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Review

Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies

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Abstract

Introduction
Historically, survival rates from out-of-hospital cardiac arrest (OHCA) have been low. In recent times, survival rates have increased substantially in some small population pockets, which sparked general interest in this field and the volume of research increased. Included was an increase in the number of strategies being investigated to improve outcomes. The aim of this review is to assemble these strategies and consolidate the findings of the pharmaceutical strategies.

Methods
This is a systematic search and review, rather than a systematic review. Four databases (MEDLINE, CINAHL, Informit, Scopus) were searched for papers published between 2007 and 2017 containing strategies that may be used by paramedics when resuscitating adult (18+ years) patients in cardiac arrest from presumed cardiac aetiology in the out-of-hospital environment. The search was undertaken in February 2017. Five separate search concepts were used on all databases. Each concept consisted of multiple search terms.

Results
This review identified 28 separate studies for final review, which formulated six strategies. These were: use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation; vasopressin administration; thrombolysis administration; application of therapeutic hypothermia. This paper reports on the full results of the pharmaceutical strategies (vasopressin or thrombolysis administration). Part B will address the non-pharmaceutical strategies.

Conclusion
There is no evidence to support the introduction of vasopressin or thrombolysis use during OHCA. Future studies should focus on study design and specific patient subsets.

Keywords:
heart arrest; emergency medical service; advanced life support

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a global health problem with a substantial public health burden. There is disparity in rates of outcomes globally (1). Success from resuscitation is dependent on multiple factors such as aetiology, presenting rhythm, time interval with no treatment, and the quality of treatment provided. Optimal management requires a systematic approach, with every stage of the chain of survival appropriately addressed (2). This includes early identification of OHCA and predisposing symptoms; early activation of emergency medical services (EMS); early high-quality cardiopulmonary resuscitation (CPR); early defibrillation; high quality intra-arrest life support (basic and advanced life support provided by EMS); access and appropriate referral to cutting edge post-resuscitation care services. It is paramount that each component of the system functions flawlessly to ensure the best possible outcomes.

Historically, rates of survival from OHCA have been fairly low, but in recent times high rates of preferred outcomes have developed in small population pockets, which has sparked interest to achieve this success more broadly. This pre-empted an increase in volume of research in the OHCA field and an increase in the number of strategies investigated to improve outcomes. It is timely that a review be undertaken to assemble these strategies and consolidate findings.

The focus of this review is the component of EMS-provided care, which includes intra-arrest and immediate post-arrest life support. This is a systematic search and review (3), rather than a systematic review. Systematic methods were used to search literature, extract data and appraise selected articles. The aim of this review is three-fold: to identify recently investigated strategies aimed at improving outcomes from adult OHCA that could be an addition to current paramedic practice in Australia; to describe the evidence for each strategy; and to synthesise the evidence and make recommendations for improved outcomes from OHCA in high-income countries with developed pre-hospital health care systems. The full search strategy and methods of the study are described in this paper, but the focus of the results is on pharmaceutical strategies. Part B will address the non-pharmaceutical strategies.

Methods

A systematic literature search of four databases (MEDLINE, CINAHL, Informit, Scopus) identified papers published between 2007 and 2017 containing strategies that may be used by paramedics to improve outcomes when resuscitating adult (18+ years) patients in cardiac arrest from presumed cardiac aetiology in the out-of-hospital environment. The search was undertaken in February 2017 and was limited to 2007 onward for pragmatic reasons and to ensure currency (as the paramedic field is rapidly evolving).

Five separate search concepts were used on all databases. Each concept consisted of multiple search terms. The concepts were linked by ‘and’ and the search terms were linked by ‘or’. Search terms consisted of keywords in all databases with the addition of MeSH terms in MEDLINE and major headings in CINAHL (Table 1).

Table 1. Search concepts and respective keyword examples

Search concepts	Keyword examples
1. Incident	Cardiac arrest, heart arrest, ventricular fibrillation, asystole, PEA
2. Environment	Emergency medical service, EMS, ambulance, prehospital
3. Resuscitation attempt	Advanced life support, basic life support, chest compressions, CPR
4. Strategy	Treatment, therapeutic, strategy, initiative, device, equipment
5. Measurable outcome	Survival, prognosis, ROSC, outcome, result, return of output

All papers identified were copied into Endnote (version 7) and duplicates removed. The remaining papers were reviewed by title and abstract for relevance against the inclusion and exclusion criteria (Table 2), and remaining papers were reviewed by full text.

Systematic reviews and meta-analyses were excluded as per ‘primary studies only’ inclusion criteria. However, the studies included in these systematic reviews and meta-analyses were assessed against the inclusion/exclusion criteria for relevance to this literature review. The primary author (KP) conducted the search. The secondary author (KW) reviewed all studies included by title/abstract and one in 10 studies excluded by title/abstract. The few contradictions on inclusion were overcome by discussion between reviewers and consensus was reached. Reference lists of all the included papers were also scanned for further relevant papers.

The findings are presented in two separate papers. This paper (Part A) describes the search methods and results in full, but the results focus on pharmaceutical strategies. Results for the non-pharmaceutical strategies will be presented in Part B. This division of strategies (pharmaceutical and non-pharmaceutical) is due to the current emphasis on high quality CPR and less on drug administration (4) to improve outcomes from OHCA.

Results

This literature search identified 28 separate studies for final review. Figure 1 outlines the results yielded by the described search process.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Strategy identified • Study has a pre-hospital focus • Strategy implemented by health care professional/s on scene • The strategy is plausible (ie. there is scientific suggestion it may provide improvement over current management/ outcomes in OHCA) • OHCA from presumed cardiac or non-specific/all aetiologies • Strategy implemented in the intra-arrest/immediate post-arrest phase • Patient cohort largely 18+ years • Patients identified/allocated to groups (randomly or non-randomly) based on the pre-hospital phase • Evaluation process with control group • Patient outcome measurement as an explicitly stated goal/ present result • Strategy (or larger part thereof) must be an addition to current practice in Australia which aims to inform the progression of current practice • Primary studies only	• Strategy undertaken in the in-hospital environment (or not clear) • Strategy involves transport destination choice only • Strategy implemented before health care professional arrival on scene (ie. community strategies) • Strategy not aimed at improving management/outcomes in OHCA patients • OHCA from non-cardiac aetiology specifically • Patient cohort largely less than 18 years • Strategy (or larger part thereof) is underway or has previously been underway (evidence not subsequent and contradictory to that change) in Australia • Secondary studies (duplicate sample) unless added to another relevant sample or reporting additional relevant endpoints • Pilot studies where the sample has been used as part of a larger sample in another study (duplicate sample) – unless additional endpoints were reported • Stated or inferred safety/feasibility study, in aims, introduction or methods. An example of inference is that the study is intentionally not powered to detect differences in patient outcomes • Published as an abstract only

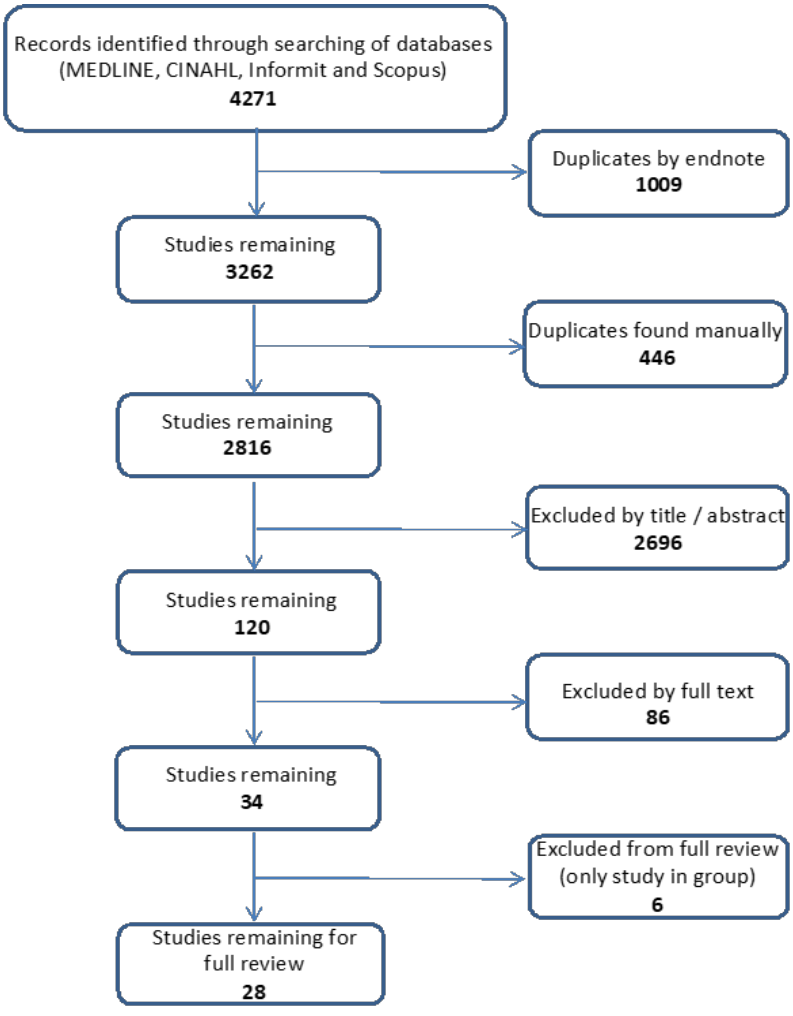

Figure 1. Literature search PRISMA flow diagram

After the process of exclusion by full text, 34 papers remained and were grouped by strategy. There were 12 groups of strategies, however for six of these there was only one relevant paper. These strategies were: passive oxygen insufflation, hypertonic saline administration, erythropoietin administration, lignocaine administration prophylactically, procainamide administration, waveform analysis-guided shock timing. In order to make rigorous recommendations for a strategy (one of the main aims of this review), evidence from more than one study is required therefore these six papers were excluded from the main focus of this review. Six groups of strategies remained, incorporating 28 separate studies for final review (Table 3). Of these, two groups focussed on pharmaceutical strategies (vasopressin or thrombolysis), compiling five studies that are fully presented in this paper (Part A). The remaining non-pharmaceutical strategies will be presented in Part B. Table 4 summarises the characteristics and results of the five studies included in this paper.

Table 3. Strategies and number of papers in full review

Strategy	Number of studies
Use of a modified resuscitation protocol*	7
Use of a mechanical chest compression device	7
Intra-thoracic pressure regulation	3
Vasopressin administration	3
Thrombolysis administration	2
Application of therapeutic hypothermia	6

*This group includes studies in which the modified resuscitation protocol was primarily aimed at improving CPR quality. This strategy was also known as minimally interrupted cardiac resuscitation, cardio-cerebral resuscitation, team-focussed CPR and pit crew approach.

Vasopressin administration

Three papers investigated use of vasopressin in the intra-arrest phase of OHCA (5-7). A double-blind randomised controlled study (RCT) of vasopressin (dose: 40 units with a maximum cumulative dose of 80 units) in conjunction with adrenaline versus adrenaline alone was conducted in France (6). Intention to treat data analysis principles were applied. Overall there were no significant differences between groups for any patient outcome measure (survival to admission, ROSC for ≥1 minutes, survival to discharge, survival with good neurological recovery, survival to 1 year). However, in the subset of pulseless electrical activity (PEA) patients, survival to hospital discharge was significantly more common among controls than cases.

The remaining two studies were both observational and had a data collection period that contained a change in protocol to include vasopressin use (5,7).

The primary endpoints of the prospective study (5) were clinical prognostic factors for outcome (end tidal carbon dioxide [$ETCO_2$] and mean arterial pressure [MAP]), which showed favourable results for vasopressin use. Positive results were also observed in direct patient outcome measures, including significant associations between hospital admission and 24-hour survival with cases in both univariate and multivariate analysis. There were no significant differences between groups in hospital discharge rates, although when the asystole subgroup was examined, hospital discharge rates were significantly higher among cases. Survival to hospital discharge was not reported for other initial rhythm subgroups. However, multivariate analysis in which shockable status was adjusted for, showed that vasopressin administration was not independently associated with hospital discharge, thus it can be assumed there were no significant differences between groups in the shockable subset. Results of the PEA subgroup were not published so remain unknown. Among all patients discharged from hospital in this study, there were significantly more cases with a preferred neurological outcome (CPC 1 or 2).

The case-control study (7) examined survival to ED, survival to 24 hours and survival to discharge, for which no significant differences between groups were found. No further analyses or results were reported.

All three studies (5-7) have some common limitations, including the unavoidable use of a poor prognosis sample (initial rhythm of PEA, asystole or, if shockable, after three unsuccessful shocks), due to the nature of the strategy. Consequently, larger samples than usual were required to provide statistical power to show significance, so the demonstration of cause and effect was harder to achieve and may explain the lack of observed associations. Further limitations of these studies include the absence of quantification of chest compression quality and the lack of standardised in-hospital care, both of which are known to impact on patient outcomes (2,10).

The observational studies (5,7) are both limited by the non-randomised design and the impacts of potential unknown/unmeasured changes in practice over time. The retrospective study allocated cases/controls strictly using the date of protocol change, whereas the prospective study used date of incident and accessibility of vasopressin to allocate patients to groups. Therefore, group allocation was likely to be more accurate (as per question objective) in the prospective study, although the majority of controls were still in the earlier years. In the prospective study, administration of adrenaline alongside vasopressin was not measured, thus it is unknown if the positive results can be attributed to vasopressin alone or a synergistic effect between vasopressin and adrenaline. Due to the nature of the retrospective study, there is greater risk of additional unmeasured and uncontrolled factors contributing to the findings.

Table 4. Evidence table for pharmaceutical strategies to improve OHCA outcomes in the pre-hospital environment

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Vasopressin administration					
2007 Mally (5)	Intra-arrest vasopressin (with/without adrenaline)	Non-randomised trial January 2000 – April 2006	Maribor, Slovenia Data collected from all calls classified as OHCA Intervention group – 146 Non-intervention group – 452	Average $ETCO_2$ in all patients and final $ETCO_2$ (primary outcomes) in patients with ROSC were significantly higher in the intervention group ($p<0.01$) Average values of initial and final MAP (primary outcomes) were significantly higher in the intervention group ($p<0.01$) Univariate outcome analysis: The following outcomes were significantly more frequent in the intervention group: ROSC ($p=0.04$), ROSC and hospital admission ($p=0.01$) and survival at 24 hours ($p=0.02$). There were no differences between groups in hospital discharge ($p=0.19$) Multivariate analysis: ROSC and admission to hospital (secondary outcome) was associated with the intervention group OR 1.63 95% CI: 1.24-2.14. Survival at 24 hours (secondary outcome) was associated with the intervention group OR 1.34 95% CI: 1.14-1.94. Hospital discharge (secondary outcome) showed no association OR 1.12 95% CI: 0.82-1.33	+
2008 Gueugniaud (6)	Intra-arrest vasopressin (in addition to adrenaline)	Double-blind placebo RCT May 2004 - April 2006	France Intervention group – 1442 Non-intervention group – 1452	ITT analysis: No significant differences between groups in survival to admission (primary outcome), ROSC for at least 1 minute, survival to discharge, good neurological recovery (CPC 1), 1 year survival (secondary outcomes)	/
2010 Cody (7)	Intra-arrest vasopressin (in addition to adrenaline)	Retrospective review November 2002 – August 2005	Oklahoma, US EMS database Intervention group – 106 Non-intervention group - 85	No differences between groups in survival to ED (primary outcome), survival to 24 hours or survival to discharge (secondary outcomes)	/
Thrombolysis administration					
2008 Bottiger (8)	Intra-arrest thrombolysis (tenecteplase vs. placebo)	Double-blind multicentre RCT January 2004 – March 2006	66 EMS systems in Austria, Belgium, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden and Switzerland Intervention group – 525 Non-intervention group – 525	ITT analysis: 30-day survival (primary outcome): 14.7% intervention vs. 17% standard treatment ($p=0.36$) No difference between groups in hospital admission; ROSC; 24-hour survival; survival to discharge and each category of neurological outcome by CPC (secondary outcomes) Early termination	/
2011 Renard (9)	Intra-arrest thrombolysis (alteplase 50 mg single bolus or tenecteplase 100 units/kg single bolus)	Case control study September 2005 – March 2007	44 physician-manned vehicles in Paris Intervention group – 107 Non-intervention group – 1154	Survival to hospital admission (primary outcome): AOR 1.7 95% CI: 1.09-2.68 In non-shockable subgroup OR 3.61 95% CI: 1.88-6.98. There was no association found in shockable subgroup	+

Overall, there is little evidence supporting the use of vasopressin. The only study (5) showing any results in favour of vasopressin was non-randomised and had internal validity issues. It may be that the degree of benefit of vasopressin use is dependent on factors not explored thoroughly in the current evidence, such as presenting rhythm, timing/prolongation of drug therapy and concomitant use with adrenaline. Further high level, rigorous studies are required before definitive conclusions can be drawn.

Thrombolysis administration

Two studies investigated the use of thrombolytic agents in the intra-arrest phase of cardiac arrest (8,9), a double blind RCT undertaken across 66 EMS systems in Europe (8) and a case-control study in Paris (9).

In the RCT (8), no significant results between groups were observed for any outcome measure. Multiple subgroup analyses were undertaken and of patients who received bystander CPR, significantly more patients in the non-thrombolysis group survived to 30 days. After almost 12 months of data collection, this study discontinued the enrolment of asystole patients, followed by full early termination a further 15 months later, due to statistical futility. Possible explanations for the lack of apparent effect include short response times, short intervals between collapse and study drug administration, lack of antithrombin/platelet agent and overall higher survival to hospital discharge rates when compared with previous similar studies. In contrast, acute myocardial infarction (AMI), rather than primary arrhythmia, pulmonary embolism (PE) or other cardiac cause, was the presumed aetiology in a larger proportion of the intervention group. The action of tenecteplase suggests it would have a more profound effect in AMI patients, which would increase the observed effect in favour of the intervention.

In the case-control study (9), significantly higher survival to hospital admission was reported. However, sub-group analyses showed that significant between group differences were only present in patients that were not shocked. Of note is that patients who were shocked were more likely to receive fibrinolysis. The lack of randomisation (physician dependant decision on administration) and broad non-specific inclusion criteria may have introduced selection bias and impacted on the reliability of these results, although this was addressed to some extent through propensity-based matching to select controls. A further limitation is the lack of consistency of the thrombolytic agent (alteplase or tenecteplase).

Overall, these studies provide little evidence in favour of the use of intra-arrest thrombolysis and have major limitations. Further studies addressing these limitations and specifics such as patient selection, timing and agent/s, are required to further inform the evidence base and future direction.

Discussion

Two strategies focussing on pharmaceuticals were identified for full review – administration of vasopressin and administration of thrombolysis. Neither of these strategies have any strong supportive evidence. Vasopressin and thrombolysis use in cardiac arrest patients in general (in-hospital as well as out-of-hospital) has been researched for some time, with no high-quality evidence for their benefit. Potentially, their use has benefit in specific patient subgroups, so although implementation of these strategies is not currently recommended from a general perspective, monitoring of the evidence base should definitely be continued.

In recent years, strategies to improve outcomes from OHCA have become more focussed on CPR quality and less on drug administration, so the findings of this review are largely unsurprising. Nevertheless, lack of rigour in conducting the studies is a possible explanation for lack of demonstrated effect. It is therefore essential that further, more rigorous studies are undertaken and the evidence base is monitored.

Limitations

There were several limitations of this systematic search and review. Although the review methodology was rigorous, it is possible that relevant studies may have been missed. Additionally, studies published in a non-English language or within grey literature only were not included. This was not a systematic review, so detailed critical appraisal of each included paper was not conducted (and was not feasible due to the broad objective of the review to include all relevant strategies). Nevertheless this may have strengthened the review.

Six studies were excluded from the review because there was only one study related to that strategy. Future research involving these strategies (passive oxygen insufflation, hypertonic saline administration, erythropoietin administration, lignocaine administration prophylactically, procainamide administration, and waveform analysis-guided shock timing) will further inform the evidence base, so should be monitored.

Conclusion

There is currently no strong evidence to support the introduction of vasopressin or thrombolysis administration in OHCA. The lack of evidence may in part be due to lack of rigour in conducting studies, or it may be that vasopressin or thrombolysis are advantageous for specific subsets of OHCA patients only. Therefore, future research should be rigorous in design and involve specific patient subsets.

Recommendations

- Future research into intra-arrest use of vasopressin or thrombolysis should be undertaken with rigorous design and investigation into different patient subsets.
- The evidence base for intra-arrest vasopressin, thrombolysis and other drugs should be monitored. There is a potential for the requirement of further investigation into the use of drugs specifically for OHCA if new scientifically plausible strategies are developed.
- Monitoring of the evidence base for other potential strategies outside the constraints (time or feasibility) of this review.

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Competing interests

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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