Searching for the evidence in pre-hospital care: a review of randomised controlled trials

Hugh Brazier, Andrew W Murphy, Caoimhe Lynch, Gerard Bury, on behalf of the Ambulance Response Time Sub-Group of the National Ambulance Advisory Committee

Abstract

Objectives—To identify randomised controlled trials (RCTs) which evaluate aspects of pre-hospital care; to perform categorisation by theme; to compare the sensitivity and precision of the search databases.

Data sources—August 1997 updates of MEDLINE and EMBASE databases, using the Datastar online system. Papers published in 1987 or later were included, with no language restrictions.

Study selection—A trial was eligible for inclusion if it was judged, by two independent and blinded assessors, that participants followed up in the trial were definitely or possibly assigned prospectively to one of two or more alternative forms of healthcare with random allocation or a quasirandom method of allocation.

Results—The literature search retrieved 849 papers, of which 569 (67%) were in MEDLINE and 486 (57%) in EMBASE. Forty one (5%) were confirmed as reports of RCTs or quasi-RCTs, and the total number of individual trials was 38. Ten of these trials dealt with thrombolytic drugs; 14 were concerned with other drugs, 12 with equipment, and two with other interventions. Four trials were based on a sample size of more than 1000, and seven reported a statistically significant effect on mortality. All 41 papers were in EMBASE, and all but one were also in MEDLINE.

Conclusions—Evidence based policy making with respect to the organisation of pre-hospital services cannot depend on RCTs. In the current relative absence of such evidence, practitioners and decision makers must use alternative information sources. A future review could examine a broader range of literature and be based on a wider search of published and unpublished material.

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Keywords: emergency medical services; pre-hospital care; outcomes; randomised controlled trials

Coronary artery disease is the leading cause of mortality in most developed countries. Over half of these deaths are due to sudden cardiac arrest and most occur outside hospital. The pre-hospital provision of the "cardiac chain of survival" is vital if such deaths are to be prevented.¹ Trauma is the leading cause of death and morbidity in the first four decades of life, with up to a half of such patients dying before reaching hospital. The potential for significant reductions in mortality (of up to 33%) and morbidity through improved pre-hospital care, especially basic airway and circulatory management, is widely acknowledged.² The organisation and delivery of pre-hospital services is clearly of paramount importance.

The importance of tracking down the best external evidence with which to answer clinical questions has recently been emphasised, and the randomised controlled trial (RCT) has been referred to as the "gold standard" in attempting such answers.³ We therefore decided to perform a review of the quality of evidence currently available regarding prehospital care. The specific objectives of the study were:

- To identify RCTs which evaluate aspects of pre-hospital care;
- To identify the themes considered in these RCTs;
- To compare the sensitivity and precision of the MEDLINE and EMBASE databases.

Methods

Relevant trial reports were identified from the MEDLINE and EMBASE databases, following methods outlined by the Cochrane Collaboration.⁴ A search for RCTs dealing with aspects of pre-hospital care, including ambulance services, was performed on the August 1997 updates of both databases, using the Datastar online system.⁵ Papers published in 1987 or later were included, with no language restrictions. The search was based on that presented in the Cochrane Library⁴ as a template for the identification of RCTs. The search strategy for each database (table 1) varied to take account of different index terms and indexing systems.

Inclusion criteria for the identification of RCTs were established. A trial was eligible for inclusion if it was judged that participants (or units) followed up in the trial were definitely or possibly assigned prospectively to one of two or more alternative forms of healthcare with random allocation or a quasi-random method of allocation (such as allocating alternate cases). HB, AWM, and CL performed a pilot assessment of 50 trials and subsequently met to clarify the inclusion criteria.

As the study database was an amalgamation of MEDLINE and EMBASE some duplication of studies occurred. Using Datastar's Star-Search system,⁵ these were identified and removed from the study database. All studies were then independently assessed by two of the

The Library, Royal College of Surgeons in Ireland, Dublin 2, Ireland H Brazier

Department of General Practice, National University of Ireland, Galway A W Murphy C Lynch

Department of General Practice, University College Dublin, Coombe Healthcare Centre, Dublin G Bury

Correspondence to: Mr Brazier (e-mail: hbrazier@rcsi.ie).

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Table 1 Search strategy used to identify RCTs in pre-hospital care (presented in Ovid format)

MEDLINE
clinical trial.pt.
exp clinical trials/
exp research design/
comparative study/
exp evaluation studies/
exp follow-up studies/
exp prospective studies/
(prospective or random\$).tw.
or/1-8
exp transportation of patients/
(pre-hospital or prehospital).ti.
or/10-11
9 and 12
limit 13 to publication date 1987 or later
EMBASE
exp controlled study/
exp clinical study/
exp clinical trial/
exp clinical trial/
exp clinical trial/ '0197'.ii.
exp clinical trial/ '0197'.ii. '0150'.ii.
exp clinical trial/ '0197'.ii. '0150'.ii. (prospective or random\$).tw.
exp clinical trial/ '0197'.ii. '0150'.ii. (prospective or random\$).tw. or/1-6
exp clinical trial/ '0197'.ii. '0150'.ii. (prospective or random\$).tw. or/1-6 ambulance/
exp clinical trial/ '0197'.ii. '0150'.ii. (prospective or random\$).tw. or/1-6 ambulance/ (pre-hospital or prehospital).ti.

authors. Duplicates which had not been identified as such by the Datastar system were noted and removed from the database. The remaining studies were categorised as follows: (1) not relevant to pre-hospital care; (2) no abstract provided; (3) not a RCT or quasi-RCT; or (4) possible RCT or quasi-RCT. Disagreements regarding any aspect of the categorisation process were resolved by discussion.

For each study categorised as a "possible RCT or quasi-RCT", a copy of the full article was obtained. These trials were then reviewed, and each of those confirmed as being a RCT or quasi-RCT was allocated to one of the following themes: thrombolytic drugs; nonthrombolytic cardiac drugs; fluids and electrolytes; other drugs; cardiopulmonary resuscitation (CPR) equipment; other equipment or other intervention. As the objective of this study was to provide a descriptive background only, no more detailed explicit methodological appraisal was performed. Where possible, the absolute reduction in overall mortality was noted or calculated; otherwise the main trial conclusion was noted.

For each database the following values were calculated: *sensitivity* (the proportion of relevant references in the database which are retrieved) and *precision* (positive predictive value: the proportion of retrieved references which are relevant).

Results

The literature search generated a list of 1055 references (table 2). Datastar's StarSearch system⁵ removed 190 of these as duplicates, leaving a set of 865 papers for review. On review 16 were found to be duplicates which had not been identified by the Datastar system, leaving a total of 849 unique papers, of which 569 (67%) were in MEDLINE, 486 (57%) in EMBASE, and 206 (24%) in both databases. A total of 144 of the 849 were categorised as "not relevant to pre-hospital care" and 72 as "no Table 2 Number of references at each stage of the literature search, and final number of individual RCTs or quasi-RCTs

Action	No
References identified in MEDLINE	569
References identified in EMBASE Combined total of MEDLINE and EMBASE	486
databases References identified as duplicates by Datastar's	1055
StarSearch system ⁵ References identified as duplicates during review	190
process	16
Unique references identified	849
Categorised as "not relevant to pre-hospital care"	144
Categorised as "no abstract available"	72
Categorised as "not a RCT or quasi-RCT"	580
Categorised as "possible RCT or quasi-RCT"	53
Confirmed as a "RCT or quasi-RCT"	41
Final number of individual trials	38

abstract provided". Of the remaining 633 papers, 580 were categorised as "not a RCT or quasi-RCT". This resulted in 53 (6% of the 849 unique references) being categorised as "possible RCT or quasi-RCT". The full texts of these were obtained. Fifty one were available locally, or were obtained through standard interlibrary loan procedures; the remaining two were obtained only after posting an appeal for assistance on the internet.

On the basis of the full text, 41 of the papers (5% of the 849) were confirmed as reports of RCTs or quasi-RCTs.⁶⁻⁴⁶ Thirty seven of these were in English, with two in German, and one each in French and Russian.

Three trials were reported in two papers each,^{7 8 10 11 16 17} so the total number of individual trials included in the review was 38. Ten of these trials dealt with thrombolytic drugs, seven with non-thrombolytic cardiac drugs, four with fluid replacement, and three with other drugs. A further four were concerned with CPR equipment, eight with other equipment, and the remaining two with other interventions. Details of the 38 trials are available on the world wide web at http://www.rsci.ie/ library/prehospital_care.html. Briefly, the findings were as follows:

THROMBOLYTIC DRUGS (10 TRIALS⁶⁻¹⁸)

There was considerable variation in the setting, the intervention and the inclusion criteria. One study of 145 patients seen within six hours of symptoms demonstrated a 21.5% reduction in absolute mortality at two years (p<0.05) for administration of intravenous streptokinase by physician staffed mobile coronary care unit versus in-hospital treatment.¹³ One trial based on 200 patients with suspected acute myocardial infarction showed a 10% reduction in absolute mortality at 30 days (p<0.05) for prehospital administration of intravenous streptokinase and heparin versus usual care.¹⁴ The other studies did not show a significant effect on mortality.

NON-THROMBOLYTIC CARDIAC DRUGS (SEVEN TRIALS¹⁹⁻²⁵)

Again, there was considerable variation in setting, type of drug intervention (lignocaine, adrenaline, methoxamine, nitroglycerin, frusemide, and morphine) and inclusion criteria. No trial demonstrated a significant effect on mortality.

FLUIDS AND ELECTROLYTES (FOUR TRIALS²⁶⁻²⁹)

All four trials dealt with trauma patients with blood pressure <100 or <90 mm Hg, and three were from the same research group. All examined the administration of 7.5% saline, with or without dextran, versus lactated Ringer's solution or normal saline. Two studies of 166 patients²⁶ and 359 patients²⁷ showed a significant increase in blood pressure (p<0.05) in those given 7.5% saline. Two trials based on 194²⁸ and 258 patients²⁹ found that mortality in the 7.5% saline group was significantly lower than predicted by TRISS (trauma and injury severity score) (p<0.001 and p<0.025, respectively).

OTHER DRUGS (THREE TRIALS³⁰⁻³²)

One trial reviewed drug treatment of adult asthmatics; another was concerned with patients with head injuries transported by helicopter. The third study, of 46 male combative patients,³² demonstrated that administration of intravenous droperidol, compared with placebo, resulted in significantly lower levels of agitation after 10 minutes (p<0.001).

CPR EQUIPMENT (FOUR TRIALS³³⁻³⁶)

One trial involving 702 adults with nontraumatic cardiac arrest compared simultaneous compression-ventilation (SC-V) CPR with standard CPR, and found that SC-V CPR was associated with a 6.8% increase in absolute mortality at hospital discharge (p<0.01).³³ The other three trials compared active compression-decompression and standard CPR, and one of them, involving 512 out-ofhospital cardiac arrests, showed a 12.4% reduction in absolute mortality at 24 hours (p<0.005) but no difference at one month.³

OTHER EQUIPMENT (EIGHT TRIALS³⁷⁻⁴⁴)

Three of the trials were concerned with acute myocardial infarction, two with patients in asystole or with bradycardia, and one with cardiac arrest; one dealt with gunshot victims and one with thermometry of patients transported by ambulance. One trial based on 1004 patients after a recent acute myocardial infarction showed that a patient instruction programme with telephonic follow up and electrocardiography (ECG) monitoring resulted in a significant reduction in clinical depression at one year (p<0.05), but made no difference to mortality.⁴⁰ One trial involving 22 patients with acute myocardial infarction found that prehospital cellular transmission of ECG led to a reduction in hospital delay to initiation of thrombolytic treatment when compared with no pre-hospital ECG (p<0.005).42 There were no other significant findings.

OTHER INTERVENTION (TWO TRIALS^{45 46})

Both trials concerned adult trauma patients transported by helicopter. One involving 574 patients compared the staffing of a helicopter by flight nurse and physician versus flight nurse and paramedic, and found that mortality of patients treated by flight nurse and physician was lower than that of those in the other group and lower than predicted by TRISS (p<0.05 in each case).⁴⁵

Overall, only four trials had more than 1000 patients.¹⁶ ¹⁷ ²¹ ³⁵ ⁴⁰ Six trials resulted in a significant reduction in mortality,¹³ ¹⁴ ²⁸ ²⁹ ³⁶ ⁴⁵ and one showed a significant increase in mortality.³³

All of the 53 possible RCTs or quasi-RCTs were included in EMBASE, and all but one were also in MEDLINE. All of the 41 papers confirmed as reports of RCTs or quasi-RCTs were in EMBASE, and 40 in MEDLINE. The sensitivity of MEDLINE was therefore 98% of that of EMBASE. The precision of the MEDLINE and EMBASE searches was 7% and 8% respectively.

Discussion

Although up to 50% of published systematic reviews are based on a search of MEDLINE alone, and one third explicitly exclude unpublished material (H Brazier, unpublished data), it is accepted that a comprehensive review requires a search of several databases and should also guard against publication bias by including unpublished trials.47-49 This preliminary review was based on only two databases, and no attempt was made to identify unpublished material. A number of potentially relevant studies may therefore have been missed. In particular, a search of the CINAHL database (the Cumulative Index of Nursing and Allied Health Literature) may have revealed further trials.

A different search strategy might have led to the identification of some more trials within MEDLINE and EMBASE. On the other hand, it is inevitable that a literature search will miss a proportion even of those papers that are included in the databases searched, and the search strategy we employed was designed to maximise sensitivity without too great a reduction in precision.

Other limitations of the study include the decision to include only trials published in 1987 or later, and the exclusion of references with no abstract. The rejection of papers with no abstract is unlikely to have resulted in the loss of many RCTs, however, as both MEDLINE and EMBASE include an abstract where the original paper has one, and it is probable that almost all published RCTs have an abstract. Sixty seven per cent of the publications rejected at this stage were short communications of three pages or less.

Of the 849 papers identified, 569 (67%) were indexed by MEDLINE, 486 (57%) were in EMBASE, and 206 (24%) were included in both databases. This overlap between the two databases is in line with the overlap in journal coverage of 34% reported elsewhere.⁵⁰ On the other hand, all but one of the studies confirmed as RCTs or quasi-RCTs were in both sources. Searching two databases instead of just one substantially increased the search workload, but made almost no difference to the number of valid and useful studies identified.

There was no significant difference in the performance of the two databases. In the absence of an independent search for all relevant trials, however, it is not possible to assess the absolute sensitivity of the database searches.

Twenty four (63%) of the 38 confirmed RCTs or quasi-RCTs related to drugs, 10 to thrombolytic drugs. This may be because the randomised controlled design is especially suited to studies of drug administration. High quality studies of other aspects of pre-hospital care are likely to have been missed by this review. The number of trials producing nonsignificant conclusions is notable. Only four trials enrolled more than 1000 patients. These two findings may be related and suggest that future trials should be based on careful sample size calculations.

In spite of the possibility that some relevant trials may have been missed by this review, we conclude that there are relatively few RCTs concerned with pre-hospital care, that those which have been published cover a wide range of different subjects, limiting the scope for synthesis of their results, and that they have produced very few significant findings. Evidence based policy making with respect to the organisation of pre-hospital services cannot depend on RCTs alone. Practitioners and decision makers, in the current absence of such evidence, must make use of alternative information sources.

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Commentary

Hugh Brazier and colleagues have undertaken an important analysis that demonstrates both the difficulties of identifying the literature relevant to pre-hospital care and describes the scarcity of research in this field. The points that they raise are sufficiently important to warrant further consideration.

It has been estimated that over 10 million medical articles exist on library shelves.¹ The enormous volume of research outputs, combined with the ever increasing number of journals, makes it increasingly difficult for clinicians, or those determining health policy, to maintain an awareness of the literature. The results of individual studies may be inconclusive; however, the integration of information from a variety of valid and relevant studies may provide sufficient evidence to warrant a change in clinical practice.² Literature reviews have become an essential means of synthesising and disseminating the results of research. Using explicit, systematic, methods limits the biases and random errors inherent in non-systematic literature reviews and thereby provides more reliable results upon which to draw conclusions or make decisions.³

Literature searches, based on electronic databases, may aim to identify papers relating to a specific clinical area, methodology, or a combination of these. The sensitivity of literature searches, aiming to identify RCTs, are related to the accuracy of indexing and to the adequacy of methodological information in titles and abstracts.⁴ Articles can be identified by searching for text words or by using an index of medical titles such as the medical subject headings (MeSH) in MEDLINE.1 Some of the available MeSH terms obviously relate to pre-hospital care (such as "transportation of patients" and "emergency medical services"). Not all the relevant articles are, however, appropriately indexed. Errors in the indexing of articles arise from mistakes, by both authors and editors, in the selection of keywords and also occur during the abstraction and grouping of articles by librarians.

Only about one third of published articles are indexed in MEDLINE.¹ Several authors have reported on the sensitivity and precision of searches of MEDLINE, which vary substantially depending on the topic of interest and the development of relevant MeSH terms (table 1). More rarely, there have been assessments of the relative effectiveness of a range of electronic databases.¹⁰ The choice of which electronic database(s) to use is determined by the reason for undertaking the search and the area of interest. MEDLINE is probably the most easily accessible electronic database but there are often substantial delays before articles are included, EMBASE focuses on drugs and pharmacology and has been reported to have better European coverage, CINAHL is a nursing and allied health database.1 11 Other important sources of information include the Co-Controlled Trials Register, the chrane Cochrane Database of Systematic Reviews and the National Research Register (a British register of trials in progress).

The need for hand searching relevant journals and the bibliographies of articles previously identified as relevant to the purposes of a review has been well documented.56 The importance of surveying experts in the field of interest has not received as much attention (table 1). A number of medical and paramedical journals are not included in the electronic databases. For example, although the journal of Pre-hospital Immediate Care was launched in March 1997, research papers published in this

Table 1 Sensitivity and precision of searches of electronic databases by topic area

	Area of interest	Sensitivity (%)	Precision (%)
Evaluations of MEDLINE			
Adams et al, 1994 ⁵	Mental health	52	59
Bender et al, 19976	Obstetrical anaesthesia	65	Not stated
Dickersin et al, 1994 ⁷	Ophthalmology	82	8
Jadad and McQuay, 1993 ⁸	Pain	87	52
Marson and Chadwick, 1996 ⁴	Epilepsy	86	35
Van der Weijden et al, 1997 ⁹	Erythrocyte sedimentation rate	91	10
	Dipsticks	98	68
Hobbs et al, 1997 ¹⁰	Near patient testing in primary care	20	6
Evaluation of electronic databases, other than MEDLINE (Hobbs <i>et al</i> , 1997 ¹⁰)			
BIDS	Near patient testing	31	17
EMBASE	- 0	11	28
Survey of active researchers		39	12