ABSTRACT

Aim: The prediction of return of spontaneous circulation (ROSC) during resuscitation of patients suffering of cardiac arrest (CA) is particularly challenging. Regional cerebral oxygen saturation (rSO_2) monitoring through near-infrared spectrometry is feasible during CA and could provide guidance during resuscitation.

Methods: We conducted a systematic review and meta-analysis on the value of rSO_2 in predicting ROSC both after in-hospital (IH) or out-of-hospital (OH) CA. Our search included MEDLINE (PubMed) and EMBASE, from inception until April 4th, 2015. We included studies reporting values of rSO_2 at the beginning of and/or during resuscitation, according to the achievement of ROSC.

Results: A total of nine studies with 315 patients (119 achieving ROSC, 37.7%) were included in the meta-analysis. The majority of those patients had an OHCA ($n = 225$, 71.5%; IHCA: $n = 90$, 28.5%). There was a significant association between higher values of rSO_2 and ROSC, both in the overall calculation (standardized mean difference, SMD –1.03; 95%CI –1.39,–0.67; $p < 0.001$), and in the subgroups analyses (rSO_2 at the beginning of resuscitation: SMD –0.79; 95%CI –1.29,–0.30; $p = 0.002$; averaged rSO_2 value during resuscitation: SMD –1.28; 95%CI –1.74,–0.83; $p < 0.001$).

Conclusions: Higher initial and average regional cerebral oxygen saturation values are both associated with greater chances of achieving ROSC in patients suffering of CA. A note of caution should be made in interpreting these results due to the small number of patients and the heterogeneity in study design: larger studies are needed to clinically validate cut-offs for guiding cardiopulmonary resuscitation.

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1. Introduction

Despite improvements in the management of cardiopulmonary resuscitation (CPR) and of the post-resuscitation care, survival after cardiac arrest (CA) remains low. The rate of return of spontaneous circulation (ROSC) is low, especially among out-of-hospital (OH) CA;[1,2] moreover less than half of the patients admitted to a hospital after CA survive the six-month follow-up.[3]

The prediction of ROSC during resuscitation is challenging. To date there is no validated tool to aid physicians in deciding how long to prolong resuscitation efforts. The decision is often made mainly on clinical judgement alone. If ROSC is achieved, the main cause of death is neurological damage, resulting from both, the initial ischaemic insult and the subsequent reperfusion injury.[4,5]

Cerebral oximetry is a near-infrared spectrometry (NIRS) non-invasive technology approved by the US Food and Drug Administration allowing the monitoring of regional cerebral oxygen saturation (rSO_2) in accessible superficial brain cortex regions, which are also amongst the most vulnerable to ischaemic–hypoxic injury.[6] Values of rSO_2 have shown a correlation with those of jugular venous bulb oxygenation.[7,8]

The feasibility of rSO_2 monitoring in CA patients has already been demonstrated in several studies, investigating the cut-off

values of rSO_2 that predict ROSC[9,10] and/or neurological outcome after CA.[11,12] Moreover, rSO_2 has been recently investigated as a tool to evaluate the quality of cardiopulmonary resuscitation (CPR).[13]

We undertook a systematic review of the available literature that evaluated rSO_2 to predict successful ROSC in patients suffering CA. We also conducted a meta-analysis with the hypothesis that ROSC was associated with higher rSO_2 values.

2. Methods

Our systematic review was based on the findings of a web-based literature search conducted using the NHS Library Evidence tool. A further manual search was conducted independently by two authors (FS and GS), exploring the list of references of the findings of the systematic search. We followed the approach suggested by the PRISMA statement for reporting systematic reviews and meta-analyses (Supplemental Digital Content–Appendix 1).[14] We attempted registration of the protocol of our systematic review and meta-analysis in the PROSPERO database; however since data extraction already started, the registration was not accepted.

Our hypothesis was that higher values of rSO_2, both at the first recorded value and the average value during resuscitation, would have been positively correlated with achievement of ROSC of CA patients.

Inclusion criteria were pre-specified according to the PICOS approach (Table 1). We excluded articles referring to the paediatric population. Since no randomized controlled studies addressing this subject were expected, a priori decision to include non-randomized prospective and retrospective clinical studies was made. Case series were included in the study if reporting at least five patients; series with a lower number of patients and single case reports were excluded.

The computerized search included MEDLINE (PubMed) and EMBASE, from inception until April 4th, 2015. The core search was structured by the combination of terms obtained from the following two groups. The first one included in alphabetical order: "cerebral oximetry", "near-infrared", "oxygen consumption", "spectrophotometry" and "spectroscopy". The second group consisted of the following: "cardiac arrest", "heart arrest", "resuscitation" and "return of spontaneous circulation". The search strategy was limited to clinical (human) studies and it is summarized in the Supplemental Digital Content – Appendix 2.

Two authors (FS and GS) independently searched these databases. Duplicates were initially filtered through automated software function and afterwards screened manually by three authors (FS, GS and CC). Study selection for determining the eligibility for inclusion in the systematic review and data extraction from the selected studies were performed independently by two reviewers (FS and GS). Discordances were resolved by involving another reviewer (MC) and/or by consensus. When needed, we contacted via email the corresponding authors for retrieving the largest

amount of available data. Meta-analysis was performed independently by two experienced authors (CC and UB).

Language restrictions were applied: only articles published in English, Spanish, German, French or Italian were considered. Findings retrieved from EMBASE as conference abstract are reported only if published after August 2012 to allow a reasonable time for multiple peer-reviewed process. Two authors (CC and GS) independently assessed the methodological quality of the included studies using the Newcastle–Ottawa Assessment Scale (NOS) which is a tool recommended by the Cochrane collaboration for assessing the quality of non-randomized studies.[15] The scale has three main domains and assigns one point for each subset of assessment criteria within the selection and exposure domains. Studies can obtain up to two points within the comparability domain. We then classified studies as high risk (1–3 points), intermediate risk (4–5 points) and low risk of bias (6–9 points).

2.1. Statistical analysis

Continuous outcome differences were analyzed using an inverse variance model with a 95% confidence interval. Values are reported as standard mean difference (SMD), P values were two-tailed and considered significant if <0.05. The presence of statistical heterogeneity was assessed using the X^2 (Cochran Q) test. Heterogeneity was likely if $Q > $ df (degrees of freedom) suggested and confirmed if $P \leq 0.10$. Quantification of heterogeneity performed using I^2 statistic. Values of 0–24.9, 25–49.9, 50–74.9 and >75% were considered as none, low, moderate and high heterogeneity, respectively.[16] If heterogeneity was quantified as low or above, a random model was used. Two sensitivity analyses were planned excluding studies with high risk of bias and studies with high and intermediate risk of bias.

3. Results

The literature search with the above mentioned criteria produced 493 total findings, 138 on MEDLINE and 355 on EMBASE; 23 duplicates were removed via automatic software leaving a total of 470 publications.

We excluded 442 findings as judged to be not relevant to our search target, leaving potentially 28 studies. We manually identified three further duplicates and the manual search did not add further findings. Of the remaining 25 abstracts, 13 were excluded; 7 studies provided data on neurological outcome but not on ROSC, the other being reviews ($n = 2$) or letters to editor ($n = 4$).

A total of 12 articles remained for possible inclusion in the qualitative synthesis but only nine were included in the meta-analysis since one group of authors (Asim et al., *Am J Emerg Med*, 2014) did not have the NIRS data requested, the authors of one conference abstract did not provide the data requested (Bougle A et al., *Int Care Med*, 2014), and another conference abstract (Genbrugge et al., *Crit Care*, 2013) was a subset of a larger study published later[17] and included among the qualitative data analysis (Fig. 1).

All nine studies included in this meta-analysis were non-randomized observational studies published in peer-reviewed journals. We did not find evidence of retrospective studies or case series. No systematic-reviews and meta-analysis have assessed this topic as yet.

Of the nine findings included in the data for meta-analysis, five studies evaluated out-of-hospital CA (OHCA) patients only,[10,17–20] other two studies included only patients presenting with in-hospital CA (IHCA),[13,21] and two studies included both OHCA and IHCA populations.[9,22] Different devices have been used in these studies (Table 2). Unfortunately, none of the studies reported the exact time between the CA and the first detected rSO_2 value; moreover, no study reported a multivariable analysis including

Table 1
"PICOS" approach for selecting clinical studies in the systematic search. NIRS = near-infrared spectrometry; ROSC = return of spontaneous circulation.

PICOS	
1. Participants	Cardiac arrest patients, including both in- and out-of-hospital setting
2. Intervention	Measurements of regional cerebral oxygen saturation via NIRS, either first recorded value or average value during resuscitation
3. Comparison	No comparison with other prognostication tool
4. Outcomes	Achievement of ROSC
5. Study design	Prospective and retrospective clinical studies; case series if reporting at least five patients