TITLE

Systematic review of the effectiveness of prehospital critical care following out-of-hospital cardiac arrest

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ABSTRACT

Background

Improving survival after out-of-hospital cardiac arrest (OHCA) is a priority for modern emergency medical services (EMS) and prehospital research. Advanced life support (ALS) is now the standard of care in most EMS. In some EMS, prehospital critical care providers are also dispatched to attend OHCA. This systematic review presents the evidence for prehospital critical care for OHCA, when compared to standard ALS care.

Methods

We searched the following electronic databases: PubMed, EmBASE, CINAHL Plus and AMED (via EBSCO), Cochrane Database of Systematic Reviews, DARE, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, NIHR Health Technology Assessment Database, Google Scholar and ClinicalTrials.gov. Search terms related to cardiac arrest and prehospital critical care. All studies that compared patient-centred outcomes between prehospital critical care and ALS for OHCA were included.

Results

The review identified six full text publications that matched the inclusion criteria, all of which are observational studies. Three studies showed no benefit from prehospital critical care but were underpowered with sample sizes of 1,028 to 1,851. The other three publications showed benefit from prehospital critical care delivered by physicians. However, an imbalance of prognostic factors and hospital treatment in these studies systematically favoured the prehospital critical care group.

Conclusion

Current evidence to support prehospital critical care for OHCA is limited by the logistic difficulties of undertaking high quality research in this area. Further research needs an appropriate sample size with adjustments for confounding factors in observational research design.

INTRODUCTION

Improving survival after out-of-hospital cardiac arrest (OHCA) is a priority for many modern emergency medical services (EMS) and prehospital research.[1,2] Reported survival rates vary widely, ranging from 4.4% to 25%[3,4] and there is great interest in the influence of prehospital treatments on outcomes from OHCA. While short ambulance response times, coupled with EMS cardio-pulmonary resuscitation (CPR) and early defibrillation can improve survival after OHCA,[5] there is little evidence to support advanced life support (ALS) interventions, such as intravenous adrenaline (epinephrine) and tracheal intubation.[6,7] Research examining ALS as a concept, rather than its individual components, has produced conflicting results.[2,8,9] Despite this lack of evidence, ALS has become the standard of care for OHCA in most modern EMS.[10] A number of further interventions, drugs and treatment modifications have been trialled, but have failed to improve outcomes consistently.[11] Another focus of research has been the impact of the prehospital provider for OHCA, with a number of studies comparing physician and paramedic care.[12] A recent meta-analysis attributed the seemingly better outcomes associated with prehospital physician care to a higher quality of ALS provided.[12] However, we would argue that the quality of ALS is a matter of provider training and experience, rather than professional background.[13] Nevertheless, prehospital physicians in some EMS can undertake interventions and make decisions outside of or in addition to ALS algorithms, thus providing prehospital critical care.[10] In the UK, the availability of prehospital critical care is gradually increasing and provided by a combination of physicians and paramedics.[14,15] Without research to support the attendance of critical care teams at OHCA,[16,17] there is a large variation in the dispatch of prehospital critical care services in the UK and worldwide. This review aims to identify and present existing evidence regarding prehospital critical care for OHCA, when compared to standard ALS care.

METHODS

The review was carried out in accordance with the International Liaison Committee on Resuscitation (ILCOR) 2015 evidence evaluation process[18] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42016039995.

We searched the following electronic databases between April and June 2016: PubMed, EmBASE, CINAHL Plus and AMED (via EBSCO), Cochrane Database of Systematic Reviews, DARE, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, NIHR Health Technology Assessment Database, Google Scholar and ClinicalTrials.gov. We excluded research published prior to 1990 as it was deemed very unlikely that it would be relevant to modern EMS. The search strategy reflects the fact that prehospital critical care is often provided by physicians or helicopter medical services (HEMS). Please see table 1 for a detailed description of the search strategy. Also included were all cited and citing articles of publications which were retrieved for full text analysis during the review process. In addition we used social media (Twitter and Research Gate) to identify further grey literature.

Review of publications identified by the search followed a three-step approach. First, two independent researchers (JVVF and JBR) reviewed all study titles and remove all publications which were obviously not related to the study question as well as duplicate results. Next, the two researchers independently reviewed the abstracts of all remaining publications, removing those that did not fulfil the inclusion criteria outlined in box 1. Finally, both researchers independently reviewed the full text of all remaining publications to assess for inclusion in the final analysis. If there were discrepancies in the researchers' opinions during step one or two, the publication in question was moved forward to the next step. If there were discrepancies in step three, consensus was sought between the two researchers. If no consensus was achieved, a third researcher (JB) was asked to review the publication. The final full analysis of all included manuscript was undertaken by one reviewer (JVVF).

All included studies were assessed for methodological quality and the risk of bias, using the STROBE checklist for observational studies as guidance.[19] Given the anticipated paucity of randomised controlled trials, we planned for a narrative analysis of the evidence.

RESULTS

The search identified a total of 4,554 publications. After excluding duplicates, 183 abstracts were reviewed of which 29 manuscripts were retrieved for further assessment. After review of the full text publications, six eligible papers remained for analysis; see table 2.[17,20-24] Two conference abstracts also fulfilled the inclusion criteria and are presented in table 3.[25,26] The authors of the conference abstracts were contacted but we were unable to obtain further information. Six full text publications did not include enough information to decide if EMS providers were practicing prehospital critical care and/or ALS. For five publications, we were successful in gaining this information by contacting the authors, resulting in two exclusions[27,28] and three inclusions in the review.[21,23,24] The remaining study was excluded after a consensus decision within the research group. Based on our best interpretation of the information provided and our knowledge of the EMS studied, we considered it unlikely that this publication from Taiwan compared prehospital critical care with ALS care.[4]

Reasons for exclusion of the other 18 publications were comparison of advanced treatment with Basic Life Support (4/18), all patients receiving critical care (3/18), non-experimental study designs such as systematic reviews (3/18) and publications classified as editorials (2/18), comparing paramedics and physicians providing ALS (2/18). Two studies reported ROSC as the only outcome, one was a secondary review of previous research, and a further study examined the effect of in-hospital emergency physicians. All four of these publications were therefore also excluded.

EVIDENCE REVIEW

Only limited information is available from the conference abstracts summarised in table 3.[25,26] We therefore provide a brief summary of key aspects for each abstract, all of which used observational study designs. Seki et al. included only cases of OHCA with non-shockable rhythm in their analysis and found no difference in 1-month survival between patients attended by prehospital physicians or paramedics.[25] Shiraishi et al. also compared physician and paramedic care in Japan.[26] In their propensity matched groups of 34 cases (68 patients in total), no difference in outcome was found.

All full text publications in this review are observational studies, four of which used prospective data collection whilst two were retrospective. Sample sizes ranged from 614 to 95,072 cases. In five publications, prehospital critical care was provided by physicians; one study describes a model of physician and paramedic-delivered prehospital critical care. The full text publications are described in chronological order.

The first publication by Mitchell et al. compares the EMS of Edinburgh (UK) and Milwaukee (USA) and their impact on survival to hospital discharge after OHCA.[20] In Edinburgh, prehospital critical care was provided by a physician-staffed mobile resuscitation team which responded to OHCA as a secondary response after initial resuscitation by BLS technicians or ALS paramedics. Physicians had access to 'full resuscitation equipment' including a mechanical chest compression device, central venous access and anti-arrhythmic medication. In contrast, Milwaukee provided a two-tier response to OHCA, with first response by BLS paramedics or firefighters, followed by ALS paramedics The ALS paramedics were able to intubate and administer intravenous drugs. They could also pronounce 'life extinct' after consultation with the directing physician. Survival to hospital discharge rates were significantly higher in the UK compared to the USA (12.4% and 7.2% respectively, $p<0.01$). However, rates of witnessed cardiac arrests and bystander CPR were also significantly higher in the UK, compared to the USA (65.7% vs 25% and 42.3% vs 27.1%, respectively, $p<0.001$). The rates of shockable first rhythm was 52.3% in the UK and 43.4% in the USA (p-value not specified). Median response times for first EMS response was 8min in the UK and 6min in the USA, ($p<0.0001$). No statistical adjustments were undertaken to address this imbalance of prognostic factors, but the authors noted that when only witnessed OHCAs with shockable rhythm were compared (n=235), there was no statistical significant difference in outcome (23.3% vs 17% in the UK and USA, respectively, $p>0.05$).

Olasveengen et al. compared rates of hospital discharge with favourable neurological outcome, defined as cerebral performance category (CPC) 1 or 2.[21] The city of Oslo had a one-tiered response to OHCA, which consisted of either ALS-paramedic or physician-staffed ambulances. The ALS-paramedics underwent yearly ALS- recertification and all undertook shifts on the physician-staffed ambulance as part of a quality improvement project. The prehospital physicians were senior anaesthesiologists, who were able to provide prehospital anaesthesia (private correspondence with the author). Prehospital physicians were first on scene in about 20% of all OHCA. These cases had significantly more favourable prognostic factors such as OHCA in public, bystander CPR and shockable rhythm. After adjusting for this imbalance, using multiple logistic regression, no significant difference in the rate of discharge from hospital with CPC 1 or 2 was observed between the physician and paramedic groups (OR 1.35, 95% CI 0.71-2.60). The authors also describe a group of 155 patients where prehospital physicians were requested as second responders. These were excluded from the analysis as they contained an unknown number of paramedic requests for support with post-ROSC treatment, and as such would have introduced bias. The unadjusted rates of discharge from hospital with CPC 1 or 2 were 16% in this group, compared to 10% and 13% in the ALS-paramedic and primary response physician groups, respectively.

With just over 95,000 cases, the largest study was undertaken by Yasunaga et al. who used data from a national cardiac arrest registry in Japan.[22] Of note, only witnessed OHCAs were included in the analysis. The prehospital care for OHCA in this study was a one-tiered system of ALS-trained Emergency Life-Saving Technicians (ELSTs). Few regions also dispatched prehospital physicians to suspected OHCA, this was the case in 3.7% of all OHCA in the registry. The ELSTs was able to insert a supraglottic airway, gain intravenous access and administer intravenous fluids and adrenaline. Critical care interventions available to prehospital physicians included central venous catheterization, infusion of catecholamines, anaesthetic drugs and thrombolytic agents. Outcomes were adjusted for prognostic factor imbalance, using logistic regression. The authors compared four interventional groups: ELST care without bystander CPR (reference), ELST care with bystander CPR, physician care without and with bystander CPR. Bystander CPR significantly increased rates of 1-month survival and good cerebral performance at one month. Physician presence showed a significant association with 1-month survival. However, for the outcome of good cerebral performance (CPC 1) at one month, the 95% confidence intervals overlapped with those of the ELST groups; see table 2. At the same time, there was a higher proportion of patients in vegetative status or brain dead at one month in the physician groups compared with the paramedic groups. In a subgroup analysis of 11,970 patients with initial shockable cardiac rhythm, physician presence was associated with significantly higher rates of 1-month survival and good cerebral performance (CPC 1) at one month, in all groups. The authors point out that prehospital physicians in their study are generally attached to and admit their patients to hospitals which 'typically provide more optimal post-return of spontaneous circulation treatments, including therapeutic hypothermia and percutaneous coronary intervention', and this may be a significant confounding factor.

Hamilton et al. provide the second largest dataset with 21,165 cases of OHCA of all aetiology, including trauma.[23] In the Danish EMS, an ambulance staffed with either BLS-technicians or ALS-paramedics was dispatched to OHCA. A mobile critical care unit was also dispatched at the same time, and was staffed either by specialists in anaesthesiology or critical care (63% of cases), or by nurse anaesthetists and ALS-paramedics (37% of cases). Prehospital physicians provide general anaesthesia and cardiovascular support and also had access to ultrasound for the later period of data collection (private correspondence with the author). ALS-paramedics and nurse anaesthetists were able to administer intravenous drugs under standing orders, nurse anaesthetists were also able to intubate. Prognostic factors were unequally distributed, favouring survival in the physician group. Propensity score matching was therefore undertaken based on Utstein variables but also included pre-OHCA morbidity measured by the Carlson Index. This resulted in a comparison between 7854 cases in each matched group. One-month survival was positively associated with prehospital physician care with an OR of 1.18 (95% CI 1.04-1.34). Secondary outcomes showed non-significant trends towards improved outcomes in the physician group with ORs for one-year survival and ROSC of 1.13 (95%CI 0.99-1.29) and OR 1.09 (95%CI 1.00-1.19), respectively.

Hiltunen et al. undertook an observational study with the primary aim of associating airway management during OHCA in Southern Finland with survival to hospital discharge and one-year survival.[24] The Finnish EMS provided a three-tiered response to OHCA, with BLS and ALS-trained prehospital emergency care nurses, followed by a third tier of prehospital physicians who were specialists in anaesthesia and critical care. Prehospital physicians attended 41% of OHCA and were able to provide general anaesthesia and cardiovascular support. The authors used multivariate analysis to evaluate the effects of supraglottic airway management and endotracheal intubation during OHCA. This also included a variable of prehospital physician presence which showed a significant association with both survival outcomes; see table 2. Given that the focus of the paper is on airway management rather than prehospital physicians, only limited information is available regarding the patient characteristics in the physician and paramedic groups. The authors also note that prehospital physicians responding to OHCA can be stood down by the first or second tier response unit, when resuscitation appears futile.

The most recent publication is from the authors of this review and used data from a regional EMS in the UK, from 2012 to 2014.[17] The standard EMS response to OHCA is ALS-trained paramedics, but during the study period a prehospital critical care service also attended about 9% of OHCAs. UK paramedics were trained and certified to follow the ALS algorithms, including intubation or use of a supraglottic airway and intravenous drug therapy. The critical care team consisted of a mix of critical care paramedics and prehospital physicians and was capable of interventions such as prehospital anaesthesia and the administration of antiarrhythmic and inotropic drugs.[10] Due to targeted dispatch of the critical care team, patients in the critical care group had significantly more positive prognostic factors for survival from OHCA than the ALS paramedic group. After adjusting with multiple logistic regression there was no significant difference in survival to hospital discharge between the two groups (OR 1.54, 95%CI 0.89-2.67). Due to the small sample size (165 cases in the critical care group), a type-two error is a possibility in this study.

DISCUSSION

There is limited evidence to support prehospital critical care for OHCA. This review identified two conference abstracts which show no benefit from prehospital critical care, however these are difficult to interpret due to the limited information available. Of the six observational studies included, three studies demonstrated an association between prehospital critical care and improved outcomes after OHCA.[22-24] The other three studies did not demonstrate any difference in patient-centred outcomes after OHCA when comparing prehospital critical care with ALS.[17,20,21] We believe that the conflicting findings can be at least partially explained by study design and the logistics of prehospital care for OHCA.

A potential reason why no benefit from prehospital critical care for OHCA was found might be a type-2 error due to small sample sizes. The three negative studies have a combined sample size of 3,214 after adjustment.[17,20,21] Likewise, the sample sizes of the conference abstracts range from 64 to 2,309. Olasveengen et al. calculated that a sample size of 8,000 would be required to demonstrate a statistically significant difference in outcome in their patient population.[21] Our pilot study showed that a sample size of about 6,000 would be required to detect an absolute improvement in survival of 3.5% with a power of 0.8.[17] We would argue that even smaller effects on survival of 1% to 2% absolute improvement would be clinically important, and require significantly larger studies. It is therefore possible that the conflicting findings are attributable to a type-2 error, with the three publications in support of prehospital critical care having a combined sample size of 111,394.

Given that the sample size of publications in support of prehospital critical care is more than 30-fold larger than that of negative studies, should we accept that prehospital critical care improves outcomes after OHCA? Before drawing any conclusions, we should also consider the logistics of providing prehospital critical care, particularly the dispatch, destination hospital and training of EMS providers for OHCA.

Despite a moderate sample size of 614 cases of OHCA, Hiltunen at al. describe a highly significant association between prehospital physician presence and mid- and long-term survival.[24] However, the authors advise caution when interpreting these results. Dispatch of the prehospital physicians in this Finnish EMS frequently depended on information provided by the first EMS resources at scene. For OHCA, the physician team might decide not to attend cases that were deemed futile, *'due to* *extensive time from collapse to EMS arrival, unsuccessful resuscitation efforts, and the presence of comorbidities'*.[24] Targeting the limited resource of prehospital critical care to patients that will benefit is a sensible strategy. However, when it comes to researching the benefit of prehospital critical care for OHCA, it introduces confounding by indication, where patients with better prognostic factors for survival are more likely to receive prehospital critical care than those with a worse prognosis.[29] In this review, in all publications that compare prehospital critical care with ALS in the same EMS, the critical care group had better prognostic factors.[17,21-24] While all of these publications use statistical methods to adjust for this imbalance, there is a strong possibility that unmeasured residual confounding factors bias the results in favour of prehospital critical care.

Another factor that might influence reporting of outcomes in favour of prehospital critical care is in-hospital treatment. Yasunaga et al. demonstrated significant associations between prehospital physician attendance for OHCA and increased survival.[22] However, the authors also clarify that prehospital physicians in their study are more likely to admit patients to hospitals providing higher levels of care following OHCA. Similar scenarios exist in some of the other publications. In our own study, prehospital critical care teams admitted 82% of their post-ROSC patients to a regional cardiac centre, compared to a 20% admission rate to the cardiac centre for ALS paramedics.[17] In Hamilton et al's study from Denmark, 39.3% of cases attended by prehospital physicians occur within a metropolitan area, compared to 14.8% in the non-physician group.[23] Patients receiving prehospital critical care in these studies are therefore more likely to receive early coronary angiography, targeted temperature management and treatment in high volume centres, all of which have been linked to better outcomes.[30-32]

Finally, the training, experience and governance structure of EMS providers needs to be considered when comparing prehospital critical care and ALS for OHCA. In all full text publications in this review, prehospital critical care is provided by senior specialist physicians and, in one study, also by specially trained critical care paramedics.[17] It is likely that these critical care providers can improve care for OHCA through a combination of critical care procedures, provider experience and triage to the most appropriate hospital.[13] While many prehospital critical care procedures require significant training and expertise, others can be integrated into ALS provider care through new equipment or guidelines.[10] In our local service, capnography-guided resuscitation and the use of vasopressors for hypotensive post-ROSC patients were initially restricted to critical care providers, but have since been integrated into ALS-paramedic practice.[10] The experience of ALS paramedics has been shown to have a significant association with survival after OHCA in a large Australian study.[33] Prehospital critical care providers will be highly experienced in the care of critically ill patients, including OHCA, through their practice in hospital or as a result of targeted dispatch to cases of severe illness or injury.[17,23] In addition, prehospital critical care providers often have the support of advanced clinical governance structures with regular case reviews and quality improvement projects, which might not be available to the cohort of ALS providers.[34] Finally, prehospital critical care providers potentially have more freedom to select destination hospitals, such as cardiac or trauma centres, as appropriate for each patient.[17] All of these aspects make it possible that prehospital providers can achieve better outcomes for an individual patient following OHCA.[22-24] However, prehospital critical care providers can potentially benefit not just the one patient in their care, but their entire EMS. Demonstrating excellence in care, trialling new procedures and interventions, implementing guidelines and training as well as providing feedback and mentoring all have the potential to improve care for OHCA throughout the EMS.[21,35] It is very encouraging that Hamilton et al. showed an improvement in survival after OHCA from 5.8% in 2005 to 11.5% in 2012. More importantly, this increase was seen in both the prehospital physician group and the paramedic group, such that when comparing only data from 2009-2012, there was no statistically significant difference in outcome between the two provider groups.[23]

LIMITATIONS

This review identified only studies with observational research designs, which raises the possibility of bias and confounding. Of particular concern is the fact that the sources of potential bias and confounding in the individual studies would invariably favour the intervention group of prehospital critical care. To control for this, one publication presented a subgroup analysis of only witnessed OHCA with a shockable rhythm,[20] four studies used regression methods[17,21,22,24] and one publication used propensity score matching.[23] While all the publications using statistical methods of adjustments included important predictors of survival (see table 2), only one publication reported measures of robustness of the statistical model.[17] There was significant heterogeneity in sample sizes, study population and EMS configurations between the studies, making meta-analysis inappropriate. We attempted to address potential confounding and bias of the full text publications in our review, but were not able to obtain further information for the conference abstracts. Both the intervention of prehospital critical care and the comparator of ALS vary in configuration in the EMS described in this review. There is limited information on the modes of dispatch, response times and interventions delivered by prehospital critical care teams. Likewise, ALS care will have varied between countries but also has developed and changed significantly over the course of the last 20 years. This heterogeneity makes the overall results difficult to generalise, and certain publications might be more pertinent than others for individual readers, depending on the configurations of their local EMS. This limitation applies in particular to EMS where prehospital critical care is delivered by paramedics, as only one publication in this review describes a system of paramedic and physician prehospital critical care[17], with the other five studies focusing exclusively on EMS physicians.

CONCLUSIONS

Prehospital critical care has the potential to improve survival after OHCA. While there is some observational research to support this, potential sources of bias limit the conclusions that can be drawn. On the other hand, studies that show no benefit from prehospital critical care are limited by inadequate sample sizes. With randomised controlled trials unlikely to gain ethical approval, the benefits of prehospital critical care would need to be proven through the use of large and detailed databases with sophisticated statistical adjustment to control for as many potential confounders as possible.

CONFLICT OF INTEREST

Both Jonathan Benger and Johannes von Vopelius-Feldt work as physicians with the prehospital critical care team of the Great Western Air Ambulance.

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